Environmental Chemistry for a Sustainable World 52

Grégorio Crini
Sophie Fourmentin
Eric Lichtfouse *Editors*

The History of Cyclodextrins

Springer

Environmental Chemistry for a Sustainable World

Volume 52

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Eric Lichtfouse
Editors

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Editors
Grégorio Crini
Chrono-environnement, UMR 6249, UFR Sciences et Techniques
Université Bourgogne Franche-Comté
Besançon, France

Eric Lichtfouse
Aix Marseille Univ, CNRS, IRD, INRAE, Coll France, CEREGE
Aix-en-Provence, France

Sophie Fourmentin
Univ. Littoral Côte d'Opale, UR 4492, UCEIV, Unité de Chimie Environnementale et Interactions sur le Vivant, SFR Condorcet FR CNRS 3417
Dunkerque, France

ISSN 2213-7114 ISSN 2213-7122 (electronic)
Environmental Chemistry for a Sustainable World
ISBN 978-3-030-49307-3 ISBN 978-3-030-49308-0 (eBook)
https://doi.org/10.1007/978-3-030-49308-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

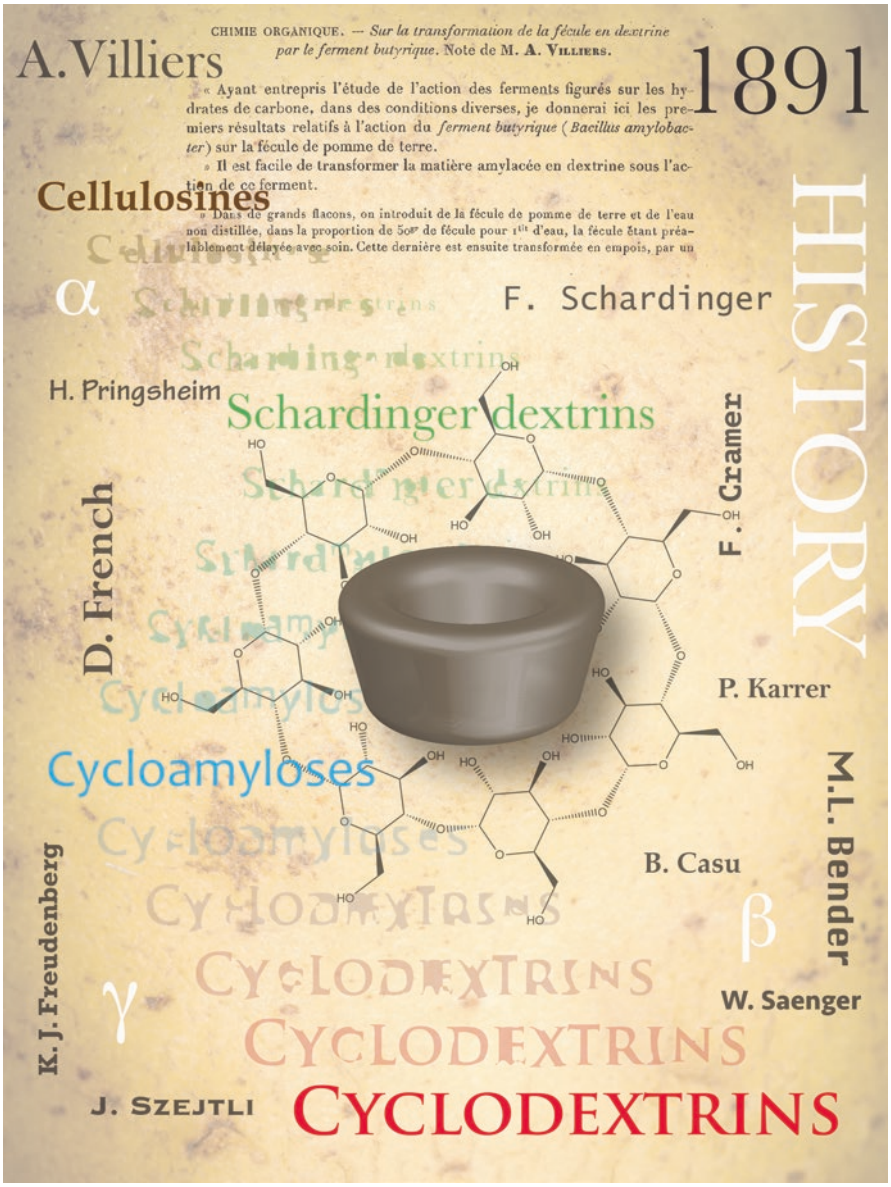
The Schardinger dextrins will continue to serve, delight, teach, and intrigue the carbohydrate chemist for many years to come.

(Professor Dexter French, 1957)

Although discovered about 130 years ago in France by the pharmacochemist Antoine Villiers, cyclodextrins are cage-like compounds that still fascinate researchers. Cyclodextrins are produced by enzymatic degradation of starch. Cyclodextrins are among the most remarkable macrocyclic molecules of major theoretical and practical impacts in chemistry, biology, biochemistry, health science and agriculture. Cyclodextrin investigations have broken frontiers between many different disciplines and, as a result, actual scientists work together to disclose new concepts and applications. The unique feature of cyclodextrins is their ability to form inclusion complexes with various molecules by host–guest interactions, which are at the origin of many applications in almost all industrial sectors.

This book, entitled *Cyclodextrin History,* is the third volume on cyclodextrins published in the series Environmental Chemistry for a Sustainable World. Written by 36 international contributors from 11 countries who are leading experts in the cyclodextrin field, the 3 volumes focus on the developments, research trends, methods and innovations related to the use of cyclodextrins for both fundamental research and applied technology. The first volume explains cyclodextrin fundamentals, synthesis and characterization[1]. The second volume focuses on cyclodextrin applications in medicine, food, environment and liquid crystals[2].

This book presents the history of cyclodextrins. In addition, the book contains invited chapters from senior scientists who have made a major contribution to cyclodextrin knowledge. The first chapter by Nadia Morin-Crini et al. outlines the historical milestones of the discovery, exploration, development and practical applications of cyclodextrins. The next two chapters review the achievements of two prestigious researchers: Professors József Szejtli and Benito Casu. Chapter 2 by Grégorio Crini et al. presents the scientific and industrial work of Professor József Szejtli, considered as the ‘godfather of cyclodextrins’. Chapter 3 by Giangiacomo



Torri et al. pays tribute to Professor Benito Casu, one of the pioneers in the dissemination of the cyclodextrin knowledge. Then, Éva Fenyvesi et al. describe the history of cyclodextrin production in Hungary in Chap. 4. Chapter 5 by Bastien Léger et al. reviews metal nanoparticles and cyclodextrin for catalytic applications. Cyclodextrin-based polymers for food and pharmaceutical applications are then described by

Max Petitjean et al. in Chap. 6. In Chap. 7, Abhishek Pandey explains how cyclodextrins and nanomaterials can be used in drug delivery systems. The last chapter by Grégorio Crini reviews the work carried out on water-insoluble cyclodextrin-epichlorohydrin polymers over the past 30 years at the Chrono-environment Laboratory in Besançon, France.

The editors extend their thanks to all authors who contributed to this book for their efforts in producing timely and high-quality chapters. The creation of this book would not have been possible without the assistance of several friends deserving acknowledgement. They have helped us by choosing contributors, reviewing chapters, and in many other ways. Finally, we would like to thank the staff at Springer Nature for their highly professional editing.

Besançon, France — Grégorio Crini
Dunkerque, France — Sophie Fourmentin
Aix-en-Provence, France — Eric Lichtfouse

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About the Editors

Grégorio Crini is Environmental Polymerist at Université Bourgogne Franche-Comté, Besançon, France. His research focuses on the environmental aspects of cyclodextrin chemistry.

Sophie Fourmentin is Professor at the Université du Littoral Côte d'Opale, Dunkerque, France. She is the president of the French Cyclodextrin Society. Her research works are at the interface between host-guest chemistry and environmental chemistry.

Eric Lichtfouse is Professor of environmental chemistry and scientific writing at Aix Marseille University and Xi'an Jiaotong University. He invented carbon-13 dating.

Contributors

Grégorio Crini Chrono-environnement, UMR 6249, UFR Sciences et Techniques, Université Bourgogne Franche-Comté, Besançon, France

Éva Fenyvesi CycloLab Cyclodextrin Research & Development Ltd, Budapest, Hungary

Marc Fourmentin Université du Littoral Côte d'Opale, Laboratoire de Physico-Chimie de l'Atmosphère (LPCA, EA 4493), ULCO, Dunkerque, France

Sophie Fourmentin Univ. Littoral Côte d'Opale, UR 4492, UCEIV, Unité de Chimie Environnementale et Interactions sur le Vivant, SFR Condorcet FR CNRS 3417, Dunkerque, France

Iñigo X. García-Zubiri Magnesitas Navarras, Zubiri, Navarra, Spain

José Ramón Isasi Departamento de Química, Facultad de Ciencias, Universidad de Navarra, Pamplona, Spain

Bastien Léger Université d'Artois, CNRS, Centrale Lille, Université de Lille, UMR 8181, Unité de Catalyse et de Chimie du Solide (UCCS), Lens, France

Eric Lichtfouse Aix Marseille Univ, CNRS, IRD, INRAE, Coll France, CEREGE, Aix-en-Provence, France

Eric Monflier Université d'Artois, CNRS, Centrale Lille, Université de Lille, UMR 8181, Unité de Catalyse et de Chimie du Solide (UCCS), Lens, France

Nadia Morin-Crini Chrono-environnement, UMR 6249, UFR Sciences et Techniques, Université Bourgogne Franche-Comté, Besançon, France

Annamaria Naggi Istituto di Chimica e Biochimica G. Ronzoni, Milan, Italy

Sébastien Nöel Université d'Artois, CNRS, Centrale Lille, Université de Lille, UMR 8181, Unité de Catalyse et de Chimie du Solide (UCCS), Lens, France

Abhishek Pandey School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India

Max Petitjean Departamento de Química, Facultad de Ciencias, Universidad de Navarra, Pamplona, Spain

Anne Ponchel Université d'Artois, CNRS, Centrale Lille, Université de Lille, UMR 8181, Unité de Catalyse et de Chimie du Solide (UCCS), Lens, France

Samahe Sadjadi Gas Conversion Department, Faculty of Petrochemicals, Iran Polymer and Petrochemical Institute, Tehran, Iran

Gábor Seres Berlini Park Research and Development Centre, Budapest, Hungary

Lajos Szente CycloLab Cyclodextrin Research & Development Ltd, Budapest, Hungary

Giangiacomo Torri Istituto di Chimica e Biochimica G. Ronzoni, 81 via G. Colombo, Milan, Italy

Chapter 1
History of Cyclodextrins

Nadia Morin-Crini, Sophie Fourmentin, Éva Fenyvesi, Eric Lichtfouse, Giangiacomo Torri, Marc Fourmentin, and Grégorio Crini

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N. Morin-Crini (✉) · G. Crini
Chrono-environnement, UMR 6249, UFR Sciences et Techniques,
Université Bourgogne Franche-Comté, Besançon, France
e-mail: nadia.crini@univ-fcomte.fr; gregorio.crini@univ-fcomte.fr

S. Fourmentin
Univ. Littoral Côte d'Opale, UR 4492, UCEIV, Unité de Chimie Environnementale et Interactions sur le Vivant, SFR Condorcet FR CNRS 3417, Dunkerque, France
e-mail: sophie.fourmentin@univ-littoral.fr

É. Fenyvesi
CycloLab Cyclodextrin Research & Development Ltd, Budapest, Hungary
e-mail: fenyvesi.e@cyclolab.hu

E. Lichtfouse
Aix Marseille Univ, CNRS, IRD, INRAE, Coll France, CEREGE, Aix-en-Provence, France

G. Torri
Istituto di Chimica e Biochimica G. Ronzoni, 81 via G. Colombo, Milan, Italy
e-mail: torri@ronzoni.it

M. Fourmentin
Université du Littoral Côte d'Opale, Laboratoire de Physico-Chimie de l'Atmosphère (LPCA, EA 4493), ULCO, Dunkerque, France
e-mail: marc.fourmentin@univ-littoral.fr

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_1

Abstract Cyclodextrins are cyclic oligosaccharides obtained by enzymatic degradation of starch. They are remarkable macrocyclic molecules that have led major theoretical and practical advances in chemistry, biology, biochemistry, health science, and agriculture. Their molecular structure is composed of a hydrophobic cavity that can encapsulate other substances to form inclusion complexes through host-guest interactions. This unique feature is at the origin of many applications. Cyclodextrins and their derivatives have a wide variety of practical applications in almost all sectors of the industry, including pharmacy, medicine, foods, cosmetics, chromatography, catalysis, biotechnology, and the textile industry.

Villiers published the first reference to cyclodextrins in 1891. Since the beginning of the twentieth century, major researchers, such as Schardinger, Pringsheim, Karrer, Freudenberg, French, Cramer, Casu, Bender, Saenger, Nagai, Szejtli, and Pitha, have paved the history of the cyclodextrins. Several time periods have marked their history. After their discovery and characterization from 1891 to 1911, there has been a period of doubt and disagreement from 1911 to 1935. Then, the 1935–1950 exploration period was marked by structural results on the "Schardinger dextrins." In 1949, Cramer introduced the cyclodextrin-based nomenclature. Research between 1950 and 1970, the period of maturation, focused on conformations and spectroscopic data of cyclodextrins and their inclusion complexes, with applications in catalysis and as enzyme models. Finally, the period of use has been ongoing since 1970 and has seen cyclodextrins find many industrial applications. Cyclodextrins have then found many industrial applications, initially in the pharmaceutical and food sectors. In 1984, the first chromatographic columns were commercialized. At that time, many cyclodextrin-based catalysts were developed for biomimetic

chemistry and other applications such as artificial enzymes. Currently, more than 2000 publications on cyclodextrins are published each year.

In this chapter, we present a historical overview of the discovery, development, and applications of cyclodextrins.

Keywords History · Schardinger dextrins · Discovery · Production · Separation · Native cyclodextrins · Development · Inclusion complexes · Applications

1.1 Introduction

Figure 1.1 shows that cyclodextrins occur in many daily products such as an ibuprofen tablet, a nonsteroidal anti-inflammatory drug, a whooping cough vaccine, a curative antidote, a hair loss solution, a stop smoking aid, toothpastes, shampoo, colognes, a deodorant toilet, razors, a turmeric-based food supplement, a butter, a mayonnaise, fish sausages, modified steaks, a horseradish powder, mustard sauces, a sweetener, honey, a cinnamon extract, green tea without bitterness, vanilla coffee, clarified fruit juices, chewing gums, chromatographic columns, biopesticides, catalysts, tubular materials, a curtain, cosmetotextiles, an ink, a detergent, a bioflocculant for swimming pool, or a bioadsorbent for water treatment.

Fig. 1.1 Commercial products containing cyclodextrins in our daily lives

Cyclodextrins are cyclic oligomers obtained from the enzymatic degradation of starch. They are one of the most remarkable macrocyclic molecules with significant impacts in our daily lives. Cyclodextrins have a particular structure composed of a hydrophobic cavity that can encapsulate other substances to form inclusion complexes through host-guest interactions. This characteristic feature is at the origin of many applications. Today, all industrial sectors are concerned, e.g., pharmaceuticals, cosmetics, food, hygiene and toiletries, biotechnology, medical, radiology, agrochemistry, catalysis, packaging, textile industry, nanotechnology, and soil and water treatment.

The French pharmacist Villiers published the first reference to cyclodextrins in 1891 (Villiers 1891a, b, c, d). Since the beginning of the twentieth century, Schardinger, Pringsheim, Karrer, Freudenberg, French, Cramer, Casu, Bender, Saenger, Nagai, Szejtli, and Pitha have marked the history of cyclodextrins (Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

The first important period on the history of cyclodextrins, from 1891 to 1911, covers their discovery by Villiers, and their characterization and chemistry by Schardinger (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998). In 1891, Villiers discovered a crystalline dextrin from the *Bacillus amylobacter* digest of potato starch, which he named *cellulosine*. At the beginning of the last century, Schardinger also observed the formation of two crystallized products during his investigations of food spoilage, which he called crystallized dextrin-α and crystallized dextrin-β. Schardinger gave the first detailed description of the preparation and separation of these two dextrins. He was also the first to isolate the strain of bacteria responsible for dextrin formation, i.e., *Bacillus macerans*. However, from 1911 to 1935 came a period of doubt and disagreement, in particular between the groups of Pringsheim and Karrer, although they published numerous studies on the composition, properties, and chemistry of the crystallized dextrins (Crini 2014).

It was not until the mid-1930s that research on dextrins developed again. The exploration period from 1935 to 1950 was marked by the numerous results obtained by Freudenberg and French on the structure of the "Schardinger dextrin" molecules. In 1935, Freudenberg was the first to develop a relatively simple method for the obtention and purification of the two Schardinger dextrins. Freudenberg also suggested in 1936 a cyclic structure for α-dextrin and β-dextrin, which was confirmed in 1938. In the 1940s, French proposed that Schardinger dextrins be called cycloamyloses and described new protocols for the preparation of cycloamyloses with high purity. In 1942, Hudson discovered the enzyme in *Bacillus macerans* responsible for the conversion of starch into dextrins, and the same year, French published the exact molecular weights of the cyclohexaamylose and cycloheptaamylose, i.e., α-dextrin and β-dextrin, respectively. In 1948, Freudenberg discovered γ-dextrin or cyclooctaamylose, and 1 year later, Cramer, his PhD student, introduced the cyclodextrin-based nomenclature. From 1950 onward, this terminology was increasingly used although the nomenclature of cyclodextrins remained a subject of debate until the end of the 1990s.

The period between 1950 and 1970, known as the period of maturation of notions, focused on inclusion complexes with Cramer's work in the foreground. At the beginning of the 1950s, French finally demonstrated the chemical cyclic structures of cycloamyloses. In 1953, Cramer gave the basis for supramolecular catalysis involving cyclodextrins, and the same year, with Freudenberg and Plieninger, he published the first patent concerning the applications of cyclodextrins in pharmaceutical formulations. In 1956, Cramer introduced and detailed the notion of an *inclusion complex*. From that time on, the interest in cyclodextrins increased. During the maturation period, the works of Casu on the conformation and spectroscopic characterization of cyclodextrins were acknowledged to have brought an important contribution. At the same time, much attention was also focused on their use for catalysis and as enzyme models, and one name stands out in particular in the enzymology and catalysis by cyclodextrins: Bender (Crini 2014). Nonetheless, until the mid-1970s, the three main native cyclodextrins, i.e., α-, β-, and γ-cyclodextrins, available only in small quantities, were long considered as just laboratory curiosities (Thoma and Stewart 1965; Caesar 1968; Kainuma 1984; Clarke et al. 1988). In the way of industrial development, the three main obstacles were their price, e.g., in 1975 1 kg of β-cyclodextrin had a price of about 1500 $ (Szejtli 1982a), their presumed toxicity (French 1957a), and the lack of sufficient knowledge of these substances (Szejtli 1982a). In addition, very few researchers were convinced of the industrial potential of cyclodextrins.

The 1970s were marked by two important events: firstly, several manufacturers started to produce and to commercialize cyclodextrins; at that time, due to improvements in the production of cyclodextrins, their prices have dropped significantly. Secondly, the first toxicological studies had established that β-cyclodextrin administrated orally was a harmless substance. As a result, this has led to spectacular progress. From then on, the period of use began and cyclodextrins found many industrial applications. During this period of utilization, four names stand out: Saenger, Szejtli, Nagai, and Pitha. In the mid-1970s, pharmaceutical and food applications started to appear and rapidly gained ground, especially in Japan (Hamada et al. 1975; Szejtli 1977; Pitha et al. 1983; Uekama and Otagiri 1987; Frömming and Szejtli 1994). In 1980, Saenger published the first comprehensive review about the potential industrial applications of cyclodextrins (Saenger 1980). The first International Cyclodextrin Symposium organized by Szejtli took place in Budapest in 1981, and 1 year later, he wrote the first comprehensive cyclodextrin book (Szejtli 1982a). At that time, many interesting catalysts based on cyclodextrins were also constructed for biomimetic chemistry and other processes of interest such as artificial enzymes (Breslow 1979; Breslow and Dong 1998). Both from an academic and industrial point of view, the number of communications then started to increase exponentially, as did the filing of patents.

In the mid-1980s, cyclodextrins were produced in large quantities and commercialized at a reasonable price, i.e., 10–15 $/kg (Szejtli 1982a). Other industrial applications have become possible. In 1984, the first chromatographic columns were marketed (Armstrong 1984; Ward and Armstrong 1986, 1988; Armstrong and Jin 1989). Since then, an increasing interest in cyclodextrins and their possible

applications has existed (Duchêne 1987, 1991; Szejtli 1988). An abundant scientific literature has built up since the 1980s. Currently, every year, more than 2000 publications, including articles and book chapters, are devoted to cyclodextrins (Cyclodextrin News, CycloLab Ltd., Hungary). Nowadays, these molecules still fascinate researchers and industrials.

The objective of this chapter is to describe historical landmarks of the discovery, exploration, and utilization of cyclodextrins. We also present some highlights of their early industrial applications. To this end, an extensive list of data from about 500 original publications has been compiled. Although this historical chapter cannot hope to be exhaustive, it does highlight the work of those researchers who have contributed to the knowledge of cyclodextrins throughout the 129 years of its history.

1.2 Discovery and First Chemical Studies of Cyclodextrins

1.2.1 Discovery: 1891–1911

During experiments on the degradation and reduction of carbohydrates under the action of ferments, Antoine Villiers, a French pharmacist and chemist, was the first to observe in 1891 the formation of unwanted crystals with particular properties, i.e., the formation of cyclodextrins. Among various Villiers' biographies, those by French (1957a), Thoma and Stewart (1965), Caesar (1968), Szejtli (1998), Loftsson and Duchêne (2007), Kurkov and Loftsson (2013), Crini (2014), and Morin-Crini et al. (2015) deserve particular mention.

Studying the degradation and reduction of carbohydrates, Villiers showed how easy it was to transform starch to yield "novel crystalline dextrins" with particular properties under the action of ferments. He first obtained a small amount of crystalline dextrins from digests of *Bacillus amylobacter*, i.e., *Clostridium butyricum*, on potato starch under certain conditions (Villiers 1891a, b): 50 g potato starch in 1 L of water at 100 °C subsequently seeded with *Bacillus amylobacter* and incubated for several days in an oven at 40 °C. Villiers presented his results to the French *Académie des Sciences* in February 1891 (Fig. 1.2). At that time, the dextrins, previously discovered in 1821, were the degradation products and/or the intermediate decomposition products of starch through heating. For Villiers, his dextrins were degradation products of starch. When purified by fractional precipitation, the crystals presented very different optical rotation properties and were difficult to hydrolyze any further. Iodine stains red those dextrins that had a high optical activity, and the intensity of the stain decreased with the optical activity. The butyric ferment caused the transformation of the starch directly into dextrin without the involvement of intermediates such as diastases secreted by the ferment. Later, Villiers considered his dextrins as the intermediate decomposition products of starch (Villiers 1891b). Villiers also obtained *un curieux sous-produit*, i.e., a curious by-product, in small

CHIMIE ORGANIQUE. — *Sur la transformation de la fécule en dextrine par le ferment butyrique*. Note de M. **A. Villiers**.

« Ayant entrepris l'étude de l'action des ferments figurés sur les hydrates de carbone, dans des conditions diverses, je donnerai ici les premiers résultats relatifs à l'action du *ferment butyrique* (*Bacillus amylobacter*) sur la fécule de pomme de terre.

» Il est facile de transformer la matière amylacée en dextrine sous l'action de ce ferment.

Fig. 1.2 Extract of the first proceedings of the French *Académie des Sciences* of February 1891 where Villiers described the action of the butyric ferment *Bacillus amylobacter* on potato starch

CHIMIE ORGANIQUE. — *Sur la fermentation de la fécule par l'action du ferment butyrique*. Note de M. **A. Villiers**.

« J'ai montré dernièrement (*Comptes rendus*, février 1891, p. 435) que la fécule de pomme de terre peut, dans des conditions déterminées, fermenter sous l'action du *Bacillus amylobacter*, les produits principaux de cette fermentation étant constitués par des dextrines.

» Il se forme en même temps, mais en très petite quantité, soit environ 3^{gr} pour 1000 de fécule, un hydrate de carbone qui se sépare en beaux cristaux radiés, au bout de quelques semaines, dans l'alcool ayant servi à la précipitation des dextrines. Ces cristaux renferment de l'eau et de l'alcool de cristallisation, la proportion de ce dernier étant très faible, environ 4 pour 100. Au contact de l'air, ils deviennent opaques, en perdant de l'alcool et absorbant de l'eau, sans que leur poids varie d'une manière notable. En les dissolvant dans une assez grande quantité d'eau chaude, on obtient, par refroidissement, de petits cristaux brillants, inaltérables à l'air, dont la composition est représentée par un multiple de la formule

$$C^{12}H^{10}O^{10} + 3HO.$$

Fig. 1.3 Extract of the second proceedings of the French *Académie des Sciences* of June 1891 where Villiers described the chemical composition of two novel crystalline dextrins which he named *cellulosines*

quantities after several weeks of incubation: 3 g of this carbohydrate was obtained as crystals after bacterial digestion of 1000 g of starch. This new substance was found in the alcohol that was used for the precipitation of dextrins (Villiers 1891b).

In a second proceedings of the French *Académie des Sciences* of June 1891 (Fig. 1.3), Villiers described the chemical composition of the novel highly crystalline dextrin having a composition between that of starch and that of dextrin (Villiers 1891c). In air, the crystals, containing water and alcohol of crystallization (the proportion of the latter is rather small, about 4%), became opaque. They lose alcohol

and absorbed water without any change in weight. After purification in large amount of hot water, Villiers obtained small brilliant crystals, most probably β-cyclodextrin, and determined the chemical composition of this crystalline carbohydrate. He gave the first empirical formula: $[(C_6H_{10}O_5)_2 + 3H_2O]$. Its solubility in water at room temperature was low but raised with temperature. The white crystals with a very slight sweetness showed extremely high optical activity, much higher than those of certain dextrins formed under the action of the butyric ferment. Villiers then considered this novel substance as an isomer of starch (Villiers 1891c, d). By manipulating the experimental conditions, Villiers obtained two distinct crystalline dextrins, most probably α-cyclodextrin and β-cyclodextrin, having a composition represented by a multiple of the formula $[(C_6H_{10}O_5) + 3H_2O]$. Villiers noted again that the white crystals with a very slight sweetness showed extremely high optical activity. Pursuing his experiments, he observed that the two dextrins, always considered as isomers of starch, were almost insoluble in water, soluble in alcohol, non-fermentable, and acid resistant, and they could also be converted into ethers under the action of acid chlorides. Villiers finally concluded that the properties of these two particular dextrins were very clearly different from those of the various saccharides and polysaccharides known at the time and proposed the name of *cellulosines* due to the similarities with cellulose, e.g., with "regard to difficulty of acid hydrolysis" (Villiers 1891c, d).

At the beginning of the 1900s, Heinrich Robert Koch, a famous German physician and microbiologist, who received a Nobel Prize in 1905, remained unconvinced by Villiers' conclusions (Crini 2014). In Koch's opinion, Villiers used "primitive bacteriological techniques and probably impure cultures." This was also pointed out by Schardinger (1904). Later, French (1957a) indicated that "Villiers used impure cultures but his digests contained sufficient *Bacillus macerans* to account for the small amount of crystalline dextrin obtained."

The recognition to cyclodextrins is attributed to Franz Schardinger, an Austrian chemist and bacteriologist. Schardinger is the first Great Scientist who has left its mark on the history of these oligosaccharides. He is considered the "Founding Father" of cyclodextrin (Szejtli 1982a; Crini 2014).

At the beginning of the last century, Schardinger also observed the formation of dextrins during his investigations of resistant microorganisms that can lead to food poisoning (Fig. 1.4). Like other researchers at that time, Schardinger studied these dextrins with the expectation that they would shed some light on the synthesis and degradation of starch. In 1903, Schardinger discovered that a type of extremely heat-resistant microorganism was able to dissolve starch and form crystalline by-products (Schardinger 1903a), remarkably similar to *cellulosines* reported by Villiers. Using the iodine test, Schardinger distinguished two types of *krystallisiertes dextrins* which he called crystallized dextrin A and crystallized dextrin B. The B form resembled Villiers' cellulosine. Indeed, the chemical behavior and the physical constants given by Schardinger for his substance agree very well with those of the dextrin previously described by Villiers. Schardinger found that it was possible to isolate pure fractions with a maximum yield of 30% crystallized dextrins from starch, the main form obtained being always dextrin B. *Krystallisiertes dextrins*

Zeitschrift
für
Untersuchung der Nahrungs- und Genußmittel,
sowie der Gebrauchsgegenstände.

Heft 19. 1. Oktober 1903. 6. Jahrgang.

Über thermophile Bakterien aus verschiedenen Speisen und Milch,
sowie über einige Umsetzungsprodukte derselben in kohlenhydrathaltigen Nährlösungen, darunter krystallisierte Polysaccharide (Dextrine) aus Stärke.

Von

Franz Schardinger.

Mitteilung aus der K. K. Allgemeinen Untersuchungsanstalt für Lebensmittel in Wien.

Im vergangenen Jahre hatte die hiesige Anstalt die Frage der Zulässigkeit des Genusses längere Zeit hindurch warm aufbewahrter Speisen zu prüfen, wobei sich im Verlaufe der Untersuchung beachtenswerte mikrobiologische Funde ergaben, über die im nachstehenden eingehender berichtet werden soll. Auf Grund der Forschungsergebnisse über thermophile Bakterien konnte es keinem Zweifel unterliegen, daß bei der in Betracht kommenden Temperatur zwischen 50—60° bakterielles Leben überhaupt möglich ist, es war also zunächst festzustellen, ob in den Speisen derartige Keime vorhanden und welcher Art die von ihnen veranlassten Zersetzungen sind, soweit eine Feststellung in letzter Beziehung derzeit möglich ist.

Fig. 1.4 First page of the article published by Schardinger on dextrins in 1903

were first considered as the degradation products of starch through heating (Schardinger 1903a). Schardinger also managed to isolate the strain of bacteria responsible for the degradation of starch – he called it *strain II* (Schardinger 1903b). He observed that this heat-resistant organism had considerable starch-fermenting power. When sub-cultured on starch, *strain II* broke down starch, giving an alcohol-insoluble "soluble starch" together with crystallized dextrin A (fine hexagonal plates) and crystallized dextrin B (stout prismatic crystals). Schardinger also observed that with time, the activity of the *strain II* microorganism decreased. Indeed, he was unsuccessful in maintaining a culture of *strain II* which had the characteristic starch-degrading activity.

In 1904, Schardinger isolated a new microorganism, considered as "an accidental contaminant," which he first called *Rottebacillus I* owing to its action on potato starch, i.e., it produced acetone and ethyl alcohol by fermentation of carbohydrate media (Schardinger 1904). The name *Rottebacillus I* was used to express the fact

Bacillus macerans, ein Aceton bildender Rottebacillus.

[Mitteilung aus der k. k. Untersuchungsanstalt für Lebensmittel in Wien.]

Von **Franz Schardinger.**

Ueber die durch den genannten Mikroben bewirkte Acetongärung wurde bereits in No. 8 der Wiener klinischen Wochenschrift, Jahrg. 1904 berichtet. Die Ergebnisse fortgesetzter Studien über diese Gärung und die Verrottung pflanzlicher Gebilde sollen im nachfolgenden einem weiteren Leserkreise unterbreitet werden.

Fig. 1.5 Abstract of the article published in the journal *Wiener Klinische Wochenschrift* by Schardinger on *Bacillus macerans* in 1904

the microorganism was able to form both acetone and ethyl alcohol. Several months later, Schardinger used the Latin term *Bacillus macerans* to name his microbe, i.e., *macerare*, to rot (Fig. 1.5). This bacillus was able to give the same crystalline dextrins as before, which he designated as *krystallisiertes polysaccharides*, i.e., crystallized polysaccharides, considered then as the intermediate decomposition products of starch (Schardinger 1904). Using the characteristic reaction that starch derivatives show with iodine, Schardinger proposed a distinction between a "crystallized amylose" and a "crystallized amylodextrin." The yields obtained were tenfold those reported by Villiers. To explain this result, Schardinger suggested that, in the conditions of sterilization described by Villiers, the bacillus used was "probably not pure" (Schardinger 1904). One year later, Schardinger was also the first to observe that different starchy substrates differed in their behavior with *Bacillus macerans*, especially in the yields obtained (Schardinger 1905).

1.2.2 The Foundation of the Cyclodextrin Chemistry

Schardinger is acknowledged as being the first to lay down the basis of the cyclodextrin chemistry (French 1957a; Thoma and Stewart 1965; Szejtli 1998). Indeed, he was the first researcher to describe the fundamental properties of *cellulosines*, to introduce the terms crystallized α-dextrin and crystallized B-dextrin, to isolate the microorganism able to synthesize the enzyme that catalyzes the degradation of starch into crystallized dextrins, to hypothesize that the crystallized substances were cyclic "polysaccharides," and also to suggest their ability to form complexes.

Between 1905 and 1911, Schardinger made several important observations (Schardinger 1903a, b, 1904, 1905, 1909, 1911). He observed that *cellulosines* were often formed in starch-based media containing putrefying microorganisms. The formation of the two crystallized dextrins depended on the type of bacteria digesting starch. The distinction between the two forms was always made through their ability to form complexes of different colors with iodine. Schardinger also studied the chemistry of the two dextrins, pointing out their lack of reducing power and hydrolysis to reducing sugar. Dextrins were non-reducing to copper reagents and

non-fermentable by yeast. Schardinger also reported their behavior in the presence of alcohols, chloroform, ether, and iodine solution. He used the complexes with these solvents as a means of precipitation of dextrins (Schardinger 1911). This was the first indication of the ability of dextrins to form "inclusion" complexes (Crini 2014). Finally, Schardinger proposed empirical formulae of dextrins. However, he did not propose a structure for his crystallized dextrins and also did not attempt their molecular-weight determinations. It will take another 20 years before the cyclic nature of Schardinger dextrins will be recognized. Professor Schardinger decided to stop his research into dextrins in 1911, and as a conclusion he wrote: "I realize that still very many questions remain unsolved; the answer to these I must leave to another, who, owing to more favorable external conditions, can deal with the subject more intensively."

In the 24 years following Schardinger's final paper (Schardinger 1911), the field of research on crystallized dextrins was dominated by the groups of Pringsheim and Karrer. Pringsheim is recognized as the first researcher to have published prolifically on dextrins. However, the works were repetitive, marred by frequently contradictory results and by even hot debate between the two groups (French 1957a; Szejtli 1998; Crini 2014; Morin-Crini et al. 2015).

1.3 Historical Landmarks in the Exploration of Cyclodextrins: From 1911 to 1970

1.3.1 Nomenclature

In 1891, cyclodextrin was initially called *cellulosine* by Villiers because he assumed that the novel crystalline substance, obtained from digests of *Bacillus amylobacter*, was *une sorte de cellulose*, i.e., a kind of cellulose (Crini 2014).

In 1903, Schardinger reported the formation of two *krystallisiertes dextrins* during his investigations of food spoilage, which he called crystallized dextrin A and crystallized dextrin B, because most of their properties were similar to the already known partial degradation products of starch, i.e., the dextrins (Schardinger 1903a, b). One year later, the *krystallisiertes dextrins*, considered as the intermediate crystallized decomposition products/by-products of starch, were designated by the term *krystallisiertes polysaccharides*, i.e., crystallized polysaccharides (Schardinger 1904). Pursuing his investigations on the structure of starch, Schardinger then introduced a distinction between a *crystallized amylose* for dextrin A and a *crystallized amylodextrin* for dextrin B, because, for him, there was an analogy between his dextrins and amylose and amylodextrin, especially with respect to their iodine color reactions (Schardinger 1905, 1907). Finally, Schardinger considered that these names were inappropriate and thus decided to rename it *crystallized dextrin*-α and *crystallized dextrin*-β (Schardinger 1911).

In the mid-1910s, the German chemist and biochemist Hans Pringsheim used the name of *krystallisiertes polyamylosen*, i.e., crystallized polyamyloses, distinguishing two series, the α-series of dextrins containing 2n D-glucose units per molecule and the β-series containing 3n D-glucose units per molecule. Four substances, i.e., α-diamylose, α-tetraamylose, α-hexaamylose, and α-octaamylose, were included in the α-series of dextrins, while the β-series only contained two substances, i.e., β-triamylose and β-hexaamylose. Indeed, for Pringsheim, the Schardinger dextrins arose through the bacterial depolymerization of starch to the fundamental units: the amylose fraction being broken down into the α-series of dextrins, i.e., polyamyloses, and the amylopectin fraction being degraded to the β-series (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Morin-Crini et al. 2015). Pringsheim also used the terms of α-amylosan, α-allo-amylosan, and α-iso-amylosan and β-amylosan, β-allo-amylosan, and β-iso-amylosan for α-dextrin and β-dextrin, respectively (Crini 2014). At the same time, the Swiss chemist Paul Karrer also introduced the notion of series of crystallized dextrins. Like Pringsheim, Karrer was convinced that the α-series of dextrins was composed of at least four distinct substances differing in molecular size. However, he disagreed with the subdivision of the β-series into triamylose and hexaamylose. For Karrer, these two products were identical. In addition, Karrer regarded maltose as the fundamental unit of the whole of the starch molecule, while Pringsheim considered the polyamyloses as the basic units of the starch molecule (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Morin-Crini et al. 2015). Like Pringsheim, Karrer also used the amylosan-based terminology (Crini 2014).

In the 1920s, as a tribute of the pioneering work of Schardinger, the German chemist Karl Johann Freudenberg called them "Schardinger dextrins" and referred to these compounds as α-dextrin and β-dextrin (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Morin-Crini et al. 2015) and later as pentaosan and hexaosan, respectively (Crini 2014). For many years, cyclodextrins were called "Schardinger dextrins" in his honor, almost up to the 1970s, or also sometimes simply as dextrins (Szejtli 1998). Schardinger dextrins were subsequently named "cycloamyloses" by the American chemist Dexter French in 1942 (French and Rundle 1942), "cycloglucanes" by Freudenberg in 1943 (Freudenberg 1943), and finally "cyclodextrins" in 1949 by the German chemist Friedrich Cramer, a pupil of Freudenberg (Cramer 1949). The model of "cycloamyloses" was constructed from glucopyranose units in the boat conformation. For French, α-dextrin, β-dextrin, and γ-dextrin must be called cyclohexaamylose, cycloheptaamylose, and cyclooctaamylose, respectively, the Greek prefix to the "amylose" corresponding to the degree of polymerization, i.e., indicating the number of glucose units in the ring (French and Rundle 1942). However, at that time, Freudenberg claimed that "this new nomenclature was inappropriate and ambiguous" (Freudenberg 1943). Again, in 1947, Freudenberg wrote: "It appears to be premature to rename the α-dextrin cyclohexa-amylose and the β-dextrin cycloheptа-amylose" (Freudenberg et al. 1947a, b). In 1943, Freudenberg proposed the cycloglucane-based nomenclature, e.g., cyclohexaglucane α(1→4), cycloheptaglucane α(1→4), and cyclooctaglucane α(1→4) for α-dextrin, β-dextrin,

and γ-dextrin, respectively (Freudenberg 1943). During the mid-1940s, there was another system in current use (Crini 2014). In the alternate system, the number of residues in the cyclic polymer was indicated by prefixing a Greek letter to the series name. Since the smallest known cycloamylose was a hexamer, it was assigned the prefix α. The cyclic heptatose, octaose, etc. were referred to, respectively, as β, γ, etc. The first system introduced by French was however preferred because it was more descriptive of the structures.

At the end of the 1940s, Cramer first proposed the cyclo-based nomenclature for the nomenclature of the Schardinger dextrins, e.g., (6-ose)-cyclo, (7-ose)-cyclo, and (8-ose)-cyclo for α-, β-, and γ-dextrins, respectively. For the first time in 1949, Cramer introduced the term cyclodextrin. This name was included in the title of his PhD dissertation entitled *Die Cyclodextrine aus Stärke* (Cramer 1949). For Cramer, the term of cyclodextrin must be used to refer to cyclic oligosaccharides made up of 6, 7, or 8 units of D-glucose joined by α-(1 → 4) linkages termed α-, β-, and γ-cyclodextrin, respectively. Because of its relative brevity, the term cyclodextrin was soon accepted, but the nomenclature of cyclodextrins remained a subject of debate until the end of the 1990s (Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015). Indeed, at that time, several laboratories proposed clarifications of the nomenclature of cyclodextrins because the term cyclodextrin only specified the nature of the sugars but did not give any information on the bonding between them. Thus, the name cyclomaltohexaose was suggested in 1997. This name is composed of first the term cyclo followed by a term indicating the type of linkage, i.e., malto for glucose unit bound by α-(1→4) linkages, and the number of sugar units with the ending ose, i.e., hexa for 6 or hepta for 7. This final term, present in cyclomaltohexaose, implies a free anomeric center, which is not present in cyclodextrins. Both the terms cyclodextrins and cyclomaltooligosaccharides were used (Crini 2014).

Other nomenclatures have also been proposed. For instance, α-cyclodextrin was named cyclohexakis-(1→4)-α-D-glycosyl or cyclo-α-(1→4)-glucohexaoside. The term of the glycosyl residue is preceded by the type of linkage between brackets, which in turn is preceded by the term cyclo plus an indication of the number, i.e., cyclohexakis, etc. The literature uses all of these nomenclatures. Nevertheless, the cyclodextrin-based nomenclature is still the most widely used in literature today. The nomenclature for large-ring cyclodextrins, i.e., LR-CDs with a degree of polymerization between 9 and >100, is more simple: each molecule is designated by an abbreviation CDn where *n* indicates the number of glucose units in the macrocycle, e.g., CD14 (boat-like structure) composed of 14 glucose units (Morin-Crini et al. 2015; Assaf et al. 2016; Sonnendecker and Zimmermann 2019a, b; Sonnendecker et al. 2018, 2019).

1.3.2 Native Cyclodextrins

Schardinger recognized only dextrin-α and dextrin-β, while Freudenberg obtained γ-dextrin in 1948, although previously regarded by him as a cyclic heptasaccharide (Freudenberg and Cramer 1948). Two years later, Freudenberg elucidated the structure of γ-dextrin (Freudenberg and Cramer 1950). The same year, using partial acid hydrolysis and enzyme digestion followed by X-ray measurements and paper chromatography, French also elucidated the structure of γ-dextrin, first named *cycloöctaamylose* and later cyclooctaamylose (French et al. 1950b). This dextrin was composed of eight glucose residues symmetrically arranged in a ring and linked together by α-1,4-glucosidic bonds. In the late 1950s, French and co-workers had established the molecular weight, the exact chemical structure, the dimensions, and the types of bonding in the three cycloamyloses, cyclohexaamylose, cycloheptaamylose, and cyclooctaamylose, i.e., α-dextrin, β-dextrin, and γ-dextrin, respectively (French and McIntire 1950; Norberg and French 1950; French et al. 1950a, b).

In 1948, the first indications of the existence of higher homologues of dextrins were published by Freudenberg and his young student Cramer (Freudenberg and Cramer 1948). Two years later, French also suggested the possible existence of cycloamyloses containing more than 8 glycosyl units (Norberg and French 1950; French et al. 1950b). The same year, Akiya and co-workers claimed the "discovery of new series of cyclic oligosaccharides" similar to the Schardinger dextrins, containing more than 8 glucose units (Akiya and Watanabe 1950a, b, c; Akiya and Okui 1951). Later, Caesar (1968) reported that these "new" compounds were the α- and β-dextrins. In fact, the existence of larger homologues of cycloamyloses was clearly demonstrated a decade later by French. In 1957, French discovered delta-dextrin or δ-dextrin and epsilon-dextrin or ε-dextrin, containing 9 and 10 units of glucose, respectively (French 1957a, b). He proved their existence using radioautography and chromatography measurements. However, French elucidated their structures only in 1965 (French et al. 1965). At that time, French also wrote: "there is no obvious reason why the series should stop here" (French 1957a), suggesting the existence of cycloamyloses with 11 and 12 units of glucose, i.e., ξ-dextrin or zeta-dextrin and η-dextrin or eta-dextrin, respectively. In the beginning of the 1960s, French continued to study cycloamyloses with a larger ring. His objective was to develop a fractionation method for isolation of larger homologues of cycloamyloses after extensive β-amylase digestion to hydrolyze maltooligosaccharides. In 1961, the existence of cycloamyloses with 11 and 12 units of glucose is confirmed using radioautography (Pulley and French 1961), and 4 years later, he was the first to propose a fractionation method for their isolation (French et al. 1965). The structure and the dimensions of ξ-dextrin and η-dextrin are reported. French finally introduced the notion of Schardinger dextrin series, "a Schardinger dextrin family" (French et al. 1965). The same year, Thoma and Stewart (1965) also published similar results, and the discovery of ξ-dextrin and η-dextrin is attributed to them (Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007).

French's results had for many years been regarded as dubious since they were not able to experimentally distinguish the large cyclodextrins from branched derivatives. As late as 1988, Szejtli expressed his doubts, in his monograph *Cyclodextrin Technology*, to whether cyclodextrins larger than γ-cyclodextrin exist (Szejtli 1988). In fact, higher cyclic cyclodextrins than the three native cyclodextrins, reported in the 1960s, were probably so-called branched derivatives such as branched diglucosyl-cyclodextrins. When a section of the amylopectin molecule containing a branching point was incorporated into a cyclic structure, one or two glucosyl or maltosyl side chains were attached by α-(1→6) linkages to the ring formed (Frömming and Szejtli 1994). During the production of native cyclodextrins, these branched cyclodextrins were also produced. It was only during the mid-1990s that the existence of the large cyclodextrins has been fully proven (Miyazawa et al. 1995; Endo et al. 1997, 1999; Larsen 2002; Qi et al. 2004; Taira et al. 2006; Crini 2014).

1.3.3 Cyclodextrin Chemistry

For over 20 years, Pringsheim and his various collaborators penned an abundant literature on dextrins. Indeed, Pringsheim is considered to be the first researcher to have published prolifically on their preparation and chemistry (Pringsheim and Langhans 1912; Pringsheim and Eissler 1913, 1914; Pringsheim 1915, 1919, 1922, 1924, 1925, 1926, 1927, 1928a, b, 1931a, b, 1932; Pringsheim and Lichtenstein 1916; Pringsheim and Persch 1921, 1922; Pringsheim and Dernikos 1922; Pringsheim and Goldstein 1922, 1923; Pringsheim and Beiser 1924, 1932; Irvine et al. 1924; Pringsheim and Leibowitz 1924, 1925a, b, 1926a, b; Pringsheim and Steingroever 1924, 1926; Pringsheim and Wolfsohn 1924; Pringsheim and Schapiro 1926; Pringsheim and Meyersohn 1927; Irvine et al. 1929; Pringsheim et al. 1930, 1931a, b). However, these studies suffered from numerous errors due to the use of dextrins that were not pure and to problems arising from separation of the fractions and from the use of unsuitable analytical methods, e.g., determination of the masses by cryoscopy (Freudenberg and Jacobi 1935; Samec and Blinc 1941; French 1957a; Thoma and Stewart 1965; Caesar 1968). In 1935, Freudenberg dismissed the work of Pringsheim as practically valueless, since "most of it was based upon work with dextrin mixtures and upon serious misconceptions relating to the structural principles of high polymers" (Freudenberg and Jacobi 1935). French (1957a) also wrote: "Pringsheim's literature was voluminous but much of it was repetitive, controversial, or based on erroneous concepts."

From 1910, Pringsheim repeated Schardinger's experiments. He reported higher yields of β-dextrin from glycogen crude preparations of amylopectin, and this is the reason why he postulated that amylose was polymerized α-diamylose and amylopectin and glycogen were polymerized β-triamylose. Like Schardinger, Pringsheim observed that the relative proportions of α- and β-dextrins depended on the different substrates used (Pringsheim and Langhans 1912). Pringsheim described the

chemical behavior of dextrins and their properties, in agreement with the previous results published by Schardinger. The dextrins were soluble in water but insoluble in alcohol, ether, and chloroform. They do not reduce Fehling's solution. To precipitate the dextrins, different solvents including benzene, toluene, xylene, bromobenzene, nitrobenzene, and petroleum ether were proposed (Pringsheim and Eissler 1913, 1914; Pringsheim 1915; Pringsheim and Lichtenstein 1916). Pringsheim confirmed that the simplest means to distinguish between the α- and β-dextrins was the iodine reaction (Pringsheim 1922; Pringsheim and Dernikos 1922). Pringsheim was the first to study the halogen complexes of dextrins (Pringsheim and Wolfsohn 1924; Pringsheim and Schapiro 1926). The first methylated β-dextrin was also obtained by his group: 43.6% of degree of methylation as against 45.6% required by theory. The compound was crystallized from ether (Pringsheim and Goldstein 1923). Several data can also be found referring to the preparation of dextrin derivatives including acetates, nitrates, and ethers (Pringsheim 1927, 1928a, b, 1931b; Pringsheim and Meyersohn 1927; Irvine et al. 1929; Pringsheim et al. 1930, 1931a, b; Pringsheim and Beiser 1932). However, all Pringsheim's data are essentially of historic interest (Samec and Blinc 1941; French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1982a; Crini 2014). From 1920 to 1925, Karrer also contributed greatly to the knowledge of the chemistry of the Schardinger dextrins (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). Karrer published several important works on dextrins (Karrer 1920, 1921, 1922, 1923, 1925; Karrer and Nägeli 1921a, b; Karrer et al. 1921, 1922; Karrer and Bürkin 1922). Like Schardinger and Pringsheim, Karrer studied the crystallized dextrins with the expectation that they would shed some light on the features of starch. In 1921, Karrer published the first conclusions on the acetolysis of α-dextrin and β-dextrins. He demonstrated that this reaction gave essentially the same excellent yield of maltose as starch or maltose itself gives, when treated similarly (Karrer 1921; Karrer and Nägeli 1921a, b; Karrer et al. 1921). Karrer also investigated the interactions between dextrins and ions such as barium, sodium, and potassium (Karrer 1922; Karrer and Bürkin 1922; Karrer et al. 1922). In 1925, Karrer summarized the whole of his works and conclusions on dextrins in a famous comprehensive book (Karrer 1925).

Between 1911 and 1935, epoch called by Crini (2014) the "period of doubt," other researchers have also published interesting works on the chemistry of the Schardinger dextrins (Biltz 1913; Biltz and Truthe 1913; Freudenberg and Ivers 1922; Miekeley 1930, 1932; Ulmann 1932, Ulmann et al. 1932; Hess et al. 1933). Miekeley (1930, 1932) published experimental data on the chemical composition of dextrins, which complemented those of Pringsheim. In 1933, Ulmann's group observed that the α-dextrin-ethanol complex had two different crystal modifications which could be interconverted. This was the first observation that a same guest may form different crystal structures with the same dextrin (Hess et al. 1933). However, this period did nothing to stimulate the development of Schardinger dextrins, considered as by-products of starch degradation. So, the work on cyclodextrins reported before 1935 was of little consequence (Samec and Blinc 1941; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). This can be explained by the fact that researchers used

incompletely separated fractions and based too much reliance on cryoscopic measurements of molecular weights, which led to many anomalous results.

From 1935 to 1950, epoch called by French (1957a) the "maturation period," the works of Freudenberg on the chemistry of the Schardinger dextrins were acknowledged to have made an important contribution to the cyclodextrin science (Freudenberg and Jacobi 1935; Freudenberg and Rapp 1936; Freudenberg et al. 1936, 1938, 1939, 1947a, b; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg 1939, 1943; Freudenberg and Cramer 1948, 1950). Indeed, Freudenberg is recognized as a pioneer in this domain (Thoma and Stewart 1965; Caesar 1968). As far back as 1922, Freudenberg was the first researcher to focus on the chemical modification of dextrins, in particular of tosylated residues (Freudenberg and Ivers 1922). Later, the Schardinger dextrins were oxidized by iodite, "probably by a glycol-cleavage reaction" (Freudenberg 1934). Enzymatic hydrolysis gave no trace of a sugar unit other than *D*-glucose (Freudenberg and Jacobi 1935). During the hydrolysis of dextrins, Freudenberg also observed an increase in rotation due to hydrolysis of the β-linkage. During acetolysis, the dextrins were shown to be more nearly similar to starch than to compounds of the levoglucosan type. Using a cryoscopic method for the determination of molecular weights, Freudenberg reported (erroneously) the number of glucose units that the Schardinger dextrins contained: five for A-dextrin and six for β-dextrin (Freudenberg and Jacobi 1935). In 1936, Freudenberg confirmed that enzymatic hydrolysis gave no trace of a sugar unit other than D-glucose. He also reported that methylation studies failed to reveal the presence of any *D*-glucose units, concluding that glucose was the only product of acid hydrolysis of dextrins (Freudenberg and Rapp 1936). The following pieces of experimental evidence were also published: (i) the rate of hydrolysis of dextrins in 51% sulfuric acid was too low for there to be any labile β-linkages present; (ii) the Schardinger dextrins were non-reducing, that is, they did not have a reducing chain termination; and (iii) methylation studies on dextrins gave no products than 2,3,6-*O*-methyl-*D*-glucose (Freudenberg and Rapp 1936). The same year, Freudenberg prepared fully methylated α- and β-dextrins and finally demonstrated that 2,3,6-tri-methylglucose was the only product of methylation of dextrins followed by hydrolysis (Freudenberg et al. 1936). Later, acetate derivatives of the dextrins were proposed and characterized for the first time (Freudenberg et al. 1947a, b). In 1955, Freudenberg published a detailed description of the chemistry of the three main cyclodextrins (Freudenberg 1955), and in 1962, he summarized all his results (Freudenberg 1962).

Between 1942 and 1950, French published numerous important contributions on the chemistry of the Schardinger dextrins (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b, 1950a, b, 1954; French and McIntire 1950; Norberg and French 1950). Very quickly, like Freudenberg, French became a pioneer in the understanding of their chemistry (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). French showed that the Schardinger dextrins, being cyclic, had no non-reducing end group and they were extremely resistant to alpha-type amylases. Using data from periodate oxidation and methylation reactions, he demonstrated that Schardinger dextrins could not be open-chain compounds. Periodate oxidation was slow with Schardinger dextrins in

comparison with that of straight-chain amylodextrin. French published protocols for the methylation of Schardinger dextrins and showed that 2,3,6-tri-methylglucose was the only product of methylation of cycloamyloses followed by hydrolysis (French et al. 1950b), in agreement with the previous results published by Pringsheim (Pringsheim 1924, 1925, 1926; Pringsheim and Beiser 1924) and Freudenberg (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). French also published solubility data on cycloamyloses, especially in presence of organic liquids. Solubility data of dextrins in water at room temperature were as follows: α-dextrin 14.5 g/100 mL, β-dextrin 1.8 g/100 mL, and γ-dextrin 23.2 g/100 mL (French et al. 1949a). Using data from periodate oxidation and methylation reactions, French definitively demonstrated that Schardinger dextrins could not be open-chain compounds and they were regarded as conical cylinders (French and McIntire 1950; Norberg and French 1950; French et al. 1950a, b). At that time, Schardinger dextrins were also found to be rather anomalous structures with interesting complexing properties when compared with the linear oligosaccharides. French indeed suggested for the first time the fact that cycloamyloses were capable of forming particular complexes. The nature of the complexes between halogen and Schardinger dextrins, particularly the iodine complexes, depended much on the amount of the halides added. However, the cavity of dextrins was referred to as hydrocarbon in nature by French. This result has been definitively abandoned in 1965 with the advent of the modern conformational theory.

1.3.4 Molecular Structure of Schardinger Dextrins

Schardinger was the first to hypothesize that the crystalline substances were "cyclic polysaccharides" (Schardinger 1907, 1909, 1911). However, he never managed to elucidate their structure.

In 1920, Karrer was the first to suggest that the dextrins were made up of several components (Karrer 1920), and 1 year later, he proved it using detailed acetolysis data (Karrer 1921; Karrer and Nägeli 1921a, b; Karrer et al. 1921). In 1923, Karrer was also the first to propose that dextrins are composed of maltose units only joined by α-(1→4) glucosidic linkages (Karrer 1923, 1925), although Pringsheim (1922, 1924) remained unconvinced by Karrer's conclusions. Figure 1.6 is a schematic illustration of two glucopyranose units of a dextrin molecule showing details of the α-(1→4) glucosidic/glycosidic linkage and the numbering systems employed to describe the glucopyranose rings. Later, Miekeley (1930, 1932) also came to the same conclusions as Karrer. In 1926, Pringsheim is finally convinced by Karrer's conclusions (Pringsheim 1926) although he continued to regard the polyamyloses as the basic units of the starch "molecule" (Pringsheim 1928a, 1931a). However, just like Schardinger, Karrer, and Miekeley, Pringsheim failed to elucidate the cyclic structure of the dextrins.

From 1934 for a period of approximately 25 years, the main contributions toward the molecular structure and size of the Schardinger dextrins were developed by

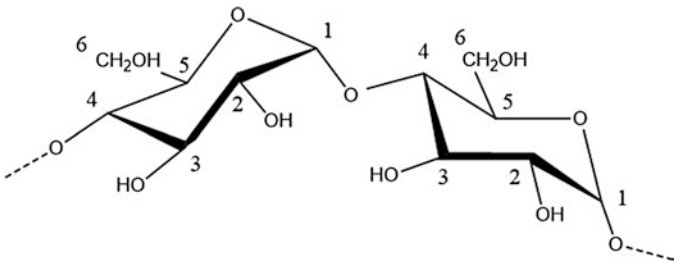


Fig. 1.6 Schematic illustration of two glucopyranose units of a dextrin molecule showing details of the α-(1→4) glycosidic linkage and the numbering systems employed to describe the glucopyranose rings

Freudenberg (Freudenberg 1934, 1939, 1943, 1955, 1957a, b; Freudenberg and Jacobi 1935; Freudenberg and Rapp 1936; Freudenberg et al. 1936, 1938, 1939, 1947a, b, 1953; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg and Cramer 1948, 1950). From 1922, Freudenberg was attracted by Schardinger dextrins since he wanted to obtain information on the degradation products of starch to be able to elucidate its structure (Freudenberg and Ivers 1922). For Freudenberg, Schardinger dextrins were first laboratory curiosities and/or unwanted by-products of starch degradation (Freudenberg 1934), and their chain molecules were intermediate between maltose and starch with non-reducing end groups. Indeed, it is only at the end of the 1930s that Freudenberg concluded that the dextrin-α and dextrin-β molecules were cyclic. In 1935, α-dextrin was considered as a mixture of chain molecules containing 4–5 *D*-glucose units (Freudenberg and Jacobi 1935). Using results of constructing molecular models with the monomer units in a boat rather than a chain conformation, the dextrins were lined with a hydrocarbon interior. One year later, studying the nature of the glycosidic bonds, Freudenberg showed that the dextrins gave rotation-time curves closely parallel to those given by starch and the rigid models such as Kekulé model did not allow free rotation about the individual bonds (Freudenberg and Rapp 1936). The presence of a *Konstellation*, i.e., a ring conformation, is suggested, and in 1936, Freudenberg hypothesized that A-dextrin and β-dextrin have a cyclic structure (Freudenberg et al. 1936). During 2 years, he tried to prove it. On the basis of results obtained from methylation reactions and enzymatic hydrolysis of the dextrins, Freudenberg came, in 1938, to the "same conclusion" as Schardinger, Karrer, Pringsheim, and Miekeley, concerning the cyclic chemical structure of A-dextrin and β-dextrin (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). Ten years later, Freudenberg and his doctoral student Cramer finally demonstrated his conclusion using optical activity data (Freudenberg and Cramer 1948). Schardinger dextrins had a cyclic structure composed of maltose units bound together by α-(1→4) glycosidic linkages. At that time, both French and Borchert also confirmed the cyclic structure of dextrins by X-ray crystallography (French et al. 1948; Borchert 1948). However, although Freudenberg had determined for the first time the correct chemical structure for the Schardinger dextrins, the number of D-glucosyl residues that he gave for the α- and β-dextrin

rings, i.e., five and six, respectively, using a cryoscopic method were incorrect. The correct values were determined by French using both X-ray diffraction and crystal density measurements.

Between 1942 and 1965, French also contributed greatly to the molecular structural knowledge of the Schardinger dextrins, or, as he preferred to call them, cycloamyloses (Caesar 1968; Szejtli 1998; Crini 2014). Very quickly, French became a pioneer in the understanding of their structure, publishing an impressive number of results on cycloamyloses which are still used as references today (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b, 1950a, b, 1954; French and McIntire 1950; Norberg and French 1950; French 1957a, b, 1960, 1962; Bailey and French 1957; Thoma and French 1958, 1959, 1960, 1961; James et al. 1959; Thoma et al. 1959; Whelan et al. 1960; Pulley and French 1961; Robyt and French 1964; French and Abdullah 1965; French et al. 1963, 1965). French's first work concerned the molecular weights of the Schardinger dextrins, considered as cyclic molecules in agreement with the previous results published by Freudenberg (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). French and Rundle (1942), using the X-ray diffraction technique and crystal density measurements, determined the molecular weights of α-dextrin and β-dextrins and discovered the exact number of glucose units per dextrin, i.e., six and seven, respectively, in disagreement with the results published by Freudenberg and Jacobi (1935). French and Rundle demonstrated that molecular weights were integral multiples of the value 162.1 for a glucose residue. They concluded that the X-ray diffraction technique was better suited to the determination of the molecular weights of high molecular weight crystalline substances since impurities, such as solvent of crystallization and inorganic ash, were of minor importance (French and Rundle 1942). In this paper, French also suggested that Schardinger dextrins were cyclic "macromolecules," formed from starch polysaccharide (French and Rundle 1942). They were non-reducing "D-glucopyranosyl polymers" containing 6, 7, or 8 units linked by α-*D*-(1→4) bonds, in agreement with the results published by Karrer (1923) and Miekeley (1932). In each cycloamylose "macromolecule," the *D*-glucose units were in the C1 conformation. Schardinger dextrins were then regarded as cylinders (French and Rundle 1942). However, Freudenberg did not agree with this point of view (Freudenberg 1943).

French pointed out three interesting features: (1) as a consequence of the C-1 conformation of the glucopyranose units, all the secondary hydroxyl groups were located on one side of the cylinder, whereas all the primary hydroxyl groups were located on the opposite side of the cylinder; (2) the interior of the cylinder consisted only of a ring of C-H groups, a ring of glucosidic oxygens, and another ring of C-H groups; and (3) the interior of the cavity was relatively apolar compared to water (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b). Freudenberg claimed again that all the structural and conformational conclusions of French were ambiguous due to "the use of products that were not pure" (Freudenberg et al. 1947a, b). One year later, Freudenberg and Cramer concurred with French's results, after studying the X-ray measurements of Borchert (1948) and also his optical rotation data, publishing similar interpretations

(Freudenberg and Cramer 1948; Cramer 1949). In 1950, French, studying the periodate oxidation of the three cycloamyloses, finally concluded that all three molecules had a cyclic structure in which each *D*-glucose unit was linked to the next by an α-*D*-(1→4)-glucosidic bond, and the interior of the cavity was apolar (French and McIntire 1950; Norberg and French 1950; French et al. 1950b). Schardinger dextrins were then regarded rather as conical cylinders than cylinders, in agreement with Cramer's suggestion. Another interesting feature is made by French: γ-dextrin was "a noncoplanar, more flexible structure," and therefore, it was the "most soluble of the three dextrins." Later, cycloamyloses were finally regarded as truncated cones or "capsules" by French (French 1957a), in agreement with the results published by Cramer (Cramer 1952, 1953, 1956; Dietrich and Cramer 1954).

Cramer also contributed greatly to the molecular structural knowledge of the Schardinger dextrins. In 1948, the young student Cramer published his first result on Schardinger dextrins (Freudenberg and Cramer 1948). Using optical activity, Cramer demonstrated the cyclic nature of α- and β-dextrins. The same year, he discovered γ-dextrin and suggested that the three dextrins possessed an apolar cavity. One year later, Cramer received his PhD at Heidelberg University, under the supervision of Freudenberg (Cramer 1949). He introduced the cyclodextrin-based nomenclature, demonstrated the cyclic nature of cyclodextrins using optical activity data, and showed that the three cyclodextrins had different internal diameters and each cavity was filled with water molecules (Cramer 1949). His doctoral work was then published between 1951 and 1952 (Cramer 1951a, b, c, 1952), adding to the previous results of Freudenberg but mostly "confirming those of French" on the physical (cavity size) and chemical (reactivity) properties, the structure, and chemistry of cyclodextrins. For instance, investigating the configuration at the anomeric centers by hydrolytic methods, Cramer came to the same conclusions as Karrer (1923), Miekeley (1932), and French (French and Rundle 1942) as to the existence of α-(1→4) glucosidic/glycosidic linkages. Cramer also published for the first time a variety of other interesting features. Studying the molecular size of the three dextrins, he showed that a same dextrin could exist in different crystal forms. Cramer then discovered the toroidal form of the cyclodextrin molecules, considering cyclodextrins as truncated cones or "capsules" rather than cylinders, like previously reported by French (French et al. 1948, 1949a, b). The numbering system employed to describe the glucopyranose rings, reported in Fig. 1.5, was then accepted, and Cramer schematized his conclusions on the chemical structure of α-, β-, and γ-cyclodextrins by the two schemes reported in Fig. 1.7. Cramer finally concluded that cyclodextrins were non-reducing oligosaccharides containing 6, 7, or 8 units linked by α-*D*-(1→4) bonds, having both hydrophobic and hydrophilic regions. On the side where the secondary hydroxyl groups were situated, the diameter of the cavity was larger than on the side with the primary hydroxyls, since free rotation of the latter reduced the effective diameter of the cavity. Figure 1.8 illustrates the hydrophobic and hydrophilic regions of an α-dextrin "capsule" (Cramer 1953, 1956; Dietrich and Cramer 1954).

In 1965, both Casu et al. (1965) and Hybl et al. (1965) confirmed the conclusions published by French and Cramer on the cyclic structure of cyclodextrin and its

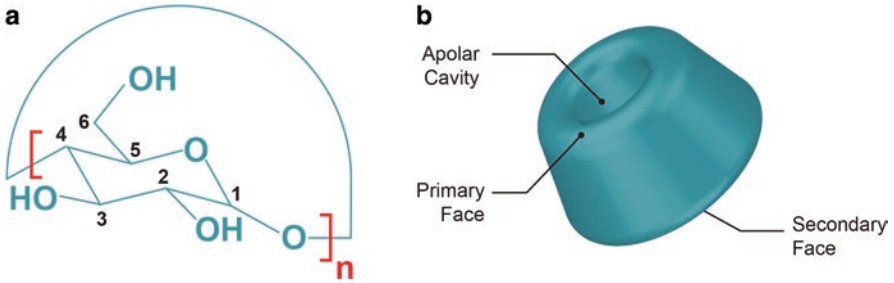


Fig. 1.7 Schematic representations of the (**a**) general chemical structure for cyclodextrins (n = number of glucose units; n = 6, 7, and 8 for α-, β-, and γ-cyclodextrin, respectively) and (**b**) their particular structure showing the apolar cavity of a cyclodextrin "capsule" or torus

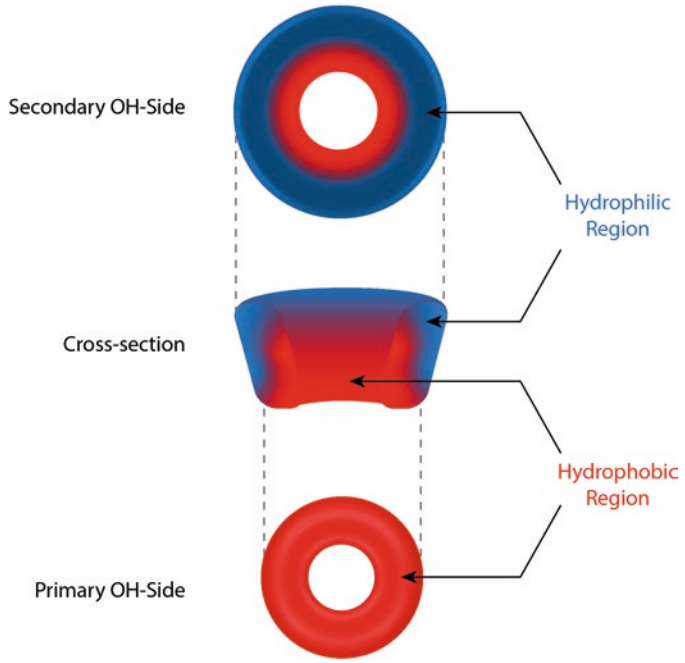


Fig. 1.8 Schematic representation of a dextrin "capsule" showing the hydrophobic and hydrophilic regions

features, using NMR spectra in dimethylsulfoxide solution and using X-ray crystallography of the α-cyclodextrin-potassium acetate complex, respectively. Their results clearly demonstrated that (i) all the glucose residues of cyclodextrins were in the ^{4}C1 chair conformation; (ii) the cavity was lined by the hydrogen atoms and the glycosidic oxygen bridges, respectively; and (iii) the nonbonding electron pairs of the glycosidic oxygen bridges were directed toward the inside of the cavity,

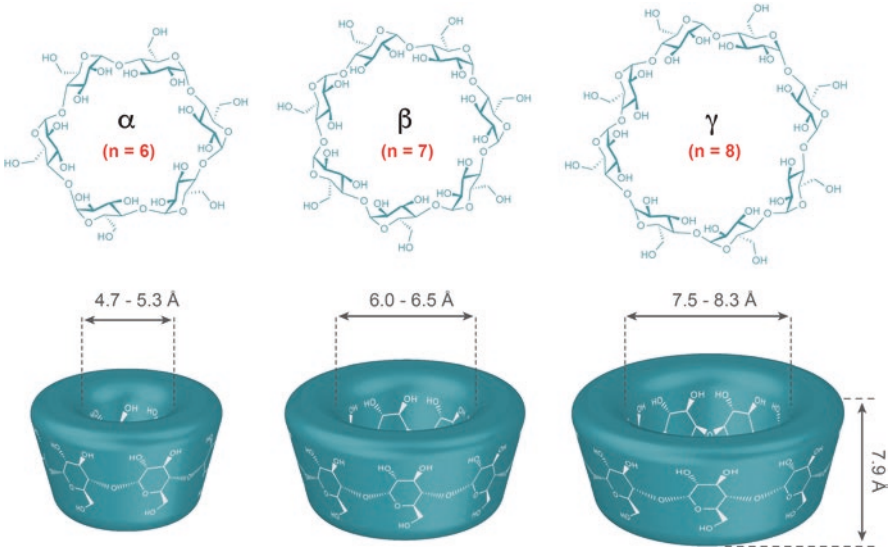


Fig. 1.9 Schematic representations of the chemical tridimensional structure and dimensions for α-, β-, and γ-cyclodextrins (*n* = 6, 7, and 8, respectively) accepted in the 1960s

producing a high electron density. The schematic diagram of two glucopyranose units of a cyclodextrin molecule showing details of the α-(1→4) glycosidic linkage reported in Fig. 1.6 and the schematic representations of the chemical tridimensional structure and dimensions (Fig. 1.9) for α-, β-, and γ-cyclodextrin are finally accepted at the mid-1960s. Later, a more precise study of the conformation of α-cyclodextrin in solution was made by Saenger's group using NMR spectroscopy (Wood et al. 1977). All six glucose units had identical conformations and the molecule had hexagonal symmetry. The secondary hydroxyl groups, which were located in one side of the torus of cyclodextrins, formed hydrogen bond with the secondary hydroxyl groups of contiguous glucose units, in agreement with the previous conclusions published by Casu et al. (1965) and by Hybl et al. (1965). In the cyclodextrin molecule, a complete secondary belt was formed by hydrogen bonds, making it a rigid structure. This was proposed to explain the fact that, among the three native cyclodextrins, β-cyclodextrin had the lowest solubility (Wood et al. 1977). The hydrogen belt was incomplete in the α-cyclodextrin molecule, and γ-cyclodextrin was a noncoplanar, more flexible structure, confirming the results published by French and McIntire (1950). At the beginning of the 1960s, French indicated the possible existence of "a Schardinger dextrin family," describing the structure of δ-dextrin, ε-dextrin, ξ-dextrin, and η-dextrin containing 9, 10, 11, and 12 glucose units, called larger homologues of cycloamyloses (Pulley and French 1961; French et al. 1965). These larger dextrins were not regular cylinder-shaped structures. Indeed, they were collapsed and their real cavity was even smaller than the γ-dextrin (Fig. 1.10).

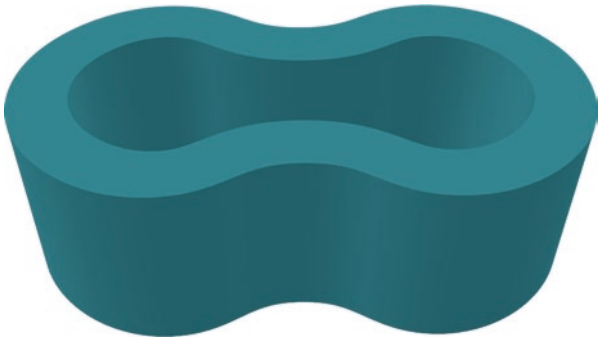


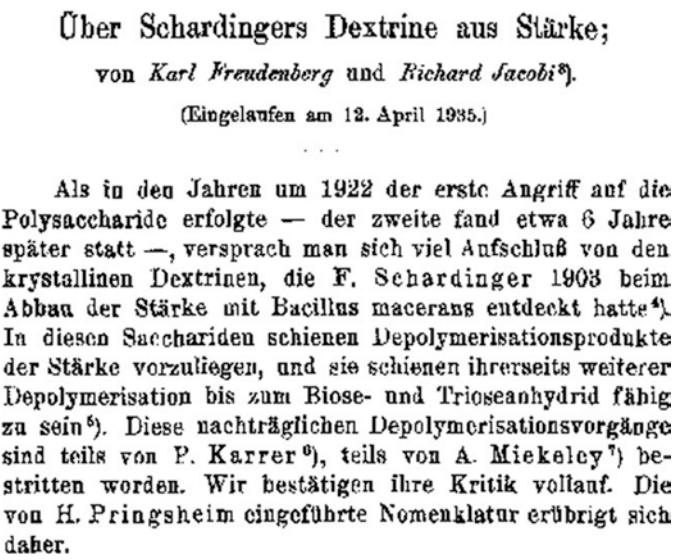
Fig. 1.10 Collapsed cylinder structure of δ-dextrin

1.3.5 Preparation and Separation of Schardinger Dextrins

Between 1905 and 1911, Schardinger studied the first preparation, fractionation/separation, and purification of the two *cellulosines* (Schardinger 1905, 1907, 1909, 1911). In 1911, he published the first fractionation and purification scheme of the dextrins. Later, both Freudenberg, French, and Cramer published other important schemes: see the references French (1957a) and Thoma and Stewart (1965).

The dextrins were synthesized from several sources of starch, e.g., potatoes, rice, and wheat, and bacteria, e.g., the formation of dextrins depended on the type of bacteria digesting starch. About 25–30% of the starch was converted to crystalline dextrins depending on these parameters. The yield was tenfold those reported by Villiers (Schardinger 1907). Schardinger also based his method of separation on the ease of crystallization of the β-dextrin from water and its low solubility, about 1.5% at room temperature, followed by precipitation of the α-dextrin from the mother liquor by the addition of alcohol. Schardinger' protocol was modified by Lange in 1925 who introduced trichloroethylene as a precipitating agent for the crystalline dextrins (Lange 1925). This protocol is described in detail in Pringsheim's book (Pringsheim 1932).

In 1935, Freudenberg and his student Jacobi described a method for the synthesis of Schardinger dextrins with high purity (Freudenberg and Jacobi 1935) (Fig. 1.11). Freudenberg is indeed recognized as the first to prepare almost pure dextrins with high yields (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998; Crini 2014). Freudenberg improved the separation of dextrins and produced a scheme based not only on solubility differences of the dextrins themselves, as initially proposed by Schardinger, but also on the differences in solubilities and rates of crystallization of their acetates (Freudenberg and Jacobi 1935). However, the protocol was difficult since it involved many acetylation and saponification reactions. During more than 10 years, this protocol was studied and modified, and in 1947, Freudenberg's group described the first scheme for the isolation of pure fractions of dextrins using bromobenzene as precipitant: α-dextrin did not precipitate, while β-dextrin and γ-dextrin were readily precipitated (Freudenberg et al. 1947a,



Über Schardingers Dextrine aus Stärke;

von *Karl Freudenberg* und *Richard Jacobi*[3].

(Eingelaufen am 12. April 1935.)

. . .

Als in den Jahren um 1922 der erste Angriff auf die Polysaccharide erfolgte — der zweite fand etwa 6 Jahre später statt —, versprach man sich viel Aufschluß von den krystallinen Dextrinen, die F. Schardinger 1903 beim Abbau der Stärke mit Bacillus macerans entdeckt hatte[4]. In diesen Sacchariden schienen Depolymerisationsprodukte der Stärke vorzuliegen, und sie schienen ihrerseits weiterer Depolymerisation bis zum Biose- und Triosean hydrid fähig zu sein[5]. Diese nachträglichen Depolymerisationsvorgänge sind teils von P. Karrer[6], teils von A. Miekeley[7] bestritten worden. Wir bestätigen ihre Kritik vollauf. Die von H. Pringsheim eingeführte Nomenklatur erübrigt sich daher.

Fig. 1.11 First page of the article of Professor Freudenberg published in 1935 where he described a method for the synthesis of Schardinger dextrins with high purity

b). This scheme was comprehensively discussed by French (1957a). In 1950, Freudenberg and Cramer also confirmed the possible existence of dextrins with 9 or 10 glucose units, identified during the preparation of α-, β-, and γ-dextrins (Freudenberg and Cramer 1950). However, these findings were only substantiated a decade later by French (Pulley and French 1961).

French was also among the early researchers, along with Freudenberg, to focus on improving the production of dextrins. French became a pioneer in the preparation of the compounds in a very pure state. Knowing the works of the group of Hudson on the enzymolysis conditions which affected the yield and proportion of the dextrins (Tilden and Hudson 1939, 1942; Tilden et al. 1942; McClenahan et al. 1942; Wilson et al. 1943) and using his own results on the solubilities of Schardinger dextrins (French et al. 1949a), French proposed in 1949 a new protocol for the separation and purification of dextrins (French et al. 1949b), which did not require the acetylation and saponification steps used by Freudenberg. Treatment of starch with the amylase of *Bacillus macerans* gave crude starch digests containing the three cycloamyloses, i.e., ~60% α-dextrin, ~20% β-dextrin, and ~ 20% γ-dextrin, together with small amounts of higher cycloamyloses. Moreover, the protocol permitted the facile separation of pure dextrins by differential precipitation using specific precipitants such as bromobenzene and propan-1-ol (French et al. 1949b). Later, French showed that high temperature cellulose column chromatography was one of the most effective methods for the quantitative analysis of mixtures of cycloamyloses (Pulley and French 1961; French et al. 1965). This method was required in connection with the production of cycloamyloses since these products were simultaneously produced from starch together with the higher series of cycloamyloses. In 1961,

French also reported the preparation, isolation, and partial characterization of large cyclodextrins with 9, 10, 11, and 12 glycosyl units in the macrocycle (Pulley and French 1961), identified during the preparation of α-, β-, and γ-dextrins like Freudenberg.

In the mid-1950s, Cramer also investigated the enzymatic production of cyclodextrins, their separation and purification, and characterization (Cramer 1955, 1956; Cramer and Steinle 1955; Cramer and Henglein 1957a, b). Cramer described an easy protocol to separate α-, β-, and γ-cyclodextrins from the digest by selective precipitation using appropriate organic compounds and optimize parameters, e.g., pH = 6 and temperature = 40 °C (Cramer 1956). The three cyclodextrins are precipitated by addition of a tetrachloroethylene-tetrachloroethane mixture, followed by the addition of *p*-cumene. α-Cyclodextrin was isolated by selective precipitation with cyclohexane, β-cyclodextrin with fluorobenzene, and γ-cyclodextrin with anthracene. Cramer explained his results by the difference in the sizes of cavities of the three cyclodextrins and concluded that the superiority of his method over previous procedures, particularly those of French, resided in the technical ease and the completeness of precipitation.

To summarize, during the periods of reaching maturity from 1935 to 1950 and of exploration from 1950 to 1970, the separation and the purification of the mixture were difficult (Crini 2014; Crini et al. 2018). The period of reaching maturity was also marked by several contradictory results, due, at least in part, to differences in the protocols used for the preparation of Schardinger dextrins and dubious purity of the samples (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998). The work during these periods was even marred by hot debate between the different laboratories, especially those of Freudenberg and Cramer and of French. In addition, in the early 1950s, researchers had not fully realized the potential of cycloamyloses and had little faith in their complexation properties (Szejtli 1998). The three main cyclodextrins were considered just laboratory curiosities difficult to produce. In 1963, French was the first to propose the preparation of cycloamyloses on a larger-than-laboratory scale (French et al. 1963). However, at the end of the 1960s, French concluded that "cycloamyloses were very promising molecules although they remained very expensive products, available only in small amounts as fine chemicals, and also toxic."

1.3.6 The Action of Amylases on Cycloamyloses

Up to 1939, the Schardinger dextrins were known only as products of the bacterial breakdown of starch. For Freudenberg's opinion, *Bacillus macerans* was able to transform starch structure into cyclic and linear breakdown products, and starch was based upon a cyclic Schardinger nucleus with side branches which would be broken in the bacterial breakdown (Fig. 1.11). During the same period, Tilden and Hudson (1942), studying the bacteria that produced the dextrins, also concluded that the resulting Schardinger dextrins were derived from some basic configuration

pre-existing in the starch "molecule." Similar conclusions were published by Kerr (1942, 1943), Myrbäck (1942), and Samec (1942).

Using this concept, Freudenberg was the first scientist to investigate the enzymatic production of dextrins and to propose a first mechanism of action for *Bacillus macerans* (Freudenberg et al. 1938, 1939; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg 1939). This mechanism indicated that the dextrins were preformed within the starch macromolecules (Freudenberg 1939), in agreement with the results of Hudson' group (Tilden and Hudson 1939). However, Freudenberg did not agree with the generally accepted point of view at that time concerning the nature of the bonding of the *D*-glucose units, and he rapidly abandoned this mechanism. Using the helical model of the structure of starch proposed by Hanes (1937) and the α-*D* nature of the glucose units, Freudenberg proposed a second mechanism based on a transglucosylation reaction (Fig. 1.12). He suggested that the enzyme involved was able to degrade the helical structure of the starch, i.e., the amylose fraction, and that there ensued a rearrangement of the glucose units which were then able to form a ring structure (Freudenberg et al. 1939; Freudenberg and Meyer-Delius 1939). Because of the helical arrangement, the first and fifth or sixth

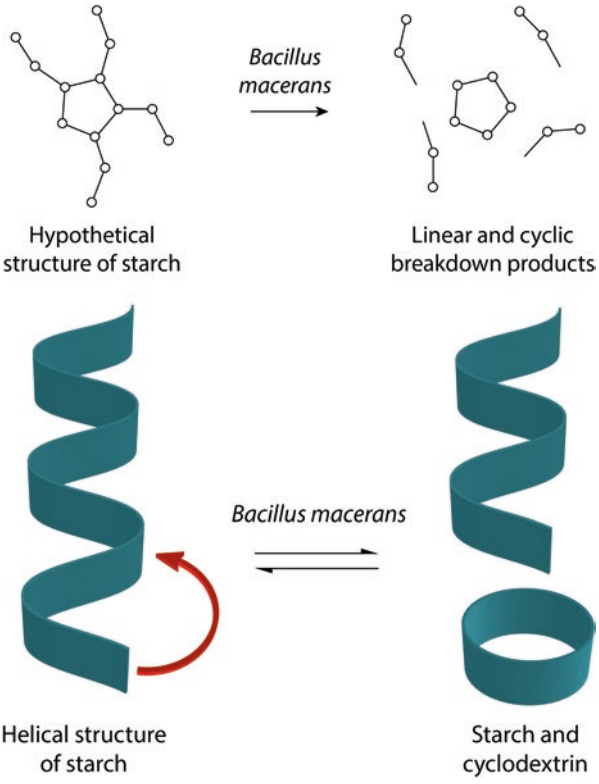
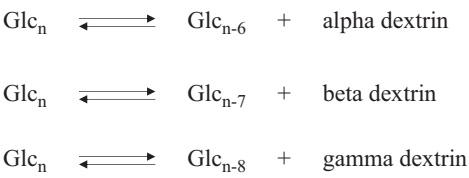


Fig. 1.12 Freudenberg's initial (above) and final (below) model of formation of Schardinger dextrins/cyclodextrin; adapted from Freudenberg (1939)



Scheme 1.1 Reactions proposed by Freudenberg (1939) to explain the formation of dextrins (Glc = a *D*-glucose or a *D*-glucosyl residue)

D-glucosyl residues were situated close to one another and were able to unite to form rings of five or six D-glucose units. The reactions proposed by Freudenberg to explain the formation of dextrins are given in Scheme 1.1 (Freudenberg 1939). Freudenberg concluded that the cyclodextrins were not preformed in starch "molecule" but that formation was made possible by the helicity of the starch chain. However, he was unable to prove this mechanism. It would be confirmed a few years later by French using chromatography (French et al. 1954) and later by Takeo and Kuge (1969) using X-ray crystallography.

From the 1940s, numerous research groups worked on the bacteria that produced the dextrins (Myrbäck 1938, 1942, 1949a, b; Samec and Blinc 1939, 1941; Myrbäck and Ahlborg 1940; Blinc 1941, 1942; Samec 1942; Tilden and Hudson 1939, 1942; Tilden et al. 1942; Kerr 1942, 1943, 1949; Kerr and Severson 1943; Wilson et al. 1943; Myrbäck and Gjorling 1945; Cori and Cori 1946; French et al. 1948; Kerr and Cleveland 1949; Hale and Rawlins 1951). However, the discovery of the enzyme in *Bacillus macerans*, responsible for the conversion of starch into dextrin, is attributed to Tilden and Hudson. In 1939, Tilden and Hudson isolated a cell-free enzyme preparation from *Bacillus macerans*, i.e., *Acrobacillus macerans*, that had the ability to convert starch into crystalline dextrins with interesting yields, ~55%, (Tilden and Hudson 1939). They introduced the name of cycloamylose glucanotransferase, i.e., CGTase or cyclodextrin glucanotransferase. Prior to this discovery, dextrins were made using live cultures of *Bacillus macerans*. In 1942, the authors proposed the following protocol (Tilden and Hudson 1942; Tilden et al. 1942): they cultivated *Bacillus macerans* on sterilized potato slices or on a medium containing 5% oatmeal, in presence of 2% calcium carbonate; after 2–3 weeks of cultivation at 37–40 °C, the cell mass was recovered by filtering or centrifuging; the filtrate contained the enzyme in an activity of 0.7 units/mL, which was separated either by freeze-drying or, after concentration, by precipitation with acetone. Their results mainly showed that it was essential to determine the optimal culturing conditions for the production of the enzyme and the optimal pH, temperature, and fermentation time for enzyme activity for effective use of the enzyme. Later, Hale and Rawlins (1951) also attained similar yields of the enzyme on a scale of 20 L in 10–12 days in an aerated culture. Tilden and Hudson were also the first to propose a simple protocol for purifying the amylase of *Bacillus macerans* using both precipitation by acetone, adsorption, and dialysis steps (Tilden and Hudson 1942; Tilden et al. 1942). The enzyme purified had an activity 140 times that of the initial enzyme solution and was able to convert 1000 times its weight of starch in 30 min at 40 °C.

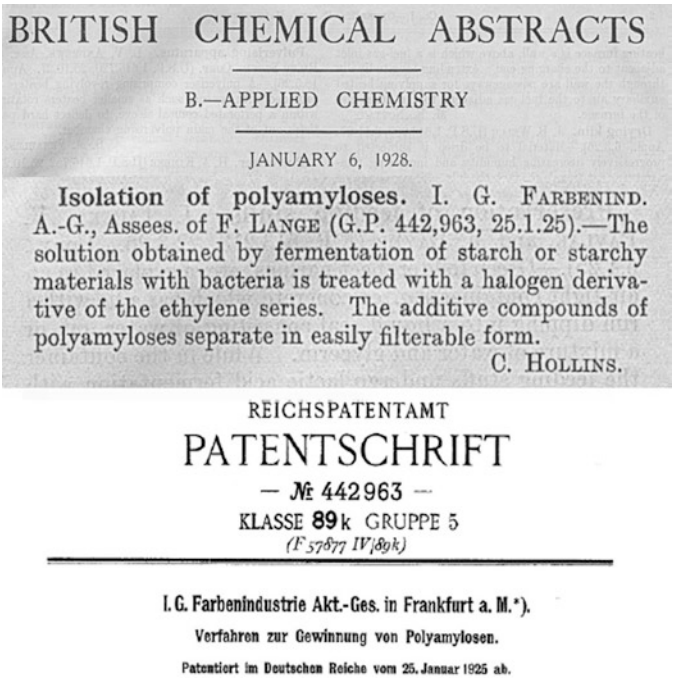
Since Tilden and Hudson's discovery of *Bacillus macerans* cycloamylose glucanotransferase, effort was devoted to working out methods for cyclodextrin

production and the details of the mechanism. These two researchers also laid down the basis of the enzymology of dextrins, and their findings were validated and used for over 30 years. Myrbäck and Gjorling (1945) and Cori and Cori (1946) also confirmed that the enzyme which catalyzed the degradation of starch into dextrins was mainly produced by bacillus strains. These two groups were the first to describe the action mechanism involved in the enzyme synthesis of Schardinger dextrins and to point out that the rate of hydrolysis of dextrins was much slower in its initial phase than later on. In addition, the authors noted that, after a few days, the Schardinger dextrins formed under the action of *Bacillus macerans* gradually disappeared. This was also observed by Kneen and Beckord (1946), by French (French et al. 1948), and later by Hale and Rawlins (1951). The explanation was given by French which introduced the reversibility of the action of the enzyme (French et al. 1948). In 1948, French's group proposed a mechanism of action based on a transglucosylation reaction to interpret the formation of dextrins by *Bacillus macerans* (French et al. 1948). Their results demonstrated that *Bacillus macerans* was capable of producing a glycosidic exchange reaction between maltose and cyclohexaamylose which resulted in the formation of higher weight saccharides, confirming the concept of glycosidic exchange introduced by Cori and Cori (1946). French pointed out that the enzyme performed three transglucosylation reactions involving cyclization, coupling, and disproportionation, as well as a hydrolysis reaction. This mechanism proposed by French and detailed in his comprehensive review (French 1957a) was only demonstrated in the 2000s (Lee and Robyt 2001; Qi et al. 2004). In 1950, Akiya and co-workers also proposed a mechanism of action and claimed the "discovery" of a new strain of *Bacillus macerans* (Akiya and Watanabe 1950a, b, c), although Hudson's group have previously shown that all examined strains of *Bacillus macerans* were capable of forming Schardinger dextrins (Tilden and Hudson 1939, 1942; Tilden et al. 1942).

1.3.7 The First Schardinger Dextrin-Related Patents

The first patent on Schardinger dextrins was registered in 1925 by the German Fritz Lange for *IG Farbenindustrie* (Fig. 1.13). This patent entitled *Verfahren zur gewinnung von polyamylosen* focused on the isolation of polyamyloses (Lange 1925).

Freudenberg, Cramer, and Plieninger filed the first industrial cyclodextrin-related patent in 1953, called "Method for preparation of inclusion compounds of physiologically active organic compound" (Freudenberg et al. 1953). The patent described the most important aspects of the applications of cyclodextrins in drug formulations (Fig. 1.14). The authors detailed specific effects that could be achieved by complexation of drugs with cyclodextrin complexation such as enhancement of solubility of poorly soluble drugs, protection of easily oxidizable substances against atmospheric oxidation, reduction of the loss of highly volatile substances, etc. In 1987, Cramer wrote: "At that time, I saw the first possibilities for a technology transfer and I took a patent. This, unfortunately, never found any industrial application" (Cramer 1987).



BRITISH CHEMICAL ABSTRACTS

B.—APPLIED CHEMISTRY

JANUARY 6, 1928.

Isolation of polyamyloses. I. G. Farbenind. A.-G., Assees. of F. Lange (G.P. 442,963, 25.1.25).—The solution obtained by fermentation of starch or starchy materials with bacteria is treated with a halogen derivative of the ethylene series. The additive compounds of polyamyloses separate in easily filterable form.

C. Hollins.

REICHSPATENTAMT

PATENTSCHRIFT

— № 442963 —

KLASSE 89k GRUPPE 5

(F 57877 IV/89k)

I. G. Farbenindustrie Akt.-Ges. in Frankfurt a. M.*).

Verfahren zur Gewinnung von Polyamylosen.

Patentiert im Deutschen Reiche vom 25. Januar 1925 ab.

Fig. 1.13 Extract of the British Chemical Abstracts announcing the first patent on polyamyloses filed by Lange in 1925

The potential use of cyclodextrins in pharmaceuticals had been launched. It was not till the 1970s and 1980s though that the first industrial-scale applications in pharmacy appeared (Szejtli 1998; Loftsson and Duchêne 2007; Morin-Crini et al. 2015).

1.3.8 Cyclodextrins as Models

Cramer knew everything about cyclodextrins, publishing an impressive number of results over a period of 25 years on their preparation, separation, characterization, structure, properties, chemistry, biochemistry, and their potential application in pharmacy, catalysis, and enzymology (Freudenberg and Cramer 1948, 1950; Cramer 1949, 1951a, b, c, 1952, 1953, 1954, 1956, 1961; Freudenberg et al. 1953; Cramer and Steinle 1955; Cramer and Henglein 1956, 1957a, b; Cramer and Dietsche 1958, 1959a, b; Lüttringhaus et al. 1958; Cramer and Kampe 1962, 1965; Cramer and Hettler 1967; Cramer et al. 1967, 1969).

In 1953, Cramer was the first to show the catalytic role that cyclodextrins could play in chemical reactions through a key-lock interaction similar to that of an enzyme-substrate complex (Cramer 1953). Later, Cramer gave the basis for supramolecular catalysis involving cyclodextrins (Cramer and Dietsche 1958, 1959a;

Erteilt auf Grund des Ersten Überleitungsgesetzes vom 8. Juli 1949
(WiGBl. S. 175)

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
5. NOVEMBER 1953

DEUTSCHES PATENTAMT

PATENTSCHRIFT

№ 895 769

KLASSE 12o GRUPPE 27

K 11126 IV c / 12 o

Dr. Karl Freudenberg, Heidelberg,
Dr. Friedrich Cramer, Heidelberg-Schlierbach und
Dr. Hans Plieninger, Heidelberg
sind als Erfinder genannt worden

Knoll A.-G. Chemische Fabriken, Ludwigshafen/Rhein

Verfahren zur Herstellung von Einschlußverbindungen physiologisch wirksamer organischer Verbindungen

Patentiert im Gebiet der Bundesrepublik Deutschland vom 26. August 1951 an
Patentanmeldung bekanntgemacht am 5. März 1953
Patenterteilung bekanntgemacht am 24. September 1953

Es ist bereits bekannt, Additionsverbindungen von organischen Stoffen herzustellen, die die zweite Komponente in den Hohlräumen ihres Molekülis oder Kristallgitters einschließen. So sind z. B. Additionsverbindungen von Desoxycholsäure, Harnstoff und von den Schardinger-Dextrinen bekannt, die die verschiedensten Stoffe eingeschlossen enthalten. Diese Additionsverbindungen, die treffender als Einschlußverbindungen bezeichnet werden, weil sie die eingeschlossenen Komponenten in getarnter Form enthalten, haben die Eigenschaft der Schwerlöslichkeit.

Während bisher bei den Schardinger-Dextrinen Addukte nur mit sauerstofffreien, physiologisch indifferenten, halogenhaltigen Kohlenwasserstoffen, insbesondere der aromatischen Reihe, und mit höheren Alkoholen bekannt waren, wurde nunmehr gefunden, daß diese Dextrine auch mit beliebigen, insbesondere mit physiologisch wirksamen Stoffen Einschlußverbindungen bilden. Diese neuen Addukte zeichnen sich ebenfalls durch Schwerlöslichkeit und meist damit verbundene protrahierte Wirkung, durch Beständigkeit gegen Körpersäfte, durch Geschmacksverbesserung und durch Lagerungsbeständigkeit aus.

Die neuen Addukte werden dadurch hergestellt, daß man konzentrierte wäßrige Lösungen der Schardinger-Dextrine mit den Einschlußkomponenten vereinigt. Zu diesem Zweck wird die heiß gesättigte, wäßrige Dextrinlösung mit der Einschlußkomponente versetzt und darauf allmählich erkalten gelassen. Nach einer anderen Ausführungsform des Verfahrens wird die gesättigte wäßrige Dextrinlösung mit der suspendierten Einschlußkomponente durchgeschüttelt. Man kann auch so vorgehen, daß man die wäßrige Dextrinlösung mit einer Lösung der Einschlußkomponente in einem mit

Fig. 1.14 First page of the first patent concerning the applications of cyclodextrin in pharmaceutical formulations filed by Karl Freudenberg, Friedrich Cramer, and Hans Plieninger in 1953

Cramer 1961; Cramer and Kampe 1962, 1965). For instance, he reported a cyclodextrin-accelerated reaction studying the hydrolysis of ethyl *p*-chloromandelate in the presence of α-cyclodextrin (Cramer and Dietsche 1958). Cyclodextrins can also be used as an asymmetric agent (Cramer 1961; Cramer and Kampe 1962, 1965). The potential use of cyclodextrins in catalysis and supramolecular chemistry had been launched. The first reports of their potential use as enzyme models were also attributed to Cramer. Enzyme-substrate interactions can be established either by non-covalent bond such as hydrogen bonding or van der Waals forces or by a covalent bond. When a covalent bond is formed, the cyclodextrin established a

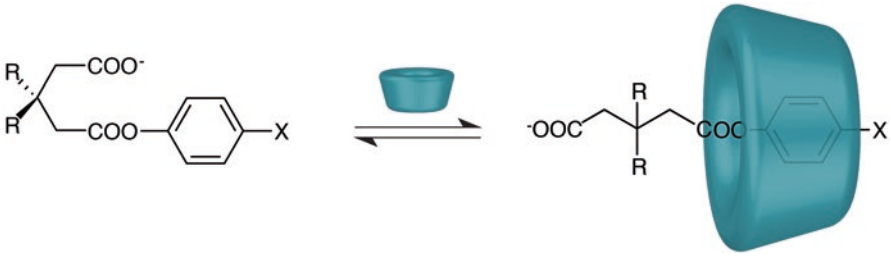


Fig. 1.15 Mechanism proposed during the hydrolysis of 3,3-disubstituted phenyl-glutarate via intramolecular catalysis; the presence of cyclodextrin suppressed this intramolecular catalysis

covalent bond with some entering or leaving component, e.g., in the case of ester hydrolysis. This process was called covalent catalysis. The model of non-covalent catalysis was inclusion complex catalysis, introduced by Cramer (1953) and later studied in detail by Bender (van Etten et al. 1967a, b; Griffiths and Bender 1973). An interesting example is given in Fig. 1.15. The hydrolysis of 3,3-disubstituted phenyl-glutarate proceeded via intramolecular catalysis. This was suppressed by cyclodextrin inclusion complex formation. The stabilizing effect depended on the cyclodextrin concentration according to the hyperbolic curve of the Michaelis-Menten enzyme kinetics. The reaction rate reached a minimum value when all the ester molecules were complexed. The hydrolysis was also independent of the pH; consequently cyclodextrin was only a binding site and was not involved directly in the reaction mechanism.

At the end of the 1950s, the numerous fundamental studies of French also led to growth in the interest in cycloamyloses not only as model enzymes but also as aroma-stabilizing agents for the food industry (Thoma and French 1958; Thoma et al. 1959; French et al. 1963), even though at the time, industrial application of cycloamyloses was still not considered feasible. This last point was only clarified in the 1970s. In the 1960s, Bender reported that cycloamyloses had a great potential for acid-base catalysis similar to that of naturally occurring enzymes. His numerous works made the creation of artificial enzymes possible. Bender, studying cycloamyloses-catalyzed reactions, showed that cycloamyloses can accelerate or decelerate various kinds of reactions including oxidation, hydrolysis, decarboxylation, nitrosation, and isomerization. The reaction rates depended on the cycloamylose used and the kind and stability of the inclusion compound formed. The first review on the phenomenon of cycloamylose catalysis has been published in 1973 by Bender (Griffiths and Bender 1973). This comprehensive review also summarized the developments in the chemistry of cycloamyloses and its derivatives used as enzyme models. It was updated by Bender in 1978 (Bender and Komiyama 1978). Cycloamylose-catalyzed reactions were classified in two categories: (i) covalent catalysis in which cycloamyloses catalyze reactions via the formation of covalent intermediates and (ii) non-covalent catalysis in which cycloamyloses provide their cavities as apolar or sterically restricted reaction fields without the formation of any covalent intermediates. Bender pointed out that non-covalent catalysis by

cycloamyloses might be the result of either a solvent effect or of a conformational effect, e.g., in decarboxylation and stereoselective reactions. Bender is recognized as the initiator of the era of biomimetic chemistry, including artificial enzymes, molecular recognition, and bio-inspired reactivity (see his famous book: Bender and Komiyama (1978)).

1.3.9 Complex Formation and Inclusion Compounds

In 1938, Freudenberg suggested, for the first time, the hydrophobicity of the inner surface of the dextrin and noted how dextrins had the ability to form complexes due to their cyclic structure (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). The dextrins exhibited a complexing capacity which was discussed in connection with the blue starch/iodine complex. For the first time, the ability of Schardinger dextrins to form complexes was suggested. To explain these complexes, Freudenberg was the first to show the involvement of hydrophobic forces in the formation of the complexes (Freudenberg 1939; Freudenberg and Meyer-Delius 1939; Freudenberg et al. 1939). Originally, however, Freudenberg was convinced that the dextrins and the amylose helix were lined with a hydrocarbon interior, and thus the cavity of the dextrins has been referred to as hydrocarbon in nature (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

Cramer was recognized not only for having introduced the cyclodextrin-based nomenclature but mostly for his important work on inclusion complexes, although they were only fully acknowledged at the end of the 1970s (Crini 2014). In 1949, in his PhD dissertation entitled *Die cyclodextrine aus Stärke*, Cramer evoked for the first time the fact that the three native cyclodextrins, considered as cylinders with different internal diameters, were able to accommodate molecules of different sizes: this was the first indication on their ability to form "inclusion" complexes (Cramer 1949). Two years later, Cramer published his first results on the complexes (Cramer 1951a, b, c, 1952). For instance, he observed that a number of dyes showed characteristic changes in their absorption spectra in aqueous solutions of the cyclodextrins (Cramer 1952). Between 1952 and 1954, Cramer discovered that the toroidal form of the cyclodextrin molecules, regarded as truncated cones, enabled them to accept various molecules inside their cavity (Cramer 1952, 1953; Dietrich and Cramer 1954). He was the first to demonstrate the hypotheses Schardinger put forward at the beginning of the nineteenth century on their ability to form complexes. In 1952, Cramer adopted the term *einschlussverbindungen*, i.e., inclusion compound, to characterize a complex (Cramer 1952), and later he also used the terms "occlusion compound" and "molecular encapsulation" (Cramer and Dietsche 1959a). In 1953, he registered his first patent where he highlighted the fact that "the formation of an inclusion complex could modify the physical, chemical and biological characteristics of a guest molecule such as a drug" (Freudenberg et al. 1953). The inclusion phenomena and the term *einschlussverbindungen* were however used by Schlenk in 1950 for the first time (Schlenk et al. 1955; French 1957a; Szejtli 1982a; Crini

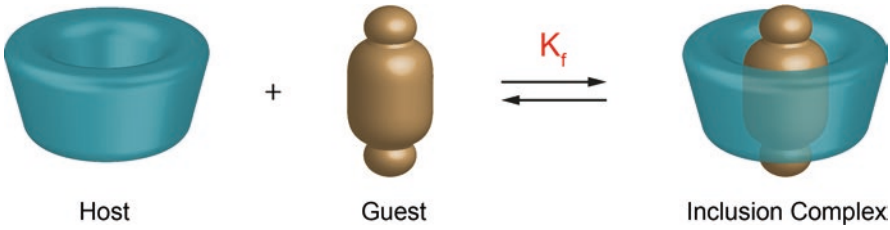


Fig. 1.16 Inclusion phenomena between a cyclodextrin molecule (the host) and an organic molecule (the guest) to form inclusion complexes; K_f is the formation constant

2014). The term "inclusion compound" has been coined to describe the positional relationship of two components which form certain types of crystals. These components were designated as host and guest, again in reference to the solid state (Schlenk et al. 1955; Schlenk and Sand 1961).

In 1956, Cramer introduced the notion of "inclusion complex" (Cramer 1956). He considered the interior of the cavity as a lipophilic microenvironment into which a non-polar hydrophobic molecule can "slide" (Fig. 1.16). The guest was maintained within the cavity by non-covalent forces, which were thus weak and enable the whole system to be reversible. Cramer showed that formation of an inclusion complex was the result of an association/dissociation equilibrium between the free guest and the free host and the complex. This was governed by a constant, denoted formation constant, K_f. The higher its value, the more stable the inclusion is, and the less dissociation that occurred. Cramer then conducted important research between 1955 and 1965 on the inclusion phenomena (Cramer 1956, 1961; Cramer and Henglein 1956; Cramer and Dietsche 1959a, b; Cramer and Kampe 1962, 1965). He studied in detail the molecular dispositions of numerous guest organic compounds in the cyclodextrin cavity in solution by the use of UV-visible and circular dichroism experiments, in order to demonstrate the formation of inclusion complexes. These experiments also permitted to calculate the formation constant or dissociation constant of the different complexes.

Figure 1.17 shows the two possible penetration pathways for benzoic acid, phenol, and methylated benzoic acids. α-Cyclodextrin complexes with phenol and benzoic acid guests in the head first position were more stable than in the tail first position, while β-cyclodextrin complexes with the same guests preferred the tail first position. A substituted benzene ring with a van der Waals radii of about 6.8 Å could only penetrate into the ring of a β-cyclodextrin molecule (diameter cavity: 7.5 Å) either "head first" or "bottom first" but never crosswise. The stability of the complex was proportional to the hydrophobic character of the substituents (Cramer and Henglein 1956; Cramer and Dietsche 1959a, b; Cramer 1961). In the 1970s, this was also demonstrated by van Hooidonk and Breebaart-Hansen (1970, 1972), Harata and Uedaira (1975), and later Szejtli (1982a) using the same methods, i.e., UV-visible spectroscopy and circular dichroism. Demarco and Thakkar (1970) were the first in a pioneering work to demonstrate the formation of inclusion complexes

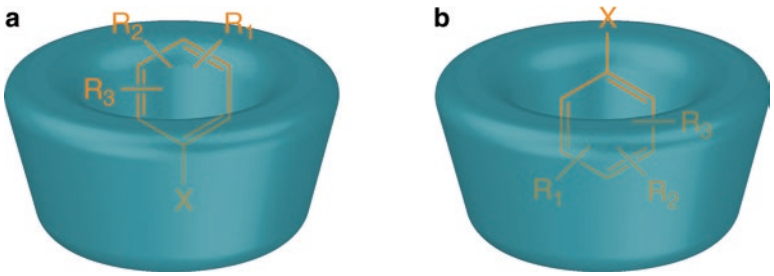


Fig. 1.17 Two possible penetration pathways (a, head first; b, right, tail first) for benzoic acid, phenol, and methylated benzoic acids (X = COOH or OH; R_1, R_2, R_3 = H or CH_3)

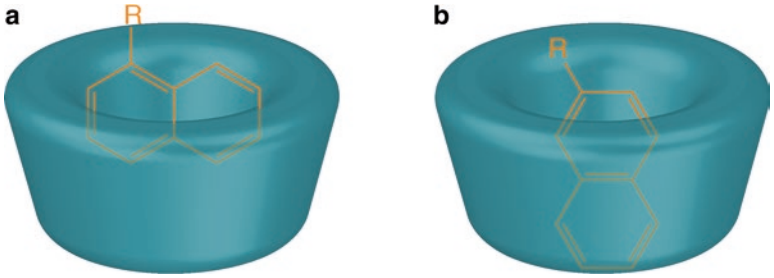


Fig. 1.18 (**a**) Equatorial inclusion of a 2-substituted naphthalene and (**b**) axial of a 1-substituted naphthalene. (Adapted from Harata and Uedaira 1975)

between several organic substances studied by Cramer and β-cyclodextrin using NMR spectroscopy.

Another interesting example was the complex between β-cyclodextrin and naphthalene substituted in position 1 or 2 (Fig. 1.18). The modification of the circular dichroism that occurred depended on the geometry of both the host and the guest molecules. A positive circular dichroism band implied axial inclusion, i.e., along the Cn symmetry axis, whereas a negative band signified equatorial inclusion, i.e., perpendicular to the Cn axis (Cramer 1961; Cramer and Kampe 1962, 1965). Later, Szejtli (1982a) also indicated that the sign and intensity of the induced Cotton effects were quite sensitive to the orientation of the guest chromophore in the cyclodextrin cavity. If the electric dipole moment coincided with the axis of the cyclodextrin, a positive Cotton effect was observed. When they were perpendicular to each other, a negative Cotton effect was observed. The circular dichroism spectra of 1- and 2-naphthols were therefore quite different: the naphthalene ring in one case was accommodated crosswise and in the other case lengthwise in the cyclodextrin cavity. In the complexes of 2-naphthalenes, the inclusion was axial (Harata and Uedaira 1975; Szejtli 1982a) (Fig. 1.18).

Cramer concluded that the preferred position for the guest compound inside the cavity depended on steric interactions, due to the chemical structure and geometry of each guest compound. The complex was strong when there was size

complementarity between the guest and the cyclodextrin cavity. In solution, two main components of the driving forces of the process are suggested: the first was the presence of repulsive forces between the included water molecules and the apolar cavity, and the second was the presence of repulsive forces between the bulk water and the apolar organic guest. Cramer also indicated that hydrogen bonding between the guest and the cyclodextrin was of only minor importance as a driving force for complex formation (Cramer 1956). The stability of cyclodextrin inclusion complexes was due to a favorable change in enthalpy during the inclusion process. However, later, Cramer also considered that a complex was stabilized not only by van der Waals forces but also by hydrogen bonds (Cramer and Kampe 1965; Cramer et al. 1967).

In 1958, Cramer was the first to propose a scheme for the preparation of so-called catenanes, compounds consisting of two rings connected to each other without chemical bond, by using cyclodextrin complexes (Lüttringhaus et al. 1958). Figure 1.19 shows the structural scheme of catenanes and the principle of their attempted preparation. Incorporating a dithiol with sufficiently long chain into cyclodextrin, and oxidizing the two protruding terminal SH groups to give an -S-S- bridge, a catenane was formed. These molecules were studied in the 1990s and proposed for the synthesis of supramolecular materials, scaffolds and templates, and in biomimetism (Nepogodiev and Stoddart 1998). In 1959, Cramer observed that, in the case of guest molecules that cannot be totally included by a single molecule, a second cyclodextrin molecule may bind: this was the first observation of 2:1 complexes in solution (Cramer and Dietsche 1959a, b). Figure 1.20 illustrates the association of free cyclodextrin and substrate to form various substrate-cyclodextrin complexes. Depending on the respective size of the guest and host molecules, one guest molecule can interact with one or two (or more) cyclodextrins, i.e., host-guest complexes 1:1 and 2:1, or two (or more) guest molecules can interact with one cyclodextrin or two (or more), i.e., host-guest complexes 1:2 and 2:2.

In 1967, Cramer comprehensively discussed all the possible penetration pathways and the effect of substituents on the stability of the inclusion complexes (Cramer and Hettler 1967). The same year, he gave the first scientific explanation to

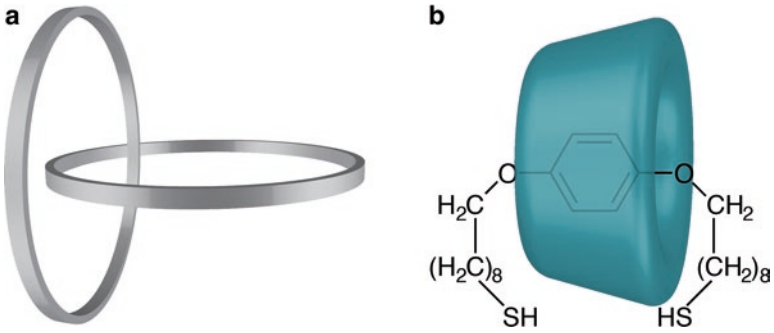


Fig. 1.19 (**a**) Structural scheme of catenanes and (**b**) principle of their attempted preparation. (Adapted from Lüttringhaus et al. 1958)

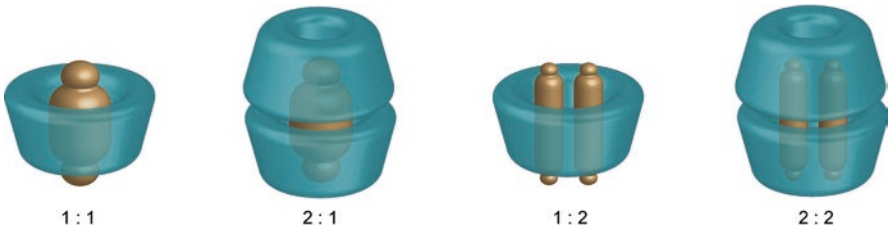


Fig. 1.20 Association of free cyclodextrin and substrate to form various substrate-cyclodextrin complexes

explain the mechanism of formation of an inclusion complex between a substrate and a cyclodextrin molecule both in solution and solid state (Cramer et al. 1967). To explain the formation of an inclusion complex, Cramer introduced five elementary steps: (1) the substrate approaches the cyclodextrin molecule; water molecules escape from the cyclodextrin cavity and acquire a new energy level, corresponding to that of the gaseous state; the van der Waals interactions and the number of hydrogen bonds decrease, whereas the degrees of freedom of translation and rotation of the freed water molecules increase; (2) the guest molecule becomes released from the layer of water that envelops it and also acquires a different state; the layer of water becomes dispersed and rearranges; (3) the guest molecule, considered to be in a perfect gas state, enters the cavity, and the complex formed is stabilized by van der Waals forces and/or hydrogen bonds; (4) the expelled water molecules are rearranged and form hydrogen bonds between each other; and (5) the structure of the water is restored around the part of the substrate that remains in contact with the solvent and that is integrated into the hydration shell around the CD. Cramer finally concluded that the most important property of cyclodextrins was the ability to establish specific interactions, i.e., molecular encapsulation, with various types of molecules through the formation of non-covalently bonded entities such as hydrophobic interactions, van der Waals forces, and hydrogen bonding (Cramer and Hettler 1967; Cramer et al. 1967). Cramer's work on inclusion complexes established much of our modern understanding of the behavior of cyclodextrins during complexation and remains a commonly cited source to this day.

At the same time as Cramer, French also studied the formation of inclusion complexes and showed that evidence for a guest inclusion into the cycloamylose cavity may be proved by analytical techniques such as UV-visible absorption spectrophotometry, optical rotatory dispersion, circular dichroism, and X-ray measurements (Thoma and French 1958, 1959, 1960, 1961; James et al. 1959; Thoma et al. 1959). The guests studied were the same as that of Cramer such as phenol, benzoic acids, or iodine. For instance, in 1958, French showed that absorption spectroscopy was an interesting method to determine the dissociation constant of the inclusion complex between cycloamylose and iodine (Thoma and French 1958). The values of dissociation constant could be easily obtained from the observed change in absorbance and the concentration of cycloamylose added according the Benesi-Hildebrand method. For French, the driving forces for complex formation included solvent

effects, van der Waals forces, and hydrogen bonds. One year later, French demonstrated that X-ray diffraction was also a powerful method to study the inclusion complexes between iodine and cycloamyloses (James et al. 1959). French also observed that, because of their structure, some guests can be included in one or two cycloamylose molecules, and depending on the cavity size, it was a different part of the guest molecule that can be included. This was clearly demonstrated in the 1970s by NMR spectroscopy (Szejtli 1982a).

Later, Lichtenthaler and Immel (1996) demonstrated, using molecular modelling, the need for compliance between hydrophobic host surfaces and hydrophobic domains in the cyclodextrin cavity. This striking tendency to optimize the reciprocal concurrence of lipophilic as well as hydrophilic domains at the guest-host interface may accordingly be concluded to be an important if not the decisive element in orienting the guest into the cavity and in determining the stability of the complex, particularly in cases where the guest is devoid of polar groups. This was the first study showing the importance of the reciprocal interplay of such interactions.

1.3.10 The First Reviews on Schardinger Dextrins

Relatively few reviews of cyclodextrins were published during the period from 1911 to 1970 as recently reported by Crini et al. (2018). The first review of Schardinger dextrins was published in German by Pringsheim in 1931 in a chapter entitled *Dextrine: Charakteristik, Gewinnung und Eigenschaften* and published in his book *Die polysaccharide* (Pringsheim 1931a). Pringsheim also published an English version in 1932 in another book *The Chemistry of the Monosaccharides and of the Polysaccharides* (Fig. 1.21). This mini-revue, entitled "The dextrins: Characteristics, Sources, and Properties," summarized the works of Schardinger on dextrins but mostly his own works (Pringsheim 1932).

Later, the dextrins were described in German by Samec and Blinc in a review dated 1941 and entitled "*Die Neuere Entwicklung der Kolloidchemie der Stärke*," in which they concluded that, "because of the use of impure dextrins, the work performed prior to about 1935 was judged to be of little consequence" (Samec and Blinc 1941). In 1954, an interesting brief overview on cyclodextrins was published by Cramer in his famous book on inclusion complexes entitled *Einschlussverbindungen* (Cramer 1954). However, the very first state of the art on the subject was only published by French in 1957 in a special volume of the journal *Advances in Carbohydrate Chemistry*. French wrote up an excellent fundamental review of over 70 pages with 159 references, entitled "The Schardinger Dextrins," where he described the history of Schardinger dextrins, their characteristics, chemistry and derivatives, and biochemical properties (French 1957a). French divided their history into two general periods, their discovery between 1891 and 1935 and their maturity from 1935 to 1950. Transfer reactions due to the *Bacillus macerans* action were also critically reviewed by French. In 1965, Thoma and Stewart also published a comprehensive review on the characteristics of *Bacillus macerans*

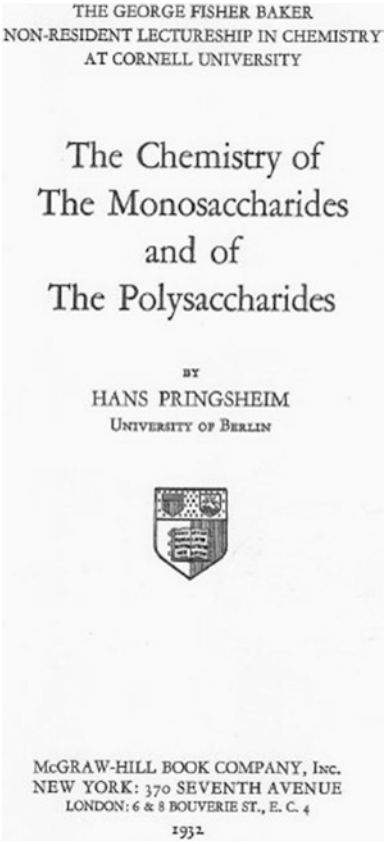


Fig. 1.21 Cover of Pringsheim's book published in 1932 where Professor Hans Pringsheim summarized the works of Professor Schardinger

amylase (Thoma and Stewart 1965). Three years later, Caesar summarized the use of cycloamyloses as models for enzymes (Caesar 1968).

1.3.11 Toxicological Considerations

Pringsheim was the first to conduct several biological tests to determine whether the dextrins were physiologically available either to plants or animals (Pringsheim and Müller 1922; Hoesslin and Pringsheim 1923; Pringsheim 1928b, 1931a). Pringsheim studied the absorption and metabolism of dextrins in rats, pigs, and humans. Polyamylose, probably α-cyclodextrin, administered in a dose of 50 g to diabetic persons, did not cause any change in the urinary glucose level, and no polyamylose was found in the feces (Pringsheim and Müller 1922). Hoesslin and Pringsheim (1923) fed polyamylose to starved rabbits and guinea pigs. No glycogen synthesis was detected in the liver 3 h after administration. Pringsheim suggested that polyamylose was metabolized in the rat. His experiments also showed that the

Schardinger dextrins were not fermentable and hence not utilized by yeast (Pringsheim 1928b). In 1931, for the treatment of diabetes, Pringsheim concluded: "α-dextrin directly utilized would be a suitable source of energy for diabetics since it only occasionally cause nausea and there is no noticeable increase in urine sugar" (Pringsheim 1931a).

However, in 1957, French wrote: "It would appear that the Schardinger dextrins exhibit a toxic effect, possibly by virtue of their remarkable complexing ability, and in any case, the suggestion of Professor Pringsheim that they be used as an energy source by diabetics looks risky" (French 1957a). Indeed, the first studies carried out by him in the rat led to the conclusion that Schardinger dextrins presented a certain toxicity (French 1957a). In the same paper, it is noted that "In unpublished attempts to investigate the ability of animals to utilize Schardinger dextrins, B.H. Thomas and D. French fed rats a diet in which a part of the carbohydrate was supplied by higher purified β-dextrin. The animals refused to eat the test diet except in very small quantities and within a week all animals on the ration were dead. Postmortem examination did not reveal the cause of death" (French 1957a). Their experiments indeed showed that the rats refused to eat food containing highly refined dextrins except in very small quantities. In spite of the small doses, rat mortality was 100% within a week of introducing "highly purified" β-dextrin into the diet (French 1957a). However, in these studies, experimental conditions, such as the purity of dextrins, the number of rats treated, or the existence of a control group, were not mentioned. Later, Szejtli suggested that one of the hypotheses was traces of solvent remaining in the dextrins which the rats could have smelt (Szejtli 1982a, 1988; Frömming and Szejtli 1994). This was the only result of French's that posed a problem and which led to extensive debate of the toxicity of the cycloamyloses (French 1957a), and most importantly this result deterred many scientists from developing cycloamylose-containing products for human use. The observations and conclusions drawn by French were only refuted much later following studies with the same animal model (Andersen et al. 1963; Lach and Cohen 1963; Lach and Chin 1964; Szejtli et al. 1980a; Chow and Karara 1986).

1.3.12 Other Works During the Period from 1911 to 1970

Other historical landmarks on the discovery of cyclodextrins published by other researchers during the period from 1911 to 1970 are reported in Table 1.1 (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

Table 1.1 Selected historical landmarks in the discovery of cyclodextrin during the period from 1911 to 1970

Year	Main results, achievements, or events	Reference(s)
1922	Amylose is converted into a diamylose, i.e., Schardinger's α-dextrin Amylopectin is converted into a triamylose, i.e., Schardinger's β-dextrin	Pictet and Jahn (1922)
1925	The first patent is registered by IG Farbenindustrie	Lange (1925)
1930	Chemical composition of dextrins The work of Schardinger on α-dextrin is demonstrated Like Karrer, Miekeley also suggests that the existence of alpha diamylose is doubtful The acetylation reaction of alpha tetraamylose, whether catalyzed by pyridine or an acid, always gives alpha tetraamylose acetate, rather than alpha diamylose acetate	Miekeley (1930)
1930	Description of the characteristics of *Bacillus macerans*	Zacherov (1930)
1932	Molecular size of α-dextrin The first attempt to determine the molecular weight of dextrins using osmotic-pressure measurements	Ulmann et al. (1932), Ulmann (1932)
1932	The existence of α-1,4-glucosidic linkages is confirmed	Miekeley (1932)
1933	Chemical modification of α-dextrin α-Dextrin ethanol complex has two different crystal modifications which could be interconverted: Ulmann's group is the first to observe that a same guest may form different crystal structures with the same dextrin	Hess et al. (1933)
1939	The enzyme in *Bacillus macerans* responsible for the conversion of starch into dextrin is discovered by Hudson's group Relationship between the constitution of the Schardinger dextrins and that of starch A mechanism of formation is suggested Different starchy substrates differ in their behavior with *Bacillus macerans* in regard to the total yields of Schardinger dextrins and to the relative proportions of α- and β-dextrins	Tilden and Hudson (1939)
1942	The discovery of the amylase "Schardinger dextrinogenase" is confirmed by Hudson's group Description of a simple protocol for purifying the amylase of *Bacillus macerans* First description of the extracellular amylase produced by *Bacillus polymyxa* The ratio of α- to β-dextrin changes during the enzymolysis of starch The name of cyclodextrin glucanotransferase or CGTase is introduced Schardinger dextrins are derived from some basic configuration pre-existing in the starch molecule With Tilden, Hudson lays down the basis of the enzymology of dextrins	Tilden and Hudson (1942), Tilden et al. (1942), McClenahan et al. (1942), Wilson et al. (1943)
1942	Acid modification of corn starch leads to greatly reduced yields of Schardinger dextrins	Kerr (1942)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1943	Both the groups of Kerr and Hudson show that the amylose fraction of starch gives much higher yields of Schardinger dextrins, up to about 70%, than does the amylopectin fraction *Bacillus macerans* is capable of transfer reactions involving only α-*D*-(1→4) glucosidic bonds of linear or cyclic compounds	Kerr (1942, 1943), Wilson et al. (1943)
1945	The reducing values and amounts of fermentable sugars gradually increase during enzymolysis of starch with *Bacillus macerans* amylase The total dextrin yield increases to a maximum and then declines to practically zero as the reducing value increased Description of the action mechanism involved in the enzyme synthesis of Schardinger dextrins	Myrbäck and Gjorling (1945)
1946	Transglycosylase mechanism in enzymic synthesis of Schardinger dextrins	Cori and Cori (1946)
1948	The cyclic structure of dextrins is confirmed by X-ray crystallography: α-dextrin has an orthorhombic unit cell with 24 *D*-glucose residues per cell; one molecule of β-dextrin has 7 *D*-glucose residues; the crystal for γ-dextrin is not identified, but a pseudo-cell is obtained which contains 16 *D*-glucose residues, in harmony with an 8-membered ring	Borchert (1948)
1948	Synthesis of cyclodextrins containing nitrates and their characterization using X-ray data The first reliable molecular-weight determinations of crystallized dextrins based upon colligative properties	Gruenhut et al. (1948)
1950	"Discovery" of a new strain of *Bacillus macerans* "Discovery" of homologues of Schardinger dextrin containing more than 8 glucose units	Akiya and Watanabe (1950a, b, c)
1950	Introduction of German term *einschlussverbindungen*, literally inclusion compounds	Schlenk et al. (1955)
1950	The stoichiometry of an inclusion compound in solution can be determined by a slope ratio method	Harvey and Manning (1950)
1951	Cycloamylose glucanotransferases are detected in various microorganisms	Hale and Rawlins (1951)
1953	The first simple protocol for the purification of the Schardinger dextrinogenase enzyme	Schwimmer (1953)
1954	The first study on a specific modification of cyclodextrin: tosylation reaction; the previous results reported by Freudenberg in the 1920s are confirmed	Lautsch et al. (1954)
1961	The first study on cyclodextrin-fatty acid complexes In presence of organic molecules, solubility decreases owing to complex formation, in agreement with Cramer's results In the case of ethanol and propanol, there is a maximum on the concentration-solubility curve: The dependence of the solubility of β-cyclodextrin on the ethanol concentration is highlighted	Schlenk and Sand (1961)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1961	Acylated β-cyclodextrins are proposed as stationary phases in gas-liquid chromatography Materials are used for the separation of olefins, aldehydes, alcohols, and esters The separation however does not involve inclusion	Sand and Schlenk (1961), Schlenk et al. (1962)
1963	Only the signal of a single kind of anomeric proton in the NMR spectrum of γ-cyclodextrin is reported, suggesting that all glucose units are similar	Rao and Foster (1963)
1964	The first infrared spectra of four different hydrates of α-cyclodextrin Casu suggests for the first time that the glucopyranose rings possess the C1 chair conformation	Casu (1964), Casu and Reggiani (1964, 1966), Casu et al. (1964)
1964	The ability of cycloamyloses to form inclusion complexes is dependent on the presence of water An inhibitory effect of β-cyclodextrin on the hydrolysis of benzocaine is reported for the first time	Lach and Chin (1964)
1964	The first application of α-cyclodextrin as reagent for detection in thin-layer chromatography	Kaufmann and Wessels (1964)
1965	The cavity of cyclodextrins has definitively no hydrocarbon character	Thoma and Stewart (1965)
1965	The first NMR spectra of α-cyclodextrin and β-cyclodextrin Using NMR data, Casu confirms that (i) the D-glucopyranose units in cyclodextrins and in maltose possess the C1 chair conformation; (ii) β-cyclodextrin possesses a perfect rigid structure; (iii) the secondary hydrogen bond belt in α-cyclodextrin is incomplete; and (iv) the primary and secondary hydroxyl groups have a similar conformation in both the dissolved and the crystalline state Casu is the first to suggest the existence in water of hydrogen bonds between the secondary hydroxyl groups	Casu et al. (1965)
1965	The first determination of the structure of the complex between α-cyclodextrin and potassium acetate using three-dimensional X-ray data: a channel-type complex is formed in the crystalline state of the complex; the contact is established between one secondary and one primary hydroxyl edges Using X-ray data, the authors demonstrate that (i) all the glucose residues of cyclodextrins are in the C1 chair conformation; (ii) the change in crystallinity as function of dehydration is reflected in the X-ray diffraction pattern; and (iii) the secondary hydrogen bond belt in α-cyclodextrin is incomplete	Hybl et al. (1965)
1965	Classification of complexes based on their phase-solubility profiles	Higuchi and Connors (1965)
1965	The first insoluble resins from the epichlorohydrin reaction with cyclodextrins	Solms and Egli (1965)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1966	The complete oxidation of all primary hydroxyl functions of α- and β-cyclodextrins is reported Using chemical experiments and NMR data, Casu demonstrates the existence in water of hydrogen bonds between the secondary hydroxyl groups Intramolecular hydrogen bonding renders the secondary hydroxyl groups in cyclodextrins more resistant to hydrogen exchange	Casu (1966)
1967	The first recognition on the fundamental role of cyclodextrins in enzymology and catalysis	Van Etten et al. (1967a, b)
1967	α- and β-cyclodextrins are separated on a column made of cellulose: the method is suitable for both analytical and preparative purposes and provides highly purified products	Lammers (1967)
1968	The degree of substitution of partially methylated cyclodextrins is determined using NMR spectroscopy First detailed discussion of the conformations of methylated and acetylated cyclodextrins	Casu et al. (1968a, b, c)
1968	The water content of cyclodextrins can be determined by gas chromatography Using gas chromatography and elementary analysis, a crystalline β-cyclodextrin hydrate is found to have the composition $C_{42}H_{70}O_{35}$ 12 ± 0.5 H_2O Temperature dependence of the solubility in water, determined by refractometry, is reported	Wiedenhoff and Lammers (1968)
1968	For large-scale manufacture of Schardinger dextrins, sago starch is proposed	Caesar (1968)
1969	Gas-liquid chromatography is proposed as direct and accurate method for the analysis of cycloglycosyltransferase products The method is also used for the quantitative assay of mixtures containing α-, β-, and γ-cyclodextrins	Beadle (1969)
1969	The enzyme involved in the mechanism of action of *Bacillus macerans* is able to degrade the helical structure of starch X-ray crystallography is an interesting method to elucidate the structure of cyclodextrins and their complexes: inclusion complex formation results in important changes in the X-ray powder diagrams of cyclodextrins The transglucosylation reaction is confirmed by X-ray crystallography The first NMR spectrum of γ-cyclodextrin	Takeo and Kuge (1969)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1970	Cyclodextrins should be regarded as truncated cones NMR data confirm that the hydrogen atoms H3 and H5 direct toward the interior of the cavity while the hydrogen atoms H1, H2, and H4 locate on its exterior, in agreement with the C1 chair conformation of glucose units The hydrogen atoms H3 and H5 are considerably shielded when guest molecules are accommodated within the cavity, while the other hydrogen atoms show only a marginal shift By measuring changes in the chemical shift, the coupling constant, the nuclear Overhauser effect, and the relaxation times of components, it is possible to determine geometrical relationships between host and guest and their dynamic features in aqueous solution	Demarco and Thakkar (1970)
1970	The 1H-NMR spectra of γ-cyclodextrin in DMSO-d_6 at 25 °C and 80 °C show that the hydroxyl protons are shifted downfield relative to the values for both α- and β-cyclodextrins: this indicates that hydrogen bonds are stronger in γ-cyclodextrin than in β-cyclodextrin Assignments of the NMR signals for the individual protons in peracetylated cyclodextrins	Takeo and Kuge (1970)
1970	Detailed conformational studies on cycloamyloses using conformation-energy maps Cyclodextrins should be regarded as a truncated cone Hydrogen bonds are stronger in γ-cyclodextrin than in β-cyclodextrin Hydrogen bonding between the C2 and C3 hydroxyls results in a lowering of energy by 20 kcal/Mol in α-cyclodextrin and of 30 kcal/Mol in β-cyclodextrin Cycloamyloses having fewer than six α-*D*-glucopyranosyl residues are not possible because of steric reasons	Sundararajan and Rao (1970)

1.4 Historical Landmarks in the Development of Cyclodextrins: From 1970 Until Now

1.4.1 Production of Cyclodextrins

At the mid-1970s, industrial-scale production really started (Horikoshi 1979). Indeed, several manufacturers started to produce and to market cyclodextrins, e.g., Nihon Shokuhin Kako, Japan; Sanraku Ocean Co. Ltd., Japan; Toyo Joso, Japan; and Chinoin, Hungary. The first pilot plant at Nihon Shokuhin Kako firm, Japan, started up in 1978 with a production capacity of about 20 tons per year (Sicard and Saniez 1987). However, cyclodextrins were expensive.

The first to believe in the possibilities of industrial production and the multiple applications of cyclodextrins was probably Szejtli, a Hungarian carbohydrate chemist who organized the cyclodextrin technology in Hungary in the 1970s (Szejtli 1988, 1998). Among the list of prestigious researchers who have contributed to the

development of cyclodextrins, Szejtli played a fundamental role as eminent scientist, visionary, and entrepreneur, creating, in 1989, a private company, CycloLab Ltd., totally devoted to cyclodextrins. Without Szejtli, the feasible production of cyclodextrins on an industrial scale probably would not be as advanced as it is today.

In the mid-1980s, advancements in biotechnology led to drastic improvements in the production and purification of cyclodextrins. Cyclodextrins were then produced in large quantities with high purity and marketed at a reasonable price, and as a result, more industrial applications have become possible. In addition, this period from 1970 to 1980 was also marked by another important event: the first toxicological studies had established that β-cyclodextrin administrated orally was a harmless substance. Pharmaceutical, food, chromatographic, and cosmetic applications started to appear and rapidly gained ground. Since then, an increasing interest in cyclodextrins as raw materials and their possible applications has existed (Szejtli 1982a, 1988; Duchêne 1987, 1991).

1.4.2 Mechanism of Inclusion Complexes

In the mid-1970s, several researchers such as Saenger, a pupil of Cramer, Bender, and Szejtli pursued and reformulated the interpretations made by Cramer on the mechanisms of formation of inclusion complexes.

On the basis of the mechanism proposed in 1967 by Cramer, Saenger gave in 1976 three important explanations for the formation of an inclusion complex with α-cyclodextrin in aqueous solution (Saenger et al. 1976): (1) the guest molecule directly replaces the water molecules in the cavity; (2) the cyclodextrin molecules absorb the energy of the water molecules retained in the cavity and take on a relaxed conformation; in this state, the water molecules can be easily substituted by another guest; and (3) the guest becomes associated with the outer surface of the cyclodextrin and only enters the cavity once it has absorbed the activation energy, i.e., transfer of the conformation from a state of high energy of the cyclodextrin-water complex to a state of lower energy of the cyclodextrin-guest molecule complex. Saenger introduced the notion of the release of the tension energy within the α-cyclodextrin molecule upon formation of the complex. This relief of strain in the cyclodextrin ring contributed to the enthalpy of association and to the stabilization of the inclusion complex. In water, the α-cyclodextrin was in a strained, high-energy conformation, and that, when another guest molecules displaced the water, thus forming an inclusion complex, a conformational change of the cyclodextrin molecule occurred, transforming the α-cyclodextrin structures into an unstrained, relaxed state. This was demonstrated using detailed X-ray diffraction studies. A scheme of inclusion-complex formation involving relief of strain energy and release of high-energy water is proposed (Fig. 1.22). This scheme shows the possible pathways of α-cyclodextrin inclusion complex formation in aqueous solution. Owing to the inclusion of water, the ring of cyclodextrin is distorted, only four of the six possible hydrogen bonds are formed, and introducing a suitable guest molecule, the ring is

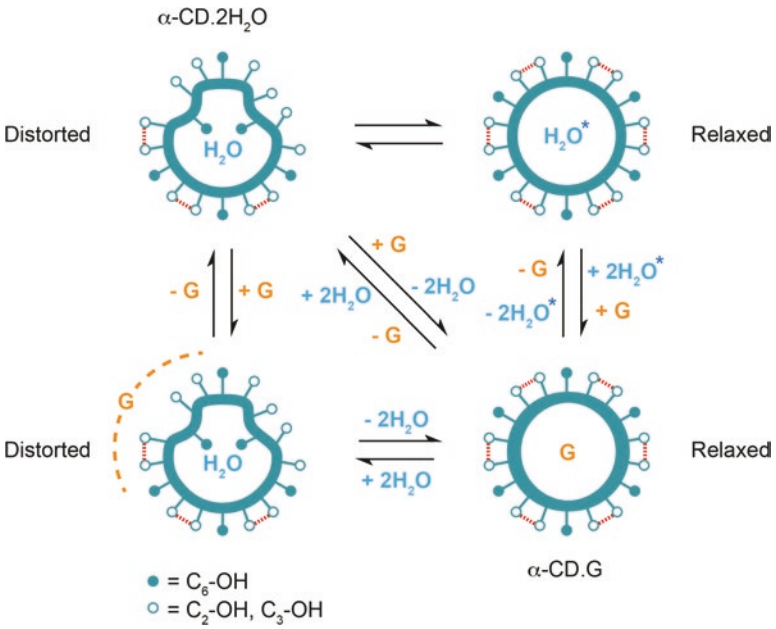


Fig. 1.22 Saenger's theory of formation of α-cyclodextrin complexes in aqueous solution: G, guest; H_2O^*, activated water. Hydrogen bonds are marked by dashed lines. (Adapted from Saenger et al. 1976)

relaxed. Later, Saenger showed that, in the cases of β- and γ-cyclodextrins, the strain energy relief mechanism did not seem to be operative and the cyclodextrin-water adducts were not strained (Lindner and Saenger 1978). In 1980, Saenger published a thorough state of the art of inclusion complexes, including his own interpretations (1980).

In 1978, Bender elucidated the mechanism of formation of the complexes developed by Saenger. He pointed out that the complexation involved hydrophobic interactions, like that of Saenger 2 years before. The driving force of inclusion is "an example of an atypical hydrophobic interaction" (Bender and Komiyama 1978). Bender proposed the fact that the complexation reaction involved a gain in enthalpy and a loss of entropy. The further the guest molecule penetrated into the cyclodextrin cavity, the greater was the change in enthalpy, and the higher was the stability of the complex. Moreover, the greater was the apolarity of the guest, the more this phenomenon was marked. The previous explanation that Bender offered to explain the favorable enthalpy change was that the empty cyclodextrin contained water molecules that were unable to form their full complement of hydrogen bonds to adjacent water molecules, and thus might be considered to enthalpy rich (Griffiths and Bender 1973). The inclusion of a guest "would then displace this high energy water from the cyclodextrin cavity, leading to a net increase in solvent-solvent hydrogen bonds and a favorable enthalpy of association."

In 1982, in his first book on cyclodextrins, Szejtli pursued and reformulated all the interpretations made by Cramer, Saenger, and Bender on the mechanism of formation of inclusion complexes (Szejtli 1982a). The gain in enthalpy is then explained by the spontaneous arrival of the guest, displacing active water molecules retained in the non-polar cavity of the cyclodextrin in aqueous solution. Szejtli illustrated his conclusions using a schematic representation of cyclodextrin inclusion complex formation (Fig. 1.23). In this famous figure, *p*-xylene is the guest molecule, and the small circles represent the water molecules which are repulsed both by the hydrophobic potential guest and the hydrophobic cavity of the truncated cyclodextrin cylinder (Szejtli 1978; Szejtli et al. 1979). The three main conclusions were as follows: (1) the guest molecule, less polar than water, directly replaced the water molecules in the cavity; these water molecules were in an unfavorable energy state owing to the polar-apolar interactions and were thus easily displaced by more suitable molecules; (2) the cyclodextrin molecules absorbed the energy of the water molecules retained in the cavity; and (3) the organic guest dissolved in water entered in the cavity because it had a preference for hydrophobic environment.

Szejtli supported the idea that, although van der Waals interactions and hydrogen bonding played an important role, the main force behind the formation of the complexes was the stabilizing reduction of the whole system's energy on the replacement of the high enthalpy water molecules in the cavity, by hydrophobic molecules leading to apolar-apolar bonding. He proposed that this bonding was too weak to be alone responsible for the higher stability of the complex and showed the parallel occurrence of steric interactions. Indeed, Szejtli demonstrated in various publications that the preferred position for the guest compound inside the cavity also depended on steric interactions. He concluded that the complexation phenomenon results from a multitude of interactions between the three components of the system cyclodextrin-substrate-solvent leading to a state that is more thermodynamically stable overall (Szejtli 1995). In the 1990s, there was a general agreement in the literature that during the formation of an inclusion complex, a whole set of intermolecular interactions come into play and that each one has its own role in the overall process.

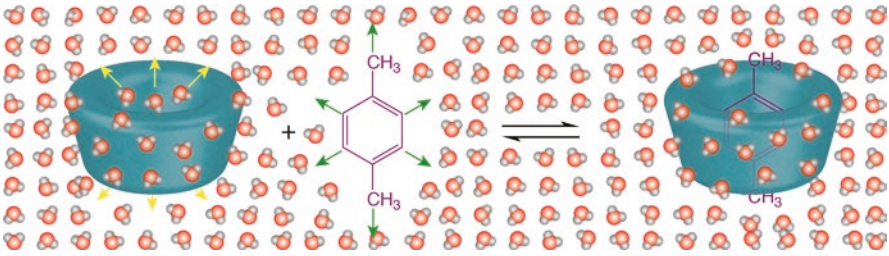


Fig. 1.23 Formation of an inclusion complex between *p*-xylene, the guest, and a cyclodextrin molecule; water molecules are repulsed by the hydrophobic potential guest. (Adapted from Szejtli (1978) and Szejtli et al. (1979)

1.4.3 Inclusion Phenomena and Its Effects

Since Cramer's discovery of inclusion phenomena, effort was devoted to physical and chemical properties of inclusion complexes and their consequences. Indeed, his results were not only of fundamental interest but also of industrial interest, and in the 1970s, this interest has grown considerably. Numerous works showed that inclusion of a guest active ingredient molecule in a host cyclodextrin molecule was a real molecular encapsulation, and the resulting inclusion complex superstructure had new physicochemical properties, stability, solubility, and also better therapeutic efficacy. So, several technological characteristics used in pharmacy could also be advantageously modified.

Rapidly, the pharmaceutical industry understood the advantages of using cyclodextrins. Szejtli (1982a, 1988) summarized them in six points:

1. The modification of the physicochemical properties of the guest molecule: e.g., liquid compounds can be transformed into crystalline, compressible forms; substances with low solubility in water become more soluble after complexation; the rate of dissolution of poorly soluble substances can also be increased; certain unpleasant tastes can be eliminated; smell can also be covered by complex forming; the color of certain substances can be altered since inclusion can change the spectral properties of the guest; etc.
2. The modification of the chemical activity of the guest: e.g., reactive substances can be protected by inclusion reducing the risks when they are mixed with other substances; chemical reactions can be carried out selectively, the cyclodextrins playing the role of catalysts; etc.
3. The stabilization of substances sensitive to light or to oxygen, etc., e.g., protection of active ingredients against oxidation, heat-promoted decomposition, or light-induced reactions.
4. The uptake of volatile substances: e.g., volatile drug can be stabilized without losses through evaporation; storage and handling of certain toxic substances such as pesticides can be improved; savings can be made on the quantity of substance required owing to reduced evaporation; etc.
5. The complexation, extraction, and transport of pollutants.
6. Several technological advantages, e.g., stable, standardized compositions, simple dosage and handling of dry powders, reduced packing and storage costs, and also saving of energy and manpower.

1.4.4 Large Cyclodextrins

Although the existence of cyclodextrins with over 8 glucose units is described and studied for the first time in the 1950s by Freudenberg, French, and Cramer, it was only in the middle of the 1990s that the cyclodextrins containing 9, 10, 11, and 12 units of glucose, called large-ring cyclodextrins, were studied in any depth

(Miyazawa et al. 1995; Endo et al. 1997, 1999; Larsen 2002; Taira et al. 2006). The difficulties to purify them and the low yields prevented their study until then. Using specific enzymes and/or particular experimental conditions, some works also reported the existence of cyclodextrins of over 100 glucose units (Terada et al. 1997; Koizumi et al. 1999; Qi et al. 2004). Larsen (2002) published the first interesting review on large cyclodextrins.

1.4.5 First Comprehensive Reviews on Cyclodextrins

From a fundamental point of view, an abundant scientific literature has built up since the 1970s. Indeed, a large number of generalist reviews, book chapters and books, and articles and patents have been published on practically all the aspects of cyclodextrins. Crini et al. (2018) recently reported that in the periods 1961–1985 (~24 years), 1986–2000 (~14 years), and 2001–2015 (~14 years), 2654, 18,856, and 42,284 cyclodextrin-related publications have been published, respectively, so many that it would not be feasible to cite them all. For this, readers should refer to the library database "Cyclodextrin News" from CycloLab Ltd. (Hungary) which is a periodical collecting all the cyclodextrin works, i.e., articles, reviews, proceedings, patents, conferences, and lectures, through different disciplines, i.e., chemistry, biology, health science, agriculture, nanotechnology, etc. This database is searchable until 2018, when it was turned into a blog and stopped collecting literature. Table 9 shows the first comprehensive reviews and book chapters on cyclodextrins during the period 1957–1998.

As already stated, the very first comprehensive review on cyclodextrins was published by French in 1957 (French 1957a). French's state of the art was continued a few years later by Kainuma (1984) and Clarke et al. (1988). Research on the action of *Bacillus macerans* on starch before 1980 was comprehensively reviewed by Kainuma. Clarke et al. discussed topics on detection, thermodynamics, and kinetics of complex formation from a literature survey of 182 previous papers. In 1980, Saenger published the very first review of industrial applications of cyclodextrins (Saenger 1980). In a very well-cited review published in the journal *Chemical Reviews*, Szejtli wrote: "Cyclodextrins can be consumed by humans as ingredients of drugs, foods, or cosmetics" (Szejtli 1998). In this review, Szejtli, pursuing the history of cyclodextrins written by French, divided the chemical and industrial developments of cyclodextrins into three stages, the discovery period from 1891 to 1935, the exploratory period in 1935–1970, and the utilization period from 1970 to the present day. The history was then updated later by Loftsson and Duchêne (2007) and by Crini (2014). Other fundamental reviews published in the period 1970–1990 are reported in Table 1.2.

Table 1.2 The first comprehensive reviews and book chapters on cyclodextrins during the period 1970–1998

Title	References
Cycloamyloses as catalysts	Griffiths and Bender (1973)
Some application possibilities of cyclodextrins in pharmaceutical industries	Szejtli (1977)
Application of cyclodextrin glycosyltransferase	Okada (1979)
Biomimetic chemistry in oriented systems	Breslow (1979)
Cyclodextrin inclusion-compounds in research and industry	Saenger (1980)
Inclusion compounds in chromatography	Smolková-Keulemansová and Krysl (1980)
Cyclodextrins as stationary phases in chromatography	Smolková-Keulemansová (1982)
Cyclodextrins in food, cosmetics and toiletries	Szejtli (1982b)
Synthesis of chemically modified cyclodextrins	Croft and Bartsch (1983)
Starch oligosaccharides: Linear, branched, and cyclic	Kainuma (1984)
Cycloamylose-substrate binding	Bergeron (1984)
Supramolecular catalysis by cyclodextrin and macrocyclic polyether	Sirlin (1984)
Structural aspects of cyclodextrins and their inclusion complexes	Saenger (1984)
Industrial applications of cyclodextrins	Szejtli (1984)
Chiral stationary phases for high performance liquid chromatographic separation of enantiomers: a mini-review	Armstrong (1984)
Improved cyclodextrin chiral phases: A comparison and review	Ward and Armstrong (1986)
Cyclodextrins: A new group of industrial basic materials	Szejtli (1985)
Production, characterization and applications of cyclodextrins	Bender (1986)
Cyclodextrins in biotechnology	Szejtli (1986)
Cyclodextrins in drug carrier systems	Uekama and Otagiri (1987)
Inclusion complexes of the cyclomalto-oligosaccharides (cyclodextrins)	Clarke et al. (1988)
Cyclodextrin-stationary phases	Ward and Armstrong (1988)
Cyclodextrin polymers in the pharmaceutical industry	Fenyvesi (1988)
Liquid chromatographic separation of anomeric forms of saccharides with cyclodextrin bonded phases	Armstrong and Jin (1989)
HPLC separation of enantiomers and other isomers with cyclodextrin-bonded phases: rules for chiral recognition	Han and Armstrong (1989)
Cyclodextrin additives	Sybilska and Zukowski (1989)
NMR studies of cyclodextrin inclusion complex	Yamamoto and Inoue (1989)

(continued)

Table 1.2 (continued)

Title	References
Cyclodextrins in the pharmaceutical field	Bekers et al. (1991)
Hydroxypropyl-β-cyclodextrins, preparation and physicochemical properties	Szente and Strattan (1991)
Cyclodextrins and their applications in analytical chemistry	Li and Purdy (1992)
Use of cyclodextrins in capillary electrophoresis	Fanali (1993)
Medicinal applications of cyclodextrins	Szejtli (1994)
Cyclodextrins as building blocks for supramolecular structures and functional units	Wenz (1994)
Cyclodextrin derivatives in pharmaceutics	Albers and Muller (1995)
Cyclodextrin derivatives	Jicsinszky et al. (1996)
The stability of cyclodextrin complexes in solution	Connors (1997)
Cyclodextrins	Robyt (1998)
Inclusion complexes of the cyclodextrins	Lincoln and Easton (1998)
Introduction and general overview of cyclodextrin chemistry	Szejtli (1998)
Methods for selective modifications of cyclodextrins	Khan et al. (1998)
Cyclodextrin-based catenanes and rotaxanes	Nepogodiev and Stoddart (1998)
Applications of computational chemistry to the study of cyclodextrins	Lipkowitz (1998)
Complexation thermodynamics of cyclodextrins	Rekharsky and Inoue (1998)
Organic reactions mediated by cyclodextrins	Takahashi (1998)
Cyclodextrin drug carrier systems	Uekama et al. (1998)
Industrial applications of cyclodextrins	Hedges (1998)

1.4.6 First Books on Cyclodextrins

The first books devoted entirely to the chemistry of cyclodextrins and their applications were only edited in 1978 and in 1982 by Bender and Komiyama and Szejtli, respectively (Table 10). Bender and Komiyama (1978) detailed the formation of an inclusion complex and covered all the aspects of catalysis by cyclodextrins. In his first book entitled *Cyclodextrins and Their Inclusion Complexes* (296 pages with more than 650 references), Szejtli reviewed the first industrial applications of cyclodextrins in pharmacy, food industry, chromatography, and chemical industry (Szejtli 1982a). In this book, Szejtli also summarized his interpretations on the concept on inclusion complex. Other important books published in the period from 1970 to 1990, which are still considered as reference works in the cyclodextrin community, are reported in Table 1.3.

Table 1.3 The first books on cyclodextrins published in the period from 1970 to 1990

Title	Author(s)	References
Cyclodextrin chemistry	Myron Lee Bender and Makoto Komiyama	Bender and Komiyama (1978)
Cyclodextrin and Their Inclusion Complexes	József Szejtli	Szejtli (1982a)
Inclusion compounds	Jerry L. Atwood, J. Eric E. Davies and David D. MacNicol	Atwood et al. (1984)
Cyclodextrins and Their Industrial Uses	Dominique Duchêne	Duchêne (1987)
Cyclodextrin technology	József Szejtli	Szejtli (1988)
New trends in cyclodextrins and derivatives	Dominique Duchêne	Duchêne (1991)
Cyclodextrins in Pharmacy	Karl-Heinz Frömming and József Szejtli	Frömming and Szejtli (1994)

1.4.7 The Dissemination of Knowledge About Cyclodextrins

Szejtli is distinguished not only for his contribution to chemistry, biology, and technology of cyclodextrins but also for his important contribution to the dissemination of knowledge about cyclodextrins. From 1975 to 2004, Szejtli published more than 500 publications on cyclodextrins (Cyclodextrin News Database, CycloLab Ltd., Hungary), including 106 patents and more than 100 general reviews and book chapters, and has given more than 200 invited lectures throughout his career. Szejtli's comprehensive reviews are still considered as reference works in the cyclodextrin community (Szejtli 1977, 1982a, b, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1994, 1996, 1997, 1998, 2002, 2003, 2004). His name is very often cited in the bibliographic references of articles dealing with cyclodextrins.

From the point of view of the dissemination of knowledge about cyclodextrins, we should also cite the publications of Duchêne (Duchêne 1987, 1991; Duchêne and Wouessidjewe 1990a, b, 1992; Duchêne et al. 1992, 2009), Loftsson (Loftsson and Brewster 1996, 2010, 2012; Loftsson and Stefansson 1997; Brewster and Loftsson 2002, 2007; Loftsson et al. 2004, 2005; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Jansook et al. 2018), and Szente (Szente and Strattan 1991; Szente and Szejtli 1996; Szente and Szemán 2013; Fenyvesi and Szente 2016; Fenyvesi et al. 2016; Szente and Fenyvesi 2018).

1.4.8 The First International Cyclodextrin Symposium

Realizing the exponentially increasing number of articles, chapters, and patents, Szejtli organized the first International Cyclodextrin Symposium in Budapest in 1981 (Szejtli 1982a). This first symposium was a great success, with participants coming from all over the world – more than 180 participants from 17 countries – while Szejtli

"expected 25-30 participants outside Hungary." The 63 submitted manuscripts filled a 544-page volume of proceedings published by Reidel Publishing (Szejtli 1982c). The second cyclodextrin symposium was organized in 1984 in Tokyo, Japan.

Since 1984 and Szejtli's initiative, a broad community of researchers has met every 2 years to exchange and share their works on cyclodextrins. Each symposium provides opportunities for scientists who work in several aspects of cyclodextrin research to discuss their advances in all cyclodextrin fields. The 19th International Cyclodextrin Symposium was held in 2018 in Tokyo, Japan, and the next will be organized in Sicily, Italy, in 2020. In Asia and in Europe, the cyclodextrin scientific community is also very active with the organization of meetings where academic researchers and industrials come together to present the latest achievements in the field of cyclodextrin science and technology, e.g., Asian Cyclodextrin Conferences, European Conferences, and French Cyclodextrin Days.

1.4.9 Cyclodextrin Derivatives

The underivatized or native β-cyclodextrin's low water solubility as showed by French in the 1940s restricted its advantage. For this reason, a number of derivatives such as hydrophilic methylated derivatives have been synthesized. Whereas the first methylated derivatives of β-cyclodextrins were studied as early as 1924 by Pringsheim and collaborators (Irvine et al. 1924), it was however not until 1969 that the alkylated cyclodextrins were comprehensively described by Gramera (1969). Indeed, in the older literature, particularly in the works of Pringsheim and Freudenberg, several methods were proposed referring to the preparation of such derivatives, but these are essentially of historic interest.

Literature on the preparation and investigation of cyclodextrin derivatives only proliferated in the 1960s. Since, numerous cyclodextrin derivatives and polymers were described, including alkylated and acylated derivatives, nitrogen- and sulfur-containing derivatives, halogenated products, and 6-deoxy derivatives. The derivatives of practical importance were the methylated and hydroxypropyl cyclodextrin derivatives in the 1980s and 10 years later the sulfobutyl ether derivatives. Casu was the first to prepare cyclodextrin derivatives such as methylated (Casu et al. 1968a, c) and acetylated (Casu et al. 1970) products. The experimental protocols were repeated in the 1980s by Szejtli (Szejtli 1982a, 1983, 1984). His work, particularly on methylated cyclodextrins, showed great promise for both human and animal use (Szejtli 1982a). Methylation could be either partial, i.e., esterification in positions 2 and 6, giving dimethyl-cyclodextrins or complete giving trimethyl-cyclodextrins. The randomized derivative called RAMEB was often used. These derivatives were much more soluble than the parent cyclodextrins, but their solubility was temperature-dependent. For this reason, hydroxypropyl cyclodextrins with high water solubility were more advantageous. However, because hydroxypropylation occurred randomly, the resulting products were not pure chemical entities but amorphous complex mixtures.

Croft and Bartsch (1983) were the first to publish a review on all the different chemically modified cyclodextrins which had been synthetized up to late 1982. In

1987, Sébille showed that cyclodextrin chemistry offered various possibilities to synthetize derivatives with different functions for various industrial uses, e.g., sulfur- and nitrogen- and imidazole- or histamine-containing derivatives, alkylated and acyl derivatives, halogenated products, polymers from cyclodextrins, etc. (Sébille 1987). By working in carefully controlled conditions, mono-, di-, and poly-substitution were possible and opened the way to several functional derivatives with catalytic or biological activity, for instance. One of the most popular derivative was mono-substituted 6-*O*-*p*-toluenesulfonyl-cyclodextrin, used as starting material to prepare modified cyclodextrins (Saenger 1980; Szejtli 1982a; Sébille 1987). Jicsinszky et al. (1996) published a comprehensive chapter (137 pages, 865 references) on cyclodextrin derivatives. In 1998, Khan et al. (1998) proposed a global schema for the modification of cyclodextrins. These two last publications are still reference today.

Thousands of derivatives containing cyclodextrin have been proposed in the literature, particularly for pharmaceutical uses. Szejtli (2004) estimated that over 15,000 derivatives had been studied. In reality, most of these derivatives will never find applications, especially for reasons of production costs and essentially lengthy and difficult synthesis involving complicated steps. Among industrially produced, standardized, and available derivatives, the most important ones are the methylated β-cyclodextrins such as RAMEB (randomly methylated-β-cyclodextrin; considered as a mixture) and DIMEB (a particular methylated cyclodextrin: heptakis(2,6-di-O-methyl-β-cyclodextrin), considered a single isomer; its solubility decreases with an increase in temperature), the 2-hydroxypropylated β-cyclodextrins or HPBCD (the real advantage of this derivative over the methylated derivatives is the lower affinity for cholesterol binding), and the sulfobutylether-β-cyclodextrins or SBEBCD (Fig. 1.24).

Brauns and Müller (1983) and Pitha (1984) registered the first patents on 2-hydroxypropyl-β-cyclodextrin. This compound called hydroxypropylbetadex was the first commonly applied cyclodextrin derivative, used as pharmaceutical excipient in drug formulations in the 1990s (Szente and Strattan 1991). Rapidly, a monograph for this substance has been published in both the US Pharmacopeia and European Pharmacopeia (Brewster and Loftsson 2002, 2007; Brewster et al. 2004). Nowadays, 2-hydroxypropyl-β-cyclodextrin is the most versatile excipient among the cyclic oligosaccharides (Malanga et al. 2016). It can be used in oral, rectal, dermal, ocular, and parenteral formulations, and several pharmaceutical products are marketed, e.g., Indocid® (eye drop), Vorzu® (tablet for fungal infection), Strepfen® (oromucosal spray with flurbiprofen), Vibativ® (i.v. infusion with telavancin), and Lubion® (injection with progesterone as active ingredient). This substance is used as excipient and/or as active component, e.g., at the end of the 2000s, it was discovered that it had beneficial effects for patients in Niemann-Pick type C disease (Liu et al. 2009). Stella and Rajewski (1992) patented the sulfobutylether-β-cyclodextrin product as a potential alternate solubilizing excipient to 2-hydroxypropyl-β-cyclodextrin. This derivative, developed by CyDex under the brand name Captisol®, was found a more efficient complex-forming host than parent cyclodextrins with no apparent toxicity and very high water solubility. Captisol® became generic worldwide in 2011, e.g., Dexolve® developed by CycloLab Ltd. (Hungary). It is used not only as a solubilizing agent but also as an osmotic agent (Puskás et al. 2015).

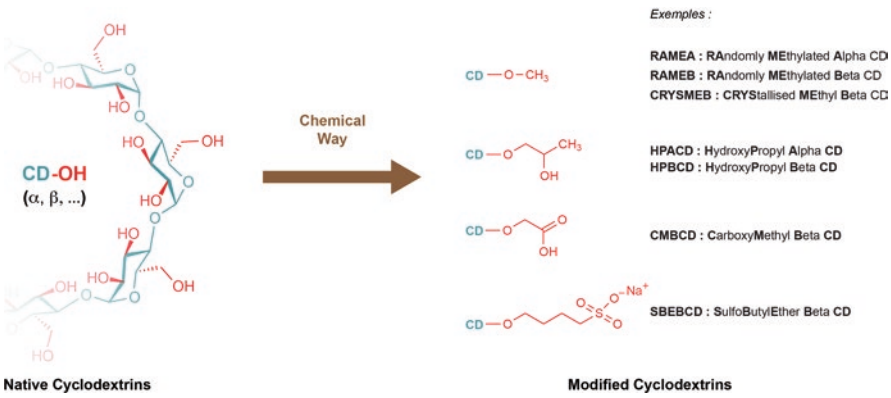


Fig. 1.24 Examples of modified cyclodextrins

In the last four decades, numerous cyclodextrin-based materials have also been synthetized. The list includes modified polymers obtained using grafting reactions (Crini and Morcellet 2002; Kozlowski and Sliwa 2010); cross-linked materials using reticulation or polymerization reaction, e.g., soluble or insoluble polymers (gels/hydrogels, beads, sponges) and fibers (Fenyvesi 1988; Armspach et al. 1999; Mocanu et al. 2001; Crini and Morcellet 2002; Crini 2005; Li 2009; Yang and Yang 2013; Aytac and Uyar 2017); functionalized materials prepared through coating or grafting such as silica beads, e.g., Cyclobond® columns, or resins (Crini and Morcellet 2002; Landy et al. 2012); and nanoporous frameworks containing cyclodextrins (Mahmud and Wilson 2016; Morin-Crini et al. 2018). These materials have been proposed for potential applications in pharmacy (Fenyvesi 1988; Van de Manakker et al. 2009; Muankaew and Loftsson 2018), chromatography (Ward and Armstrong 1988; Schneiderman and Stalcup 2000; Szejtli 2002; Vetter and Bester 2006; Xiao et al. 2012), electrophoresis (Fanali 1993; Chankvetadze 2004; Escuder-Gilabert et al. 2014), textile (Buschmann et al. 1998; Szejtli 2003; Buschmann and Schollmeyer 2004; Ammayappan and Moses 2009; Andreaus et al. 2010; Voncina 2011), supramolecular chemistry (Wenz 1994; Nepogodiev and Stoddart 1998; Schneider and Yatsimirsky 2000; Wenz et al. 2006; Schneider 2012; Zhang and Ma 2013), enzymology (Komiyama 1996; Villalonga et al. 2007; Sonnendecker and Zimmermann 2019a), food industry (Han 2005; Fenyvesi et al. 2016), and cosmetics (Buschmann and Schollmeyer 2002, 2004; Bilensoy 2011) and for environmental purposes (Gruiz et al. 2011; Morin-Crini et al. 2018; Crini et al. 2018).

1.4.10 The First Applications of Cyclodextrins

Table 1.4 shows selected historical landmarks in cyclodextrin fundamental science and applications during the period of their development, from 1970 to 1990. Since the 1990s, a large number of generalist reviews and book chapters have been published on

Table 1.4 Selected historical landmarks in cyclodextrin science during the period of their development, from 1970 to 1990

Period	Main fundamental result, achievement, or event	Reference(s)
1970	The first patent applications on cyclodextrin production at enhanced scale	Armbruster (1970)
1971	Powder X-ray diffractometry is a simple and useful method for the determination of cyclodextrin inclusion compounds in powder or microcrystalline states The diffraction pattern of an inclusion compound is clearly distinct from the superposition of each component if a true inclusion compound exists The first evidence of the possible formation of ternary complexes: a molecule, which alone does not form stable complexes with cyclodextrins, may be incorporated into the cavity when accompanied by another molecule, e.g., diethyl ether in presence of anthracene	Takeo (1971)
1972	In Hungary, Szejtli organized the cyclodextrin research laboratory which became, in 1987, the first private research institute for the technological transfer between cyclodextrin research and industry	Szejtli (1982a)
1973	The presence of two different forms of inclusion complexes in the crystalline state, i.e., channel and cage-type structures, is suggested	McMullan et al. (1973a, b)
1973	The Raman spectra of amylose and cyclodextrins are studied	Cael et al. (1973)
1973	Calorimetry is proposed to detect inclusion compound formation: thermodynamic parameters, enthalpy, and entropy changes can be obtained	Lewis and Hansen (1973)
1973	The interaction of α-cyclodextrin with certain phenol derivatives is enthalpy driven rather than entropy driven, unlike classical hydrophobic interactions which are characterized by a large positive entropy contribution	Griffiths and Bender (1973)
1975	Freeze-drying is proposed to prepare inclusion compounds in an industrial scale	Kurozumi et al. (1975)
1975	Preparation of Schardinger β-dextrin on an industrial scale by cyclodextrin glycosyltransferase of an alkalophilic *Bacillus sp*.	Matzuzawa et al. (1975)
1976	The precise geometry of an inclusion compound can be established by single-crystal X-ray structure analysis Introduction of the notion of the release of the tension energy within the cyclodextrin molecule upon formation of the complex A new concept is suggested for the first time: cyclodextrins are packed within a crystal lattice of one of two types, i.e., cage and channel structures, depending upon the size and characteristics of the guest molecules	Saenger (1976), Saenger et al. (1976)

(continued)

Table 1.4 (continued)

Period	Main fundamental result, achievement, or event	Reference(s)
1976	The first cyclodextrin-based pharmaceutical is marketed in Japan: Prostarmon E™ Ono Pharmaceutical Co. Japan authorizes the use of α-cyclodextrin and β-cyclodextrin as food additives	Szejtli (1977), Uekama and Hirayama (1978), Hirayama et al. (1980), Uekama and Otagiri (1987), Frömming and Szejtli (1994)
1977	A detailed 1H-NMR spectrum of α-cyclodextrin is given NMR data and computer simulation show that all six glucose units in α-cyclodextrin have identical conformations	Wood et al. (1977)
1977	Polarography is used to prove the formation of inclusion compounds with electroactive guests	Osa et al. (1977)
1978	Bender elucidates the mechanism of formation of the complexes developed by Saenger The complexation reaction involves a gain in enthalpy and a loss of entropy	Bender and Komiyama (1978)
1978	Japan permits the use of cyclodextrins in food products	Hashimoto (1996), Hedges (1998)
1978	Cyclodextrin inclusion compounds accommodate many water molecules in the lattice as crystal lattice These water molecules are involved in the formation of hydrogen bonding networks	Lindner and Saenger (1978)
1979	Circular dichroism spectroscopy is particularly useful to detect cycloamylose inclusion compounds in aqueous solution	Bergeron and McPhie (1979)
1980	The X-ray structural analysis of the cyclodextrin/iodine complex is detailed, showing that the iodine chain is slightly zigzag and discontinuous	Saenger (1980)
1980	The hydrolysis rate of some esters is accelerated between 10^6- and 10^7-fold by cyclodextrin if the reactive site of the guests is fixed in an optimum binding geometry with respect to the catalytic hydroxyl group of the host	Breslow et al. (1980)
1980	Two naphthalene molecules can be included within one γ-cyclodextrin cavity	Ueno et al. (1980)
1981	Three forms of hydrated α-cyclodextrin were comprehensively studied: the crystalline structures are classed in two categories, cages and channels, according to the overall appearance of the cavities	Chacko and Saenger (1981)
1981	A relationship between the position of the guests in the cavity and the changes in the ^{13}C chemical shift is proposed	Komiyama and Hirai (1981)
1981	Organization of the First International Cyclodextrin Symposium in Budapest	Szejtli (1982c)
1981	The first edible coating for food packaging	Hiroshi (1981)

(continued)

Table 1.4 (continued)

Period	Main fundamental result, achievement, or event	Reference(s)
1982	The nontoxicity of cyclodextrins by oral administration appears to be highly probable Modified cyclodextrins are interesting to improve the spatial complementarity of the host with respect to the guest and to extend molecular recognition processes	Szejtli (1982a)
1982	The detection of the inclusion compound formation using a potentiometric titration is proposed Cyclodextrins favor the non-ionized guest molecules with higher hydrophobicity, rather than the ionized ones	Connors et al. (1982)
1982	Cyclodextrin inclusion compounds in solution can be studied by Raman spectroscopy	Higuchi et al. (1982)
1983–1985	Patents on 2-hydroxypropyl-β-cyclodextrin	Brauns and Müller (1983), Pitha (1984)
1983	The Hungarian Ministry of Health approves the use of β-cyclodextrin for stabilization of natural flavors	Szejtli (1984)
1984	The strength of interaction varies with the shape of the guest: the guests that fit the cavity best give the most stable compounds Crystal structures of complexes show that, in the case of a polar guest, hydrogen bond formation stabilizes the orientation According to neutron diffraction data, water molecules are involved in the formation of hydrogen bonding networks between host/host, host-guest, or each other with a definite regularity, i.e., circular or flip-flop hydrogen bonds, to stabilize the packing modes	Saenger (1984)
1984	The first chromatographic columns are marketed	Armstrong (1984), Ward and Armstrong (1986)
1984	Szejtli demonstrated the nontoxicity of cyclodextrins by oral administration	Szejtli (1984)
1984	Cyclodextrins are extensively hydrolyzed in the human colon: the products of hydrolysis include glucose and maltooligosaccharides	Antenucci and Palmer (1984)
1988	Piroxicam-β-cyclodextrin tablets marketed by Chiesi Farmaceutici, Italy	Szejtli (1977), Uekama and Otagiri (1987), Frömming and Szejtli (1994), Hashimoto (1996)

practically all the aspects of cyclodextrins, so many that it would not be feasible to cite them all. In this section, we chose to highlight selected works on the first applications of cyclodextrins. A recent review on this topic can be found in the review by Crini et al. (2018) who summarized the literature published in the last four decades. Readers interested in cyclodextrin applications should also refer to the library database "Cyclodextrin News" from CycloLab Ltd., Hungary.

Cyclodextrins have been used in pharmaceutical industry since the 1970s (Szejtli 1977; Uekama and Hirayama 1978; Uekama and Otagiri 1987; Frömming and Szejtli 1994). With a more accurate picture of their toxicity and better

understanding of molecular encapsulation, several inclusion complexes appeared on the market (Davis and Brewster 2004; Brewster and Loftsson 2007).

In 1976, the first product, i.e., prostaglandin E2/β-cyclodextrin Prostarmon E™ sublingual tablet, was marketed in Japan (Ono Co.) (Uekama and Hirayama 1978; Hirayama et al. 1980). Prostaglandin E2, a substance with potent oxytocin-like effects, was of interest as a possible agent for the induction of labor in childbirth (Davis and Brewster 2004). However, this substance was highly unstable, and this feature complicated its formulation and development. The solution was to encapsulate it using β-cyclodextrin, resulting in a significant increase in its solid-state stability. This led to spectacular progress in pharmaceutical domain. The second prostaglandin marketed was Prostavasin®, a complex between prostaglandin E1 and α-cyclodextrin. In 1979, this product was approved for the treatment of peripheral vascular complications. Uekama's group studied the molecular motions of prostaglandin $F_{2\alpha}$-cyclodextrin inclusion compounds (Uekama and Hirayama 1978; Hirayama et al. 1980; Uekama et al. 1984). As a consequence of the inclusion, the internal motion of the ϖ-side alkyl chain of the prostaglandin is selectively reduced by α-cyclodextrin, while the internal motion around the five-membered ring, as well as the overall motion, is decreased by β-cyclodextrin. In the case of the γ-cyclodextrin inclusion compound, total motion of the prostaglandin is reduced. The inclusion of prostaglandin E_1 in γ-cyclodextrin increased its heat stability and slowed down its conversion to prostaglandin A_1 (Uekama et al. 1984). The structures proposed by Uekama's group and illustrated in Fig. 1.25 were demonstrated using NMR data (Uekama and Hirayama 1978; Hirayama et al. 1980).

Another interesting formulation was the complex β-cyclodextrin/piroxicam, used, e.g., in the treatment of acute pain of rheumatic disease. In 1988, Chiesi Farmaceutici, Italy, has put on the market this complex Brexin® or Cycladol® (Fig. 1.26). Nine years later, the first US-approved product, 2-hydroxypropyl-β-cyclodextrin/itraconazole oral solution (Sporanox® Janssen), was introduced (Fig. 1.26). Itraconazole is an orally active triazole antifungal agent to inhibit most human fungal pathogens but is practically insoluble in water at physiological pH. In 2002, two formulations containing sulfobutylether β-cyclodextrin were introduced by Pfizer in the USA and Europe: an intravenous formulation of the antifungal agent voriconazole (Vfend®) and an intramuscular dosage form for the antipsychotic agent ziprasidone (Geodon®).

All these formulations are preformed prior to be administrated. There are also some cases when the complexes are formed within the body. The best-known example is the one containing the active compound sugammadex (Bridion®): it is a modified γ-CD used as an antidote to certain curare-like muscle relaxants in anesthesia since 2008. After intravenous administration, it neutralizes steroid curare-like agents such as rocuronium and vecuronium by forming an inactive complex (Fig. 1.26) in the plasma which is then eliminated in the urine.

Actually, more than 80 pharmaceutical products can be found (CycloLab Ltd., Hungary). In these formulations, native cyclodextrins and their derivatives, such as the hydroxypropyl derivatives of β- and γ-cyclodextrins, sulfobutylether β-cyclodextrin, and maltosyl-β-cyclodextrin (this derivative might be a component of several drugs

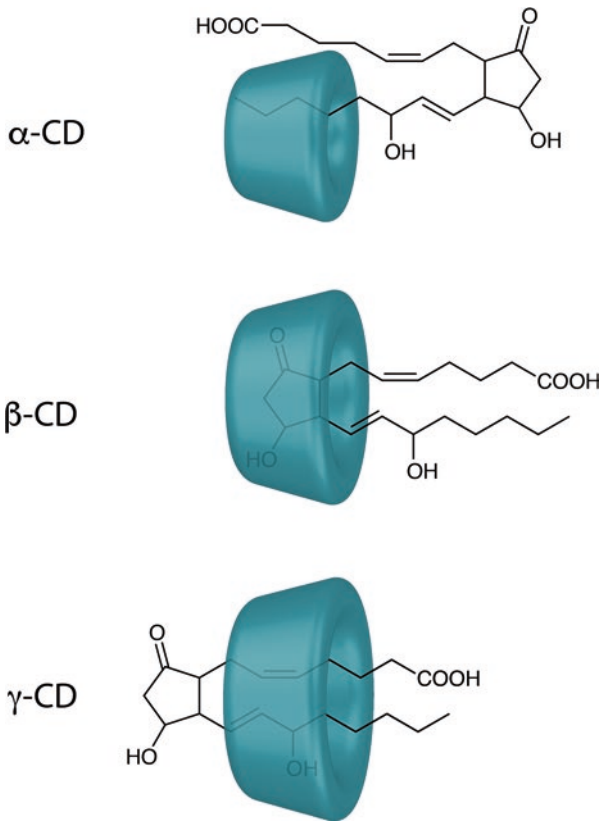


Fig. 1.25 Inclusion mode of cyclodextrin-prostaglandin $F_{2\alpha}$ inclusion compounds in aqueous solution. (Adapted from Uekama and Hirayama (1978) and Hirayama et al. (1980))

marketed in Japan, but information are scarce), are mainly used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs, to increase their stability and bioavailability. Cyclodextrins are also used to replace organic solvents in parenteral and topical formulations, to reduce gastrointestinal irritation, and to increase dermal availability of drugs. Initially, cyclodextrins were mainly used in solid dosage forms for oral administration, but rapidly, other administration routes were proposed such as ocular, nasal, parenteral, rectal, or dermal route. For instance, RAMEB is included in Clorocil® eye drop (Oftalder, Portugal) and Aerodiol® nasal spray (Servier, France). Both are non-parenteral, and the latter was withdrawn from the market because of economic reasons.

Food applications also started to appear in the mid-1970s. Japan authorized the use of cyclodextrin as a food additive in 1976 (Szejtli 1982a, 1998; Vaution et al. 1987; Hedges et al. 1995; Hashimoto 1996; Hedges 1998). Powdered flavors, e.g., apple and citrus fruits; spices, e.g., horseradish wasabi and mustard; and herbs such as peppermint were marketed. Other marketed food products containing cyclodextrins or made by cyclodextrin-aided technology included chocolate (Choco Bar™), chewing gum

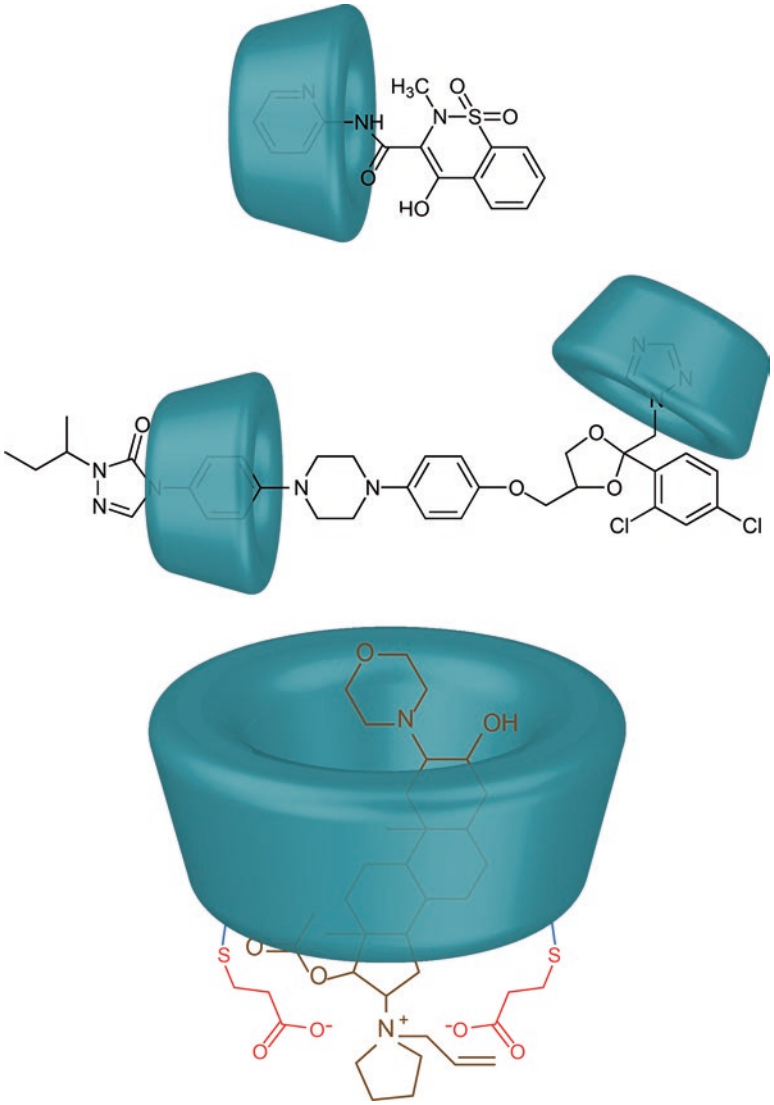


Fig. 1.26 β-cyclodextrin/piroxicam (top), 2-hydroxypropyl-β-cyclodextrin/itraconazole (middle), and sugammadex/rocuronium (bottom) complexes

(Flavono™), powdered green tea (Stick Lemon™), and dietary fibers (Hedges 1998; Hashimoto 2002). In 1992, low-cholesterol butter, prepared by mixing cyclodextrin with the melted butter, under the trade name of Balade™ was marketed in Belgium (Comini and Mentink 1991). Other low-cholesterol milk products such as cheese (Natual™, France), cream, and egg (Simply Eggs™, USA) were produced. Other examples include bubbling coffee (Nescafé®, Nestlé), beer (FlavorAktiv™, Great

Britain), and supplements. In the 2000s, the three native cyclodextrins were introduced into the generally regarded safe list of the US Food and Drug Administration for use as a food additive (Hashimoto 2002). Now the food industry, along with the pharmaceutical domain, is one of the sectors that consumes the most cyclodextrins, at least in Japan.

Hinze (1981) was the first to describe the application of cyclodextrins in analytical chemistry, focusing on their use in chromatography and purification methods. At that time, the first studies had established that cyclodextrins were interesting complexing agents, chiral selectors, and/or additives in chromatography (Smolková-Keulemansová and Krysl 1980; Hinze 1981; Smolková-Keulemansová 1982; Sybilska and Smolková-Keulemansová 1984; Krysl and Smolková-Keulemansová 1985; Li and Purdy 1992). Cyclodextrins were first proposed for thin-layer chromatography, gel electrophoresis, gas chromatography, and liquid chromatography and later for capillary electrophoresis, electrokinetic chromatography, and dialysis (Armstrong 1980, 1984; Smolková-Keulemansová and Krysl 1980; Smolková-Keulemansová 1982; Hinze 1981; Cserhati et al. 1983; Ward and Armstrong 1986; Li and Purdy 1992; Fanali 1993; Fanali et al. 1994; Schneiderman and Stalcup 2000). The first cyclodextrin-based chiral gas chromatography was published by Smolková-Keulemansová (1982).

At the beginning of the 1980s, Armstrong laid down the fundamentals of cyclodextrin-assisted separation science. Between 1980 and 1988, Armstrong and his collaborators pioneered the development and optimization of analytical methods suitable for cyclodextrin-based isomer separation. In 1984, the first chromatographic columns were marketed (Advanced Separation Technologies Inc., Whippany, NJ), and this led to spectacular progress in chromatography (Armstrong 1980, 1984; Hinze 1981; Ward and Armstrong 1986, 1988; Armstrong and Jin 1989; Han and Armstrong 1989; Menges and Armstrong 1991). These chromatographic packings consisted of cyclodextrin molecules linked to silica gel via a 6–10-atom spacer. Both the linkage and the cyclodextrin were hydrolytically stable under high-performance liquid chromatography. Easily the most popular cyclodextrin-based stationary phases were based on β-cyclodextrin, e.g., they have been shown to be very effective at resolving the enantiomers of many compounds. Subsequently, other stationary phases were developed, based on other native cyclodextrins, e.g., α- and γ-cyclodextrin, or derivatized cyclodextrins such as naphthyl-ethyl-carbamate derivative. The α-cyclodextrin and γ-cyclodextrin columns, while less broadly applicable in the reversed-phase mode than the β-cyclodextrin columns, were useful for specific applications such as the separation of enantiomers of underivatized aromatic amino acids and substituted analogues or of polycyclic aromatic compounds and steroid stereoisomers. The aromatic-derivatized cyclodextrin phases were used to separate the enantiomers of many classes of compounds including pesticides, biological compounds, drugs, and amino acids (Menges and Armstrong 1991; Mitchell and Armstrong (2004). The chiral recognition mechanisms in analytical separation sciences were reviewed by Scriba (2012). Li and Purdy (1992) and later Szente and Szemán (2013) comprehensively reviewed the application of cyclodextrins in diverse fields of analytical chemistry and covered the structural aspects of

cyclodextrins that enabled the improvement of different chromatographic separations.

The first comprehensive review on potential applications in cosmetology, toiletry, and hygiene has been published by Szejtli (1982b). This topic was later updated by Vaution et al. (1987), Hashimoto (1996, 2006), Citernesi and Sciacchitano (1995), Buschmann and Schollmeyer (2002), and Duchêne et al. (2009). In the mid-1980s, some products appear in the market although the cyclodextrins were often used without any indication of their precise role: Epicutin® TT, Chemishes Laboratorium Dr Kurt Richter, a complex between cyclodextrin and *Melaleuca alternifolia* leaf oil, used in skin care applications; Vivace®, Shiseifo Co., a powder cologne; Klorane®, Klorane Laboratories, a dry shampoo; Novoflex®, Revlon, a vitamin shampoo; Eucerin® Vital Active, Beiersdorf, a vitamin A cream; etc. In the cosmetic industry, cyclodextrin complexes were useful for modifying solubility, improving stabilization, transforming liquids into solids, preserving color, decreasing an unpleasant smell, or diminishing the odor of mercaptan used in permanent hair preparations. Cyclodextrins were used as empty capsules in dry shampoos to eliminate fatty substances such as sebum, or in toothpaste and mouthwash to remove undesirable odors (Duchêne et al. 2009).

In the 1980s, applications were found in textiles including textile finishing and functional textiles (Szejtli 1985; Hashimoto 1996; Buschmann and Schollmeyer 2002). The permanent fixation of cyclodextrin molecules offered textiles with interesting properties, e.g., the formation of body odor was reduced by the complexation, the release of perfumes from cyclodextrins was possible, etc. The first cellulose-cyclodextrin copolymer was described in 1980 by Szejtli's group. Alkali-swollen cellulose fibers were reacted with epichlorohydrin. The chemically bound cyclodextrin retained its complex-forming ability and could be loaded with chemically and/or biologically active guests such as perfumes to prepare perfumed textiles or drugs to prepare medical bandages (Szejtli et al. 1980b). For instance, Fig. 1.27 illustrates a guest exchange by a cellulose fiber containing cyclodextrin. The process consists to load the fixed cyclodextrin molecules with perfume molecules. During wearing and by sweat humidity, excreted short-chain fatty acids displace and release the perfume molecules and will be in turn entrapped (Szejtli 2003). Procter & Gamble recognized that similar effects can be achieved without chemical fixation by simple spraying of hydroxypropyl-β-cyclodextrin solution on the fabric. This odor-eliminating spray (Febreze®) has become a great success in the USA marketed since 1998 ensuring a continuous demand for cyclodextrin production. Actually, cyclodextrins play an important role in the textile industry as a tool to remove odors, e.g., encapsulation of sweat or cigarette smoke components permits to reduce the intensity of odors of clothing or furniture textiles, as showed in Fig. 1.28. The mechanism of drug release is similar from medical textiles such as antimicrobial textiles for wound dressing (Aubert-Viard et al. 2019), intraperitoneal meshes (Chai et al. 2019), and other implants (Vermet et al. 2017). CycloMesh™, a polyester visceral implant soaked in ropivacaine hydrochloride developed for slow anesthetic release and in situ activity after inguinal hernia surgery, will be soon subjected to clinical trials in France.

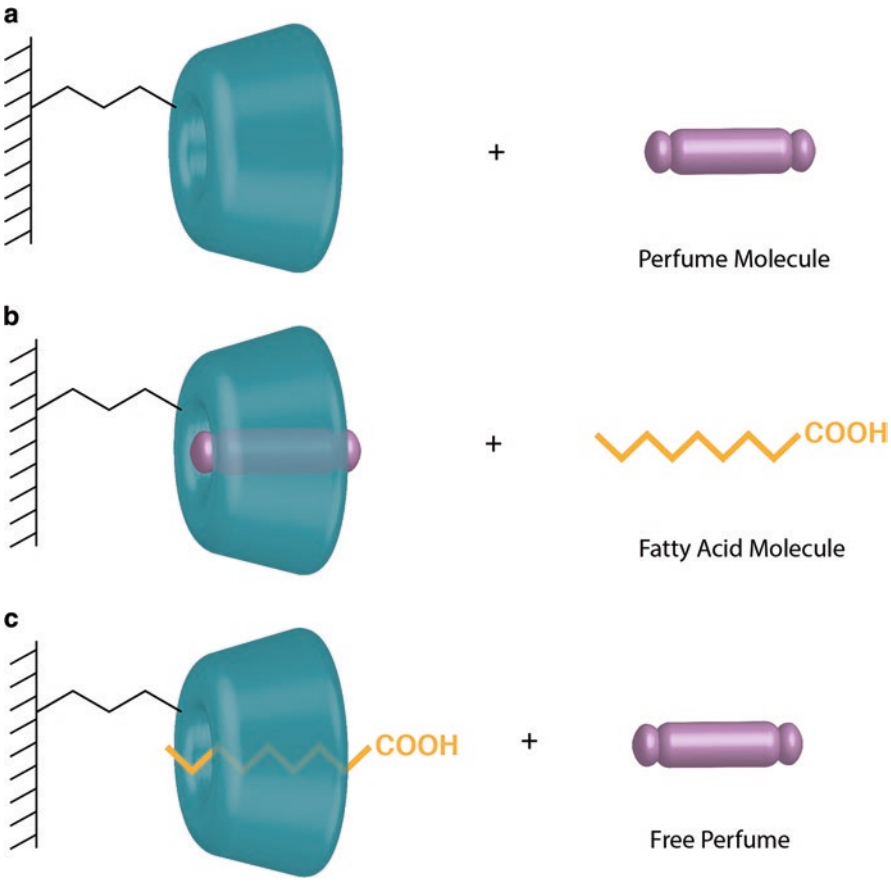


Fig. 1.27 Guest exchange by a cellulose fiber containing cyclodextrin: the process consists to load the fixed cyclodextrin molecules with perfume molecules; then during wearing and by sweat humidity, excreted short-chain fatty acids displace and release the perfume molecules and will be in turn entrapped. (Adapted from Szejtli 2003)

During the period from 1980 to 1990, manufactured products using cyclodextrins have emerged such as pesticide formulations, reproduction processes, e.g., photography and inks, tobaccos, corrosion inhibitors, industrial detergents, sterilizing agents, anti-foam agents, glues, wood treatment, etc. (Szejtli 1982a, 1984, 1988; Vaution et al. 1987). In the agricultural sector, the use of complexation by cyclodextrins has facilitated the formulation of pesticides in many ways, e.g., by enhancing water solubility and biological activity, through stabilization of labile substances, by enabling easier handling of hazardous substance, and also through the formation of crystalline substances from volatile liquids. An important feature of the cyclodextrin-formulated pesticides is the water-triggered release of the active compounds. A large number of patents concerning the use of cyclodextrins in agrochemistry were filled (Szejtli 1982a, 1984; Szente and Szejtli 1996; Morillo 2006).

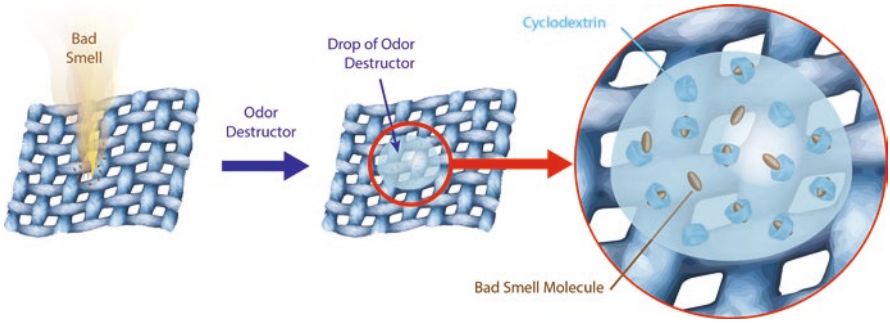


Fig. 1.28 Elimination of odors by a textile fiber containing cyclodextrin molecules either permanently fixed by chemicals bonds or just adsorbed on the fibers

1.4.11 Cyclodextrins: Trends and Outlook

Although an important number of works, patents, and products have been realized, the sector of cyclodextrin-based pharmacy continues to interest the scientific community. Cyclodextrins are still regarded as "novel" excipients, active ingredients, drug delivery vehicles, and anti-aggregation agents (Conceição et al. 2018). New formulations continue to be reported, generating new interests in medicine and biomedicine (Higashi et al. 2018; Higashi 2019; Menezes et al. 2019; Pawar and Shende 2019). The 18 ongoing clinical trials in 2019 give the promise of new marketed formulations (Cyclodextrin News, CycloLab Ltd., Hungary).

The recent research has clearly revealed that cyclodextrins cannot be considered inactive excipients any more (Arima et al. 2017). Hydroxypropyl-β-cyclodextrin was found by serendipity to be useful for slowing down the progression of Niemann-Pick type C disease, the fatal genetic disorder. Based on the promising results of the clinical trials, this cyclodextrin received orphan drug status both from Food and Drug Administration and European Drug Agency. The mechanism of action which was thought first to be based on cholesterol complexation is still under debate.

Yokoo et al. (2015) demonstrated that hydroxypropyl-β-cyclodextrin was a potential anticancer agent in leukemia. This derivative was found effective in inhibition of leukemic cell proliferation at various leukemic cell lines. It was proved to influence autophagy, a catabolic process with an essential function in the maintenance of cellular and tissue homeostasis. As solubilizing agent to increase cholesterol solubility, hydroxypropyl-β-cyclodextrin is used for prevention and treatment of atherosclerosis, a chronic inflammatory disease driven primarily by a continuous retention of cholesterol within the subendothelial space to hinder its precipitation in the form of cholesterol crystals (Zimmer et al. 2016).

Several research groups are developing special cyclodextrin derivatives with various functions, for instance, for targeted drug delivery. Folate-appended cyclodextrins are recognized by folate-receptor-expressing tumor cells; therefore they can be utilized as potent anticancer agents (Motoyama et al. 2015). Lactosyl-β-cyclodextrin

was found effective for hepatomegaly in Niemann-Pick type C disease (Maeda et al. 2019). Cyclodextrins decorated with a photosensitizer group can be used for drug delivery in phototherapy where the release of active ingredients is controlled by light (Benkovics et al. 2017). Multifunctional cyclodextrin derivatives having nitric oxide-releasing moiety in addition to the photosensitizer are efficient antimicrobial and anti-tumor agents in photodynamic therapy (Malanga et al. 2019). Many bacteria display mannose-binding lectins on their surfaces, and so mannosylated cyclodextrins are target-specific antimicrobial delivery systems to be used in fighting against antimicrobial resistance (Cutrone et al. 2018).

Another direction of recent cyclodextrin research is the design and synthesis of specific cyclodextrins tailored to the guest molecules to be entrapped. Encouraged by the extreme success of sugammadex tailored for encapturing rocuronium muscle relaxant, further cyclodextrin-based detoxicants were prepared: e.g., a cyclodextrin dimer as antidote for cyanide poisoning (Yamagiwa et al. 2014), another dimer designed for binding and removal of bisretinoid lipofuscins from the eye to prevent aging-related blindness (Nociari et al. 2014), and specially substituted cyclodextrins to catalyze the decomposition of organophosphorus chemical weapons getting importance in view of increasing terrorist threat (Müller et al. 2013). Even the social media shared the news on methyl- and hydroxypropyl-β-cyclodextrins as possible antidotes to box jellyfish venom (Lau et al. 2019). Similarly, quaternary amino β-cyclodextrin was found to bind ochratoxin A, a widely spread nephrotoxic contaminant mycotoxin, with an association constant more than 200-fold higher than that of β-cyclodextrin, making this derivative useful for decontamination of ochratoxin A-contaminated drinks (Poór et al. 2015).

Actually, fundamental research is also focusing on cyclodextrin-based nanoparticles/nanomaterials for pharmaceutical and biomedical applications and nanomedicine, e.g., molecular diagnosis, medical imaging, antifungal treatment, antimicrobial therapy, gene therapy, or tissue engineering, and on self-association of cyclodextrins for applications not only for formulation and drug delivery, and medicine, but also for materials science, supramolecular chemistry, and asymmetric catalysis (Hirakawa and Tomita 2013; Morohoshi et al. 2013; Zhang and Ma 2013; Chilajwar et al. 2014; Melotti et al. 2014; Simoes et al. 2014; Dong et al. 2015; Macaev and Boldescu 2015; Mavridis and Yannakopoulou 2015; Miller et al. 2015; Perez-Anes et al. 2015; Wu et al. 2015; Brackman et al. 2016; Junthip et al. 2016; Okano et al. 2016; Oliveri and Vecchio 2016; Ryzhakov et al. 2016; Sharma and Baldi 2016; Silva et al. 2016; Yuan and Zhang 2016; Saokham and Loftsson 2017; Egele et al. 2019; Fenyvesi et al. 2019; Hammoud et al. 2019; Kumar and Rao 2019; Neva et al. 2019; Pawar and Shende 2019; Topuz and Uyar 2019; Zhang et al. 2019a).

Nanoparticles of various compositions have been engineered in ever smaller sizes to function in both diagnostic and therapeutic capacities. They are available on a scale similar to many biological molecules and infectious agents, thereby opening the possibility of biological intervention on the molecular level (Gilmore and Colson 2011). Nanoparticle-based systems can improve bioavailability, reduce immunogenicity, modify drug metabolism, reduce toxicity, and increase the biological half-life of drugs after systemic administration. The use of cyclodextrin-based

nanoaggregates both in oral and ophthalmic drug delivery could be a promising strategy to improve the bioavailability of poorly soluble drugs (Loftsson and Stefansson 2017; Kumar and Rao 2019). Nanomaterials are also interesting because they can be formulated as oral, parenteral, topical, or inhalation dosage forms (Chilajwar et al. 2014). They can be targeted by using specific components and/or moieties, e.g., antibody-targeted cyclodextrin-based nanoparticles were developed for siRNA delivery in the treatment of myeloid leukemia (Guo et al. 2017). Various innovative ideas for the purpose-oriented design of such systems have been published, e.g., "ship-in-a-bottle" (Xu et al. 2019), modern Trojan horse (Gilmore and Colson 2011), and molecular Lego approach for the diversity-oriented synthesis of cyclodextrin analogues as scaffolds for multivalent systems (Lepage et al. 2015). Promising developments for nanoparticles are under way in emerging domains such as nutraceuticals and cosmeceuticals (Fenyvesi et al. 2016; Adeoye et al. 2017). Further contributions are also expected in the near future in bacterial resistance and chemotherapy (Carneiro et al. 2019; Zhang et al. 2019b).

Recently, Higashi et al. (2018) introduced a new concept in pharmaceutical sciences termed "supramolecular pharmaceutical sciences" which combines pharmacy domain and supramolecular chemistry. This concept is focused on the development of cyclodextrin-based supermolecules, such as polyspeudorotaxanes, polyrotaxanes, polycatenanes, and daisy chains, as active pharmaceutical ingredients used, for instance, against Niemann-Pick type C disease, leukemia, Alzheimer's disease, chronic renal failure, or sterility. These biodegradable polyrotaxanes ensure longer residence time and slow release of the cyclodextrin – mostly hydroxypropyl-β-cyclodextrin – as active ingredient. The low local concentrations result in reduced toxicity even in the case of the methylated derivatives.

The number of publications on the use of nanofibers containing cyclodextrins, e.g., prepared by electrospinning, is also growing (Celebioglu and Uyar 2012, 2013; Aytac et al. 2015, 2016; Topuz and Uyar 2019). These nanofibers are proposed as innovative products for medicine, biomedicine, and nanomedicine applications, e.g., for medical devices, tissue engineering scaffolds, stents, prosthesis, and bone implants. Most of these studies are in the proof-of-concept stage, and only a few therapeutic nanosystems/nanomaterials have been comprehensively investigated. Nanofibers are also proposed for textile and environmental applications (Celebioglu et al. 2016), e.g., innovative clothing, filtration media, and membranes.

The use of cyclodextrins for veterinary purposes seems to be a promising domain (Chiu et al. 2016). New formulations continue to be reported, e.g., Itrafungol™, Voriconazole Dexolve™, Nexterone™, Cereni™, Vetmedin™, Suvaxyn™, etc. Itrafungol™ is an antifungal containing 2-hydroxypropyl-β-cyclodextrin used as antimycotic drug in oral form in cats. Another example is Voriconazole Dexolve™, a commercial formulation containing sulfobutylether-β-cyclodextrin as an excipient, used as an antimycotic drug for veterinary and human use. Suvaxyn™ containing a sulfolipo-cyclodextrin as adjuvant is used as vaccine for the active immunization of pigs.

The global market of cyclodextrins used in food industries is continuously increasing (Fenyvesi and Szente 2016; Fenyvesi et al. 2016). The main application

is the stabilization of flavors and aromas. α-Cyclodextrin, being non-digestible, is recognized a dietary fiber with beneficial effects on digestion of fat and carbohydrates (Artiss et al. 2006). It has been marketed for body weight control in several countries. Further studies and industrial developments are expected in the near future in the following domains: functional food, nutritional supplements, nutraceuticals, wrapping materials, and packaging. One of the most promising functional food groups is those enriched in antioxidant compounds of a lipophilic nature (Fenyvesi and Szente 2016; Kfoury et al. 2016; Zarzycki et al. 2016).

Other applications have been reported in sectors such as supramolecular catalysis (Hapiot et al. 2014; Chen et al. 2019; Fernandez et al. 2019), asymmetric and stereospecific synthesis (Macaev and Boldescu 2015), click chemistry (Celebioglu et al. 2016; Hou et al. 2016), metal-organic frameworks (Rajkumar et al. 2019), agrochemistry (Campos et al. 2015; Yusoff et al. 2016), supercritical fluid chromatography (Xiao et al. 2012; West 2014), imprinting techniques (Lay et al. 2016), nanofibers (Topuz and Uyar 2019), and environment (Taka et al. 2017; Crini et al. 2018).

Research on cyclodextrins is also very active in fields such as the formulation of detergents and sugar-based surfactants (Valente and Söderman 2014), glues and adhesives (Osaki 2019), silicon industry (Grachev et al. 2019), flame-retardant formulation (Luda and Zanetti 2019), the sector of plastics for packaging or for automotive (Szente and Fenyvesi 2018), the industry of fibers and paper, soil remediation (Atteia et al. 2013; Lau et al. 2014; Madrid et al. 2019; Gruiz et al. 2019), materials for wastewater treatment (Cova et al. 2018; Morin-Crini et al. 2018; Barbosa et al. 2019), biodiesel production (Zhang et al. 2018), and hydrogen storage (Han et al. 2018).

The slide ring gels (polyrotaxane gels) found their application in the car industry and telecommunication (Ito 2017; Kashiwagi et al. 2018; Jiang et al. 2018). There are also many possibilities for the development of new textiles and cosmetic products, called cosmetotextiles (Singh et al. 2011), with advanced properties (Shende and Trotta 2019; Yao et al. 2019). Their applications seem promising.

Cosmeceuticals containing cyclodextrins also seem to be a promising domain for medicine, dermatology, and aromatherapy (Adeoye et al. 2017; Kaur et al. 2018). These products are cosmetics with pharmaceutical and therapeutic benefits.

1.5 Conclusion

In this chapter, we described historical landmarks of the discovery, exploration, and utilization of cyclodextrins, cyclic oligosaccharides obtained from the enzymatic degradation of starch and discovered serendipitously in 1891 by Villiers. Of course, this historical chapter cannot hope to be exhaustive, but it highlighted the work of those researchers who have contributed to the knowledge of cyclodextrins throughout the 129 years of its history.

Expensive to produce, the three main native cyclodextrins, i.e., α-, β-, and γ-cyclodextrins, were long considered just laboratory curiosities. Until the mid-1970s, the main obstacles were the lack of sufficient knowledge of these molecules, their high price, and also their presumed toxicity. In addition, very few researchers were convinced of the industrial potential of cyclodextrins.

As reported in this comprehensive chapter, since Villiers' discovery, several great scientists, including Schardinger, Freudenberg, Cramer, French, and Szejtli, have left their mark on the history, characterization, properties, and potential applications of these molecules over a period of 86 years, from 1903, i.e., the first paper on cyclodextrin chemistry published by Schardinger, to 1989, i.e., the creation by Szejtli of the first company totally devoted to cyclodextrins.

Since the 1980s, cyclodextrins have considerably attracted the interest of scientists and industries in different disciplines including health science, agriculture, chemistry, biochemistry, and environment. The main reason for this growing interest was their ability to form inclusion complexes with various molecules through host-guest interactions.

Today, cyclodextrins continue to offer new horizons to scientists and industrials with a wide range of possible modifications and forms for multiple classical, e.g., pharmacy, food industry, chromatography, cosmetology, and biotechnology, and emerging, e.g., biomedicine, agrochemistry, and nanomaterials, applications.

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Chapter 2
Professor József Szejtli: The Godfather of Cyclodextrins

Grégorio Crini, Éva Fenyvesi, and Lajos Szente

Contents

G. Crini (✉)
Chrono-environnement, UMR 6249, UFR Sciences et Techniques, Université Bourgogne Franche-Comté, Besançon, France
e-mail: gregorio.crini@univ-fcomte.fr

É. Fenyvesi · L. Szente
CycloLab Cyclodextrin Research & Development Ltd, Budapest, Hungary
e-mail: fenyvesi.e@cyclolab.hu; szente@cyclolab.hu

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_2

Abstract Cyclodextrins, natural oligosaccharides obtained from starch by enzymatic degradation, have been discovered more than 129 years ago by the pioneering work of the French pharmacist and chemist Antoine Villiers. These molecules still fascinate researchers and industrials because they are remarkable macrocyclic molecules with major impacts in chemistry, biology, and health science.

When we look at cyclodextrin chemistry today and reflect on how it has developed over the last five decades, no other scientist has been more determining, focused, and inspiring than Professor József Szejtli. Indeed, among the list of prestigious researchers who have contributed to the development of cyclodextrins, Professor Szejtli played a fundamental role as eminent scientist and visionary. Since the mid-1950s, he has devoted his life to cyclodextrins, publishing more than 500 publications, including 106 patent applications. Professor Szejtli knew virtually everything about them. He was most likely the first to believe in the possibilities of industrial production and the multiple applications of cyclodextrins. Professor Szejtli was also an ambitious entrepreneur, creating in 1989 CycloLab Ltd., an independent company totally devoted to cyclodextrins. He is internationally recognized for his outstanding contribution to the cyclodextrin science and considered to be the "Godfather of Cyclodextrins."

This chapter is a tribute to his scientific oeuvre. Firstly, we give a general overview of his outstanding career. Secondly, we have chosen to highlight some of the important works published by Professor Szejtli in more than 50 years of career.

Keywords Tribute · Professor Szejtli · Production · Native cyclodextrins · Cyclodextrin derivatives · Structure · Inclusion complexes · Foods · Cosmetics · Chromatography · Catalysis · Biotechnology · Industry · Awards and distinctions

2.1 Introduction

Cyclodextrins, natural oligosaccharides obtained from starch by enzymatic degradation, were discovered serendipitously in 1891 by the French pharmacist Villiers (Villiers 1891; Cramer 1954; French 1957; Thoma and Stewart 1965; Caesar 1968; Szejtli 1982a; Clarke et al. 1988). However, expensive to produce, the three main native cyclodextrins, i.e., α-, β-, and γ-cyclodextrins, were long considered just laboratory curiosities (Szejtli 1998; Loftsson and Duchêne 2007; Crini 2014). Indeed, until the mid-1970s, the main obstacle was not only their price but also their presumed toxicity (French 1957). Another factor traditionally stood in the way of industrial development was the lack of sufficient knowledge of these molecules. In addition, very few researchers were convinced of the industrial potential of cyclodextrins (Szejtli 1982a; Duchêne 1987; Hedges 1998; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

Native cyclodextrins were only produced on an industrial scale after 1979 (Szejtli 1982a, 1988a; Duchêne 1987, 1991), and they only really took off in the 1980s with the

first applications in the chromatography, pharmaceutical, and food industries (Saenger 1980; Smolková-Keulemansová 1982; Szejtli 1982a; Uekama and Otagiri 1987; Armstrong and Jin 1989; Li and Purdy 1992; Hedges 1998; Crini 2014). With a more accurate picture of their toxicity and better understanding of molecular encapsulation, several inclusion complexes also appeared on the market in the 1980s. The introduction of cyclodextrins into pharmaceutical chemistry led to spectacular progress (Szejtli 1988a, 1998; Duchêne 1991; Uekama et al. 1994; Duchêne and Wouessidjewe 1996; Loftsson and Brewster 1996; Stella and Rajewski 1997; Irie and Uekama 1997).

Several great scientists have left their mark on the history, characterization, properties, and potential applications of these molecules (Crini 2014), e.g., Antoine Villiers from France, Franz Schardinger from Austria, Hans Pringsheim, Karl Freudenberg, Friedrich Cramer, and Wolfram Saenger from Germany, Paul Karrer from Switzerland, Dexter French, Myron L. Bender, Ronald Breslow, and Joseph Pitha from the USA, Benito Casu from Italy, and Tsuneji Nagai from Japan. The list of prestigious researchers who have contributed to the development of cyclodextrins also includes József Szejtli (Fig. 2.1), a Hungarian carbohydrate chemist.

In the mid-1950s, the young Szejtli studied chemical engineering at Technical Sciences of Budapest where he obtained his PhD in starch chemistry in 1961. He also started to study cyclodextrins but published his first results in the 1970s. In the mid-1970s, Professor Szejtli developed cyclodextrin technology in Hungary. He had many varied scientific, technological, and industrial interests in their development.

Professor Szejtli summed up his feelings in the following way: “A starch derivative can be a multifunctional auxiliary agent of real industrial significance” (Szente 1994). At that time, the nontoxicity of cyclodextrins became increasingly accepted, and several manufacturers such as Hungarian Chinoin Pharmaceutical Chemical Works, Japanese Nihon Shokukin Kako, and German Wacker Companies started to produce and to market cyclodextrins.

Professor Szejtli was most likely the first to believe in the possibilities of industrial production and the multiple applications of cyclodextrins (Szente and Fenyvesi 2016; Szente et al. 2016). He believed that cyclodextrins were “cheap, nontoxic, useful, and versatile molecules,” when nobody else believed it (Szente and Fenyvesi 2016).

Fig. 2.1 Professor József Szejtli. (Image credit: CycloLab)

At the beginning of the 1970s, the work on cyclodextrin research started in the Biochemical Research Laboratory of Chinoin. This lab became an independent unit in 1989, and then Professor Szejtli created CycloLab, a private company totally devoted to cyclodextrins. Indeed, he was not only an engineer and academic, occupying a central place in the scientific knowledge of cyclodextrin, but also an entrepreneur and businessman. In the 1980s, Professor Szejtli made an important contribution to chemistry of cyclodextrins, to the dissemination of results and in their industrial applications.

Over a period of 30 years, from 1975 to 2004, Professor Szejtli published more than 500 publications on cyclodextrins and has given more than 200 invited lectures throughout his career. In particular, numerous significant and comprehensive reviews were published on their fundamentals, properties, and applications. His name is very often cited in the bibliographic references of articles speaking of cyclodextrins.

Professor Szejtli is internationally recognized and considered as an eminent scientist and visionary, the "Godfather of Cyclodextrins" (D'Souza and Lipkowitz 1998; Loeve and Normand 2011; Crini 2014). The Professor Tsuneji Nagai designated him as "Mr. Cyclodextrin."

This chapter is a tribute to his scientific oeuvre. First, it gives a general overview of his outstanding scientific career. Then, we highlight selected important works on starch and cyclodextrins published over five decades by Professor Szejtli.

2.2 József Szejtli, 1933–2004

2.2.1 Early Years

József Szejtli was born on December 28, 1933 in Nagykanizsa, Hungary. During 1953–1962, Szejtli studied chemical engineering at the University of Technical Sciences, Budapest, where he received his M.Sc. in 1957 (chemical engineer) and his PhD in starch chemistry in 1961. He worked under the supervision of Professor János Holló, Head of the Department of Agricultural Chemical Technology. During this period, Szejtli studied the structure of starch, its hydrolysis, and the mechanism of starch-iodine reaction (Holló and Szejtli 1957a, b, c, 1958, 1959a, b, 1968; Holló et al. 1959a, b, c, 1962, 1964). At that time, the young student also studied cycloamyloses with the expectation that they would shed some light on the molecular structure of amylose helix.

2.2.2 His Scientific Career

During 1963–1964, Dr. Szejtli was a postdoctorate fellow at the Technical University of Trondheim, Norway, invited by the Royal Norwegian Academy. During this period, he pursued his studies on the hydrolysis of starch and also studied seaweed

polysaccharides (Szejtli 1965a, b, 1965c, 1966). From there, Dr. Szejtli moved to Germany, to the Institute of Nutrition of Potsdam, where he took up the position of research fellow (1965–1966). In this institute, he studied the molecular conformation of amylose and its iodine complexes in aqueous solutions (Richter and Szejtli 1966; Szejtli and Augustat 1966; Szejtli et al. 1967a, b, 1968).

"After spent considerable time in rather cold and foggy climates" (Szente 1994), Dr. Szejtli accepted in 1967 a position of professor at the University of Havana, Cuba, "a decidedly warmer venue." Dr. Szejtli often alluded to the importance of the sun to polysaccharide scientists, saying "as long as the sun shines photosynthesis will provide starch, the inexpensive raw material for polysaccharide scientists" (Szente 1994). In Cuba, Professor Szejtli worked as an advisor of the Cuban government and UNESCO expert for 3 years. At that time, he studied new polysaccharides such as chondroitin sulfate and pursued his studies on cycloamyloses-cyclodextrins, "a fascinating group of compounds with interesting industrial potentialities" (Szejtli 1982a; Szente 1994, 2004; Szente and Fenyvesi 2016).

Following this period (1967–1970), Professor Szejtli returned in Hungary as Head of Biochemical Research Laboratory at the Hungarian CHINOIN Pharmaceutical & Chemical Works. CHINOIN was one of the biggest pharmaceutical companies in Hungary and in Europe. Professor Szejtli served this position from 1971 to 1988, where he first connected universities in Hungary and harmonized the work of the Hungarian teams working on carbohydrate chemistry, enzymology, biotechnology, and technology. Professor Szejtli then connected the best scientists working on cyclodextrins around the world and developed the International Cyclodextrin Science. Its ultimate objective was to create an international cyclodextrin network.

In 1971, Professor Szejtli indeed organized the Biochemical Research Laboratory, renovated an old building, and recruited scientists (Szente 1994, 2004). One year later, Professor Szejtli started the research on polysaccharides including cyclodextrins (Fig. 2.2). This laboratory was the cradle of the Cyclodextrin Research and Development Laboratory, CycloLab Ltd., an independent research organization founded 15 years later (Szente 1994, 2004). He became the managing director of this private company with the main objective to create commercial cyclodextrin-based products from his ideas, by "maintaining a balance between academic research and industrial affairs." Professor Szejtli has acted as a scientific, innovator, inventor, and industrial at the same time (Szente and Fenyvesi 2016; Szente et al. 2016). Actually, CycloLab Ltd. is a worldwide recognized leader of cyclodextrin technology.

In the mid-1970s, Professor Szejtli published his first experimental data on cyclodextrins and also started to collaborate with several universities, research institutes, and companies. He organized the Hungarian Cyclodextrin Workshops twice a year, where the Hungarian and invited researchers could present and discuss their latest results. In 1973, he began "his crusade." Indeed, Professor Szejtli travelled extensively to convince everyone, from scientists and students to industrials, that cyclodextrins held great commercial promise. In the meantime, the first

Fig. 2.2 Professor Szejtli when he received the permission from Chinoin to establish the Biochemical Research Laboratory in 1972. (Source: CycloLab archives)

toxicological studies had established that cyclodextrin administrated orally was a harmless substance.

In 1974, an important research project on cyclodextrins was launched at CHINOIN with the support of Research Director Professor Zoltán Mészáros. In 1982, Professor Szejtli wrote: "Professor Mészáros supported this project by every means, running substantial financial risks" (Szejtli 1982a). The two main objectives of this innovative project were to produce cyclodextrins at a reasonable price and, especially, to investigate every possible field of application for cyclodextrins and their inclusion complexes. In a few years, several patents are registered (Szejtli et al. 1976, 1977a, b, c, 1978c, d, 1980c, d, e, 1981b, 1982b, 1983d, 1985a, b). At the end of the 1970s, Professor Szejtli also published his first general reviews on the potential applications of cyclodextrins (Szejtli 1977a, 1978; Szejtli et al. 1978a, b).

Realizing the exponentially increasing number of articles, chapters, and patents, Professor Szejtli organized the first International Cyclodextrin Symposium in Budapest in 1981 with participants from 17 countries. The eighth symposium was again in Budapest in 1996, organized by him. In the mid-1980s, with his English colleague Professor Pagington, Professor Szejtli founded the scientific monthly newsletter, "Cyclodextrin News" (first issue: November 1986), in order to create a source of information for everyone active in the field, from students and colleagues to industrial engineers (Szente 1994).

During 1975–2004, Professor Szejtli published plentiful experimental data on almost every field of cyclodextrin with major theoretical and practical impacts in chemistry, biology, health science, and agriculture. He knew virtually everything about them. In spring 2004, Professor Szejtli retired from his position in CycloLab but remained active in science (Fig. 2.3). He has devoted his life to cyclodextrins. József Szejtli tragically passed away on November 26, 2004.

Fig. 2.3 With Professor Nagai celebrating the birthday of Professor Szejtli (70), a few months before his death. (Source: CycloLab archives)

2.2.3 Professor Szejtli: An Entrepreneur

Professor Szejtli was really a pioneer making systematic research to answer many unanswered scientific questions about cyclodextrins and also to find new industrial applications. He was an entrepreneur. Indeed, Professor Szejtli made an important contribution in the industrial application of cyclodextrins, notably by the creation of a research lab in 1972 and a private company in 1989, CycloLab Ltd., both totally devoted to cyclodextrins: "From toy to tool with industrial interest" (Szente 1994, 2004; Szente and Fenyvesi 2016; Szente et al. 2016). CycloLab was the first private research institute for the technological transfer between cyclodextrin research and industry. CycloLab grew and evolved into a key organization in the world of cyclodextrins (Szente et al. 2016).

Without Professor Szejtli, the feasible production of cyclodextrins on an industrial scale probably would not be as advanced as it is today. At that time, there was the important question whether these substances will be available in bulk quantities at a reasonable price. Indeed, in 1975, one kilogram of β-cyclodextrin had a price of about 1500 $. At the beginning of the 1980s, cyclodextrins were produced in large quantities and "marketed at a reasonable price" (10–15 $/kg).

2.2.4 Szejtli's Scientific Oeuvre

The scientific oeuvre of Professor Szejtli is remarkable both in its variety of topics and its depth. He published an impressive number of results on cyclodextrins as author and co-author from 268 scientific papers, 184 proceedings, 106 patents, more than 100 general reviews (Table 2.1) and book chapters (Table 2.2), and 5 books (source: Cyclodextrin News Database). Professor Szejtli has given more than 200 invited lectures and regularly presented his research findings within universities and industries throughout Europe, North America, and Asia. CycloLab was also among the registered places for education of students.

Professor Szejtli has supervised numerous graduate students, postdoctoral students, and visiting scientists from various countries. During five decades, more than 20 PhD dissertations were written and defended under the supervision of Professor Szejtli.

In 1982, his first famous book entitled *Cyclodextrins and Their Inclusion Complexes* is published (Fig. 2.4), in which he reviewed the first industrial applications of cyclodextrins in pharmacy, food industry, chromatography, and chemical industry (Szejtli 1982a). In 1988, Professor Szejtli wrote another comprehensive book, *Cyclodextrin Technology*, which is still considered as a reference work in the cyclodextrin community (Szejtli 1988a).

In 1998, while traveling by plane, one of the authors, G. Crini, a French postdoctoral fellow student in Milano, Italy, under the supervision of Research Director Torri and Professor Casu, has just returned from the Ninth International Cyclodextrin Symposium organized in Spain and had the opportunity to speak with Professor Szejtli during flight. He told him: "If you want to be a future expert in cyclodextrin, write a book, not just an article." 17 years later, Crini edited his first cyclodextrin book (Morin-Crini et al. 2015).

2.2.5 Professor Szejtli and the Cyclodextrin Scientific Community

In 2004, Szente wrote: "József was a very energetic person, full of new ideas and always ready to travel the world to propagate cyclodextrin news and technologies" (Szente 2004). Indeed, Professor Szejtli gave numerous conferences and invited lectures throughout the world and was visiting professor in several universities. He was an active member of the Editorial Board of Journal of Inclusion Phenomena. In 1994, a special issue – volume 18, number 3, pp. 207–314 – was dedicated to Professor Szejtli on the occasion of his 60th birthday. His last article was also published in this journal (Fig. 2.5).

During the period 1975–1985, significant collaborations have also been put in place with Japanese, e.g., Professors Koki Horikoshi, Makoto Komiyama, Tetsuo Osa, Tsuneji Nagai, and Kaneto Uekama; English, e.g., Professor James Pagington

Table 2.1 Reviews on cyclodextrins published by Professor Szejtli

Year	Title	Journal	Reference
1977	Some application possibilities of cyclodextrins in pharmaceutical industries	*Starch-Stärke*	Szejtli (1977a)
1978	New analytical methods in chemistry of cyclodextrins	*Starch-Stärke*	Szejtli (1978)
1978	Cyclodextrin polymer	*Starch-Stärke*	Szejtli et al. (1978a)
1982	Cyclodextrins in food, cosmetics, and toiletries	*Starch-Stärke*	Szejtli (1982c)
1983	Physiological effects of cyclodextrins on plants	*Starch-Stärke*	Szejtli (1983a)
1985	Cyclodextrins: A new group of industrial basic materials	*Nahrung Food*	Szejtli (1985a)
1985	Cyclodextrins in pesticides	*Starch-Stärke*	Szejtli (1985b)
1986	Cyclodextrins in biotechnology	*Starch-Stärke*	Szejtli (1986a)
1987	Cyclodextrins and the molecular encapsulation	*Chimica Oggi*	Szejtli (1987a)
1987	Applications of cyclodextrins in the chromatography	*Starch-Stärke*	Szejtli (1987e)
1988	Cyclodextrins in diagnostics	*Kontakte*	Szejtli (1988b)
1990	Complexation of metal ions by cyclodextrins	*Starch-Stärke*	Szejtli (1990a)
1990	The cyclodextrins and their applications in biotechnology	*Carbohydrate Polymers*	Szejtli (1990b)
1992	The properties and potential uses of cyclodextrin derivatives	*Journal of Inclusion Phenomenon*	Szejtli (1992b)
1993	Fatty-acid cyclodextrin complexes: Properties and applications	*Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*	Szente et al. (1993)
1994	Medicinal applications of cyclodextrins	*Medicinal Research Reviews*	Szejtli (1994)
1997	Utilization of cyclodextrins in industrial products and processes	*Journal of Materials Chemistry*	Szejtli (1997)
1998	Introduction and general overview of cyclodextrin chemistry	*Chemical Reviews*	Szejtli (1998)
1998	Non-chromatographic analytical uses of cyclodextrins	*Analyst*	Szente and Szejtli (1998)
1999	Highly soluble cyclodextrin derivatives: Chemistry, properties, and trends in development	*Advanced Drug Delivery Reviews*	Szente and Szejtli (1999)
2000	Drug/cyclodextrin/hydroxyl acid multicomponent systems. Properties and pharmaceutical applications	*Journal of Pharmaceutical Sciences*	Redenti et al. (2000)

(continued)

Table 2.1 (continued)

Year	Title	Journal	Reference
2001	Cyclodextrin complexes of salts of acidic drugs. Thermodynamic properties, structural features, and pharmaceutical applications	*Journal of Pharmaceutical Sciences*	Redenti et al. (2001)
2002	The role of cyclodextrins in chiral selective chromatography	*Trends in Analytical Chemistry*	Szejtli (2002)
2003	Cyclodextrins in the textile industry	*Starch-Stärke*	Szejtli (2003)
2004	Past, present, and future of cyclodextrin	*Pure and Applied Chemistry*	Szejtli (2004a)
2004	Cyclodextrins as food ingredients	*Trends in Food Science and Technology*	Szente and Szejtli (2004)
2005	Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins	*European Journal of Pharmaceutics and Biopharmaceutics*	Szejtli and Szente (2005)
2005	Cyclodextrin-complexed generic drugs are generally not bioequivalent with the reference products: therefore the increase in number of marketed drug/cyclodextrin formulations is so slow	*Journal of Inclusion Phenomena and Macrocyclic Chemistry*	Szejtli (2005)

and Sir James Fraser Stoddart, the "English-Connection"; Italian, e.g., Professor Benito Casu; German, e.g., Professors Wolfram Saenger and Karl-Heinz Frömming; American, e.g., Professor Josef Pitha; and French, e.g., Professors Jean-Marie Lehn and Dominique Duchêne, groups.

Professor Szejtli also worked with the industrial sector, e.g., Chiesi Farmaceutici Italy, Schwarz Pharma and Hexal Germany, as well as Novartis, Switzerland on the developments of cyclodextrin-based pharmaceutical products, e.g., Brexin® (piroxicam), Prostavasin® (alprostadil), Omebeta® (omeprazole), Xund® (garlic extract), and Voltaren® (diclofenac).

Professor Szejtli not only pioneered the scientific knowledge on cyclodextrin science and technology, but also he had outstanding merits in organizing international life in this field of research (Szejtli 1982a). In 1981, he organized the First International Cyclodextrin Symposium in Budapest, Hungary. This symposium was a great success, with participants coming from all over the world, i.e., more than 180 participants from 17 countries, while Professor Szejtli "expected 25–30 participants outside Hungary." The 63 submitted manuscripts filled a 544-page volume of proceedings published by Reidel Publishing (Szejtli 1982b). Since 1984 and Szejtli's initiative, a broad community of researchers has met every 2 years to exchange and share their works on cyclodextrins. The 20th International Cyclodextrin Symposium will be organized in Sicily, Italy in 2020.

Table 2.2 Book chapters on cyclodextrins published by Professor Szejtli

Year	Title	Book	Editor(s)	Reference
1982	Cyclodextrins in foods, cosmetics, and toiletries	*Proceedings of the First International Symposium on Cyclodextrins*	Szejtli J	Szejtli (1982b)
1983	Molecular encapsulation of drugs by cyclodextrins and congeners	*Controlled Drug Delivery*	Bruck SD	Pitha et al. (1983)
1984	Industrial applications of cyclodextrins	*Inclusion Compounds*	Atwood JL, Davies JED and MacNicol DD	Szejtli (1984b)
1984	Limits of cyclodextrin application in oral drug preparations	*Clathrate Compounds, Molecular Inclusion Phenomena, and Cyclodextrins*	Atwood JL, Davies JED and Osa T	Szejtli (1984c)
1984	Non-oral drug preparations containing cyclodextrin complexes	*Clathrate Compounds, Molecular Inclusion Phenomena, and Cyclodextrins*	Atwood JL, Davies JED and Osa T	Szente et al. (1984c)
1987	The metabolism, toxicity, and biological effects of cyclodextrins	*Cyclodextrins and their Industrial Uses*	Duchêne D	Szejtli (1987b)
1987	Cyclodextrin use in separations	*ACS Symposium Series*	ACS Publisher	Szejtli et al. (1987)
1988	Stabilization of flavors by cyclodextrins	*ACS Symposium Series*	ACS Publisher	Szente and Szejtli (1988)
1991	The use of cyclodextrins in biotechnological operations	*New Trends in Cyclodextrins and Derivatives*	Duchêne D	Szejtli (1991a)
1991	Helical and cyclic structures in starch chemistry	*Biotechnology of Amylopectin oligosaccharides*	Friedman R	Szejtli (1991c)
1992	Cyclodextrins in the resolution of environmental pollution	*Minutes of the Sixth International Symposium on Cyclodextrins*	Hedges RA	Szejtli (1992a)
1996	Historical background	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Szejtli (1996a)
1996	Chemistry, physical, and biological properties of cyclodextrins	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Szejtli (1996b)
1996	Inclusion of guest molecules, selectivity, and molecular recognition by cyclodextrins	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Szejtli (1996c)
1996	Use of cyclodextrins in chemical products and processes	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Szejtli (1996d)

(continued)

Table 2.2 (continued)

Year	Title	Book	Editor(s)	Reference
1999	Cyclodextrins as reagents in analytical chemistry and diagnostics	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Hinze et al. (1999)
1996	Cyclodextrins in pesticides	*Comprehensive Supramolecular Chemistry*	Szejtli J and Osa T	Szente and Szejtli (1999)
1999	Application of cyclodextrins in nuclear waste management	*Proceedings of Ninth International Cyclodextrin Symposium*	Torres Labandeira JJ and Vila-Jato JL	Szente et al. (1999b)
1999	Sulfated cyclodextrin derivatives	*Proceedings of Ninth International Cyclodextrin Symposium*	Torres Labandeira JJ and Vila-Jato JL	Morva et al. (1999)
2004	Cyclodextrins	*Chemical and Functional Properties of Food Saccharides*	Tomasik P	Szejtli (2004b)
2004	Cyclodextrins: applications	*Encyclopedia of Supramolecular Chemistry*	Marcel Dekker	Szejtli (2004c)

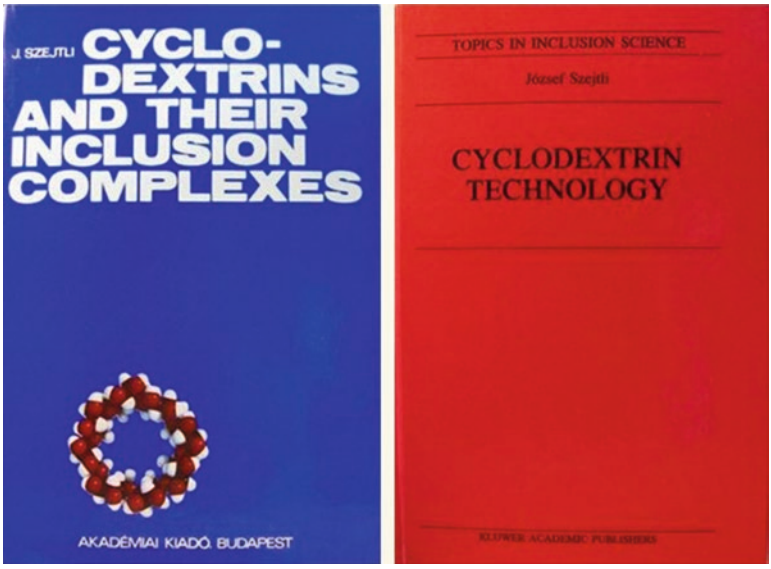

Fig. 2.4 Two books published by Professor Szejtli in 1981 (left) and in 1988 (right). (Source: CycloLab archives)

Journal of Inclusion Phenomena and Macrocyclic Chemistry (2005) 52: 1–11
DOI 10.1007/s10847-004-7161-z

Review Article

Cyclodextrin Complexed Generic Drugs are Generally not Bio-equivalent with the Reference Products: Therefore the Increase in Number of Marketed Drug/ Cyclodextrin Formulations is so Slow

JÓZSEF SZEJTLI†
Cyclolab Ltd., 1525 Budapest P.O.B. 435, Hungary; E-mail: Cyclolab@cyclolab.hu

(Received: 28 May 2004; in final form: 2 July 2004)

Key words: advantages of complexation, approval status of CDs, bioavailability, cyclodextrin, drug, supergeneric drugs

Fig. 2.5 Extract of the last article published by Professor Szejtli. (Source: Szejtli (2005), with the permission of Springer Nature)

2.2.6 Awards and Distinctions

Professor Szejtli was a member of various academic committees and organizing boards of symposia, e.g., Cyclodextrin Symposia, Symposia on Molecular Recognition. He has received a D.Sc. degree by the Hungarian Academy of Science (1976) and has been Professor since 1980 at Kossuth L. University, Debrecen (Szente 1994). Professor Szejtli received many distinctions for his cyclodextrin research, e.g., Academic Award of Budapest (1986), Gold Medal of the Incheba of Brastislava (1988), the Moët-Hennessy Prize of Paris (1991), and the Széchenyi Prize (Budapest, 2003).

2.2.7 Szejtli Prize

At the 80th anniversary of his birth, in 2013, CycloLab established the Szejtli Prize (Fig. 2.6) to preserve his legacy, keep his memory alive, and recognize his groundbreaking achievements in the area of cyclodextrin research, development, and commercialization of related technologies. This prize aimed to award young researchers demonstrating outstanding results in the cyclodextrin science and technology. It is presented biennially during the International Cyclodextrin Symposium.

The first award was assigned in 2014 to Professor Keiichi Motoyama, Kumamoto University, Japan, in Saarbrücken, at the 17th International Cyclodextrin Symposium for his works in the design of new active pharmaceutical ingredients as anticancer agents. The winner of Szejtli Prize 2016 was Professor Tamer Uyar, Bilkent University, Turkey, for his studies on electrospinning of functional nanofibers with cyclodextrins. In 2018, Dr. Nicolas Blanchemain, University of Lille, France, received the award for his works in the applications of cyclodextrins in biomedicine.

Fig. 2.6 The József Szejtli medal. (Source: CycloLab)

With the ceremony at the International Cyclodextrin Symposia, the CycloLab's team hopes to keep Professor Szejtli in memory for long.

2.3 Szejtli's Scientific Achievements

2.3.1 Early Work in Starch

The young student Szejtli first concentrated on the field of starch chemistry at the University of Technical Sciences, Budapest, between 1957 and 1963, working under the supervision of Professor János Holló. Szejtli studied the structure and conformation of the two components of starch, i.e., amylopectin and amylose. With Professor Holló, Szejtli proposed a new "helical-segment theory" to characterize the possible conformations of amylose in aqueous solution.

The most characteristic feature of starch known for long was its blue color on contacting with iodine. It was well-known that amylopectin was of highly branched structure and gave a violet-red (or brown-red) color with iodine, while blue coloring with iodine occurred only in amylose which consisted of glucose with bonds α-1,4, a linear polymer without branched structure. However, there was a debate on the mechanism of the reaction, i.e., a phenomenon due to adsorption and aggregation or due to the formation of complexes. In addition, at that time, the studies on the conformation of amylose were even marred by hot debate between the different laboratories (Szejtli 1969).

Three "schools of thought" were established (Fig. 2.7): that describing the conformation using a rigid, rod-like helical form, that describing the conformation using a segmented flexible coil-like helical structure, and that describing a random coil (Szejtli 1969). Many studies were also conducted on the retrogradation of amylose from different origins, and this has also remained a subject of debate (Kainuma 1984).

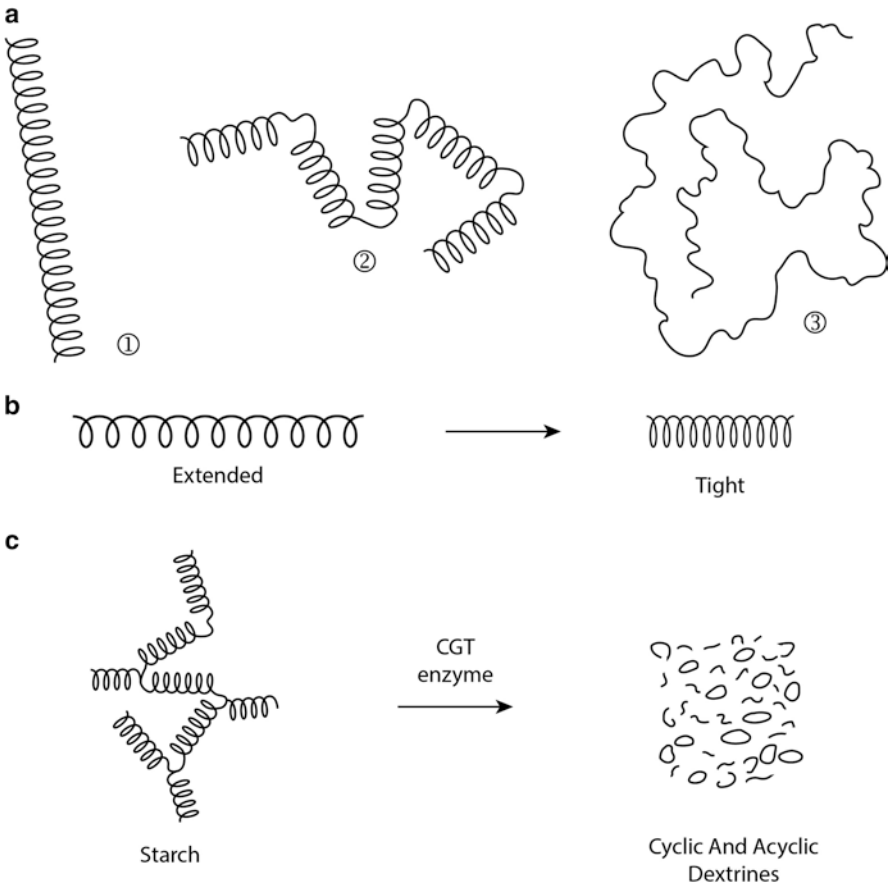

Fig. 2.7 (**a**): The rigid, rod-like helix (1), the segmented flexible coil-like helical structure (2), the random coil (3); (**b**) the extended helix is contracted to a tight-helix upon inclusion complex formation with iodine; and (**c**) degradation of starch to a mixture of cyclic and acyclic dextrins by cyclodextrin-glycosyl-transferase enzyme. (Adapted from Szejtli 1971, 1975, 1982a)

Holló and Szejtli (1957a, b, c, 1958), studying the mechanism of starch-iodine reaction, were among the first to propose that amylose existed as a helix in aqueous solutions. Their conclusions were based on amperometric titration (an innovative method at that time), streaming dichroism (amylose-iodine complex in solution caused dichroism), and on the viscosity studies of amylose. Holló and Szejtli showed that the amylose molecule dissolved in water was not linear and had a structure similar to some helix, in which helical segments were connected by disordered segments. The extended helix was contracted to a tight helix upon inclusion complex formation with iodine (Fig. 2.7). The viscosity remained unchanged until amylose became saturated with iodine but increased thereafter. In the complex formed with iodine, iodine was bound by hydrogen bonds (Holló and Szejtli 1957c). This

was in disagreement with the "theory of physical solution," i.e., a physical solution occurred when iodine dissolved in the helices as in hydrocarbons (Kainuma 1984).

At that time, the young student also studied the formation of cycloamyloses-cyclodextrins with the expectation that they would shed some light on the molecular structure of amylose. Indeed, for him, the degradation of starch to a mixture of cyclic and acyclic dextrins (Fig. 2.7) by the action of *Bacillus macerans* was an interesting reaction in the elaboration of a possible interpretation of the amylose conformation. This was a first step closer to cycloamyloses-cyclodextrins. Later, Professor Szejtli clearly demonstrated that the formation of cyclodextrins, catalyzed by cyclodextrin-glycosyl-transferase enzyme, delivered further proof for the helical structure of amylose (Szejtli 1971, 1991c).

At the end of the 1960s, Szejtli investigated the hydrolysis of starch (Holló and Szejtli 1959a, b), retrogradation of amylose (Holló et al. 1959a, b, c), and mechanism of the gelatinization of potato starch by measuring the amount of the adsorption of iodine and the polarographic maxima suppression power and by the measurement of the light permeability of the suspension (Holló et al. 1962, 1964; Szejtli 1963).

The results showed that the hydrolysis reaction was the resultant of two simultaneously occurring processes, the splitting of the terminal and of nonterminal bonds. The velocity of retrogradation decreased with increasing temperature and potato amylose containing one to two ramifications per molecule aged less rapidly than wheat amylose containing no ramification. The mechanism consisted of three stages: (1) the randomly linked helices were stretched by an intake of energy; (2) after losing their hydrate water hulls, the chains arranged themselves one after the other; and (3) a crystalline structure was formed due to the formation of hydrogen bonds between the hydroxyls of amylose.

At the Technical University of Trondheim, Dr. Szejtli pursued his studies on the characterization of structure and hydrolysis of starch (Szejtli 1965a). He also studied the hydrolysis of other polysaccharides such as dextran (Szejtli 1965b) and alginic acid (Szejtli 1965c). He highlighted a relation between the composition and the IR spectra of polysaccharides of different origins (Szejtli 1966).

During his postdoctoral stay at Potsdam, Dr. Szejtli continued to study the molecular configuration of amylose and its complexes in aqueous solutions (Richter and Szejtli 1966; Szejtli and Augustat 1966; Szejtli et al. 1967a, b, 1968). Studying the amylose-iodine complex at low pH (Fig. 2.8), Dr. Szejtli demonstrated that helices existed in segments and pointed out the fact that the stability of the complexes was dependent on the length of the polyiodide chains, and this length is dependent on the degree of polymerization of amylose (Szejtli et al. 1967a). A value of 100–200 for the chain length was the limit where the rigid linear helix was replaced by a flexible segmented coil form (Szejtli and Augustat 1966; Szejtli et al. 1967a). Other factors, such as temperature, pH, and concentration of iodide and starch, were also important (Szejtli et al. 1967b). For the first time, Dr. Szejtli suggested the host-guest complexes with amylose helix: this was another step closer to cycloamyloses-cyclodextrins.

Molecular Configuration of Amylose and Its Complexes in Aqueous Solutions. Part II. Relation between the DP of Helical Segments of the Amylose–Iodine Complex and the Equilibrium Concentration of Free Iodine

J. SZEJTLI,* M. RICHTER, and S. AUGUSTAT,
Institut für Ernährung der Deutschen Akademie der Wissenschaften zu Berlin, Potsdam-Rehbrücke, DDR

Fig. 2.8 Extract of the article published by Professor Szejtli where he described the interaction between amylose helix and the "guest" substrates. (Source: CycloLab archives)

Fig. 2.9 Profesor Szejtli referring to the *Comandante* Fidel Castro, University of Havana, Cuba, 1970. (Source: CycloLab archives)

At the end of the 1960s, Professor Szejtli summarized all the results on the structure and conformation of amylose and on the reaction of starch with iodine in three comprehensive reviews (Holló and Szejtli 1968; Szejtli 1969, 1971) that were reference works. In particular, he pointed out an interesting relationship between the conformation of the glucopyranoside units and the molecular configuration of amylose, in agreement with the results published by his colleague and friend Professor Casu (Szejtli 1971).

During his position at the University of Havana (Cuba), Professor Szejtli presented his innovative data on polysaccharides to the *Comandante* Fidel Castro (Fig. 2.9). Professor Szejtli then turned exclusively to the cyclodextrins from the

1970s onward. Indeed, after his return in Hungary, he initiated a comprehensive cyclodextrin research and development.

2.3.2 *Fields of Research on Cyclodextrins Studied by Professor Szejtli*

During more than 30 years, Professor Szejtli and his collaborators have written an abundant literature on all the topics related to cyclodextrins as reported in Table 2.3. His works were spread across different disciplines: chemistry, biochemistry, biology, health science, agriculture, environmental sciences, etc. With his results, cyclodextrins have broken barriers between different disciplines.

In the 1970s, Professor Szejtli first focused on the fundamental aspects of native and modified cyclodextrins. He studied their preparation and production at industrial scale, their description and characterization, their structure and properties, and also their solution and solid-state behavior.

Professor Szejtli, investigating in details the complex-forming capacities of cyclodextrins toward a large range of substances, demonstrated that these remarkable encapsulation properties can modify and/or improve the physical, chemical, and/or biological characteristics of the guest molecule, in agreement with the previous conclusions published by Professors Freudenberg, French, and Cramer (Crini 2014). Professor Szejtli also studied various methods for the preparation of cyclodextrin complexes and used various techniques for their characterization.

At the same time, Professor Szejtli also turned his attention to the practical aspects of these molecules. His objective was to find applications in all sectors of industry (Fig. 2.10). With his collaborators, he published numerous patents during the period 1975–1985. Rapidly, his research on cyclodextrins was very active in fields such as chromatography and analytical chemistry, food and cosmetic industries, pharmacy, agrochemistry, catalysis, enzymology, and environmental chemistry.

During the period 1975–1990, Professor Szejtli used cyclodextrins as host molecules for separation and molecular recognition, e.g., separating agents of racemic mixtures or in chiral resolution of enantiomers, as analytical reagents for chemistry and diagnostics, as solubilizing agents for lipophilic drugs, as excipients in formulation pharmaceutical development for stabilization, as capsules for molecular entrapments, as promoters or catalysts of different reactions, as multifunctional ingredients and complexing agents in food applications, as active agents for masking of undesired odor and taste, as plant growth regulators, and as complexing agents for purification purposes or pollutant removal.

Professor Szejtli claimed that the majority of these applications were based on the ability to form inclusion complexes. In 1987, he wrote: “Cyclodextrins can be considered as a new group of industrial basic materials, thanks to the constantly broadening versatility of their applications” (Szejtli 1987a).

Table 2.3 Selected works on cyclodextrins published by Professor Szejtli during the period 1975–2005

General topic	References
Native cyclodextrins	Szejtli (1978, 1982a, 1985a, 1996a, b, c, d, 1998, László et al. (1980, 1981), Neumarkt and Szejtli (1980), Dalla Bella and Szejtli (1983), Kajtár et al. (1989), Szejtli and Osa (1996), Szente et al. (1998a), Fenyvesi et al. (1999a)
History	
Preparation, industrial production	
Technology of conversion	
Structure, structural aspects	
Characterization, analytical chemistry, spectroscopy	
Physical and chemical properties	
Chemical reactivity	
Biological properties	
Inclusion complexes	
Aggregation	
Large cyclodextrins	
Inclusion compounds	Szejtli and Bánky-Elöd (1975a, b), Szejtli (1977b, 1980, 1982a, 1987a, 1990a, 1991b, 1996b, c), Szejtli and Budai (1977); Szejtli et al. (1978b, 1980a, 1981a, 1982a, 1983a, b), Szejtli and Budai (1979), Szejtli and Szente (1979), Szejtli and Bolla (1980), Budai and Szejtli (1981), Paal and Szejtli (1981), Szejtli and Szente (1981), Szente and Szejtli (1981), Pobozsny et al. (1981), Buvari et al. (1982), Daruhazi et al. (1982), Kajtár et al. (1982), Darwish et al. (1984), Habon et al. (1984a), Szemán et al. (1987a), Tetenyi and Szejtli (1984), Lopata et al. (1985), Stadler-Szöke et al. (1985), Furo et al. (1986), Bajor et al. (1988), Fenyvesi et al. (1988, 1999a), Suzuki et al. (1989, 1994), Kato et al. (1992, 1993, 1994), Kralova et al. (1992), Csabai et al. (1993, 1998), Redenti et al. (1994, 2000, 2001), Cserháti et al. (1996), Szente et al. (1998b, 1999a), Szejtli (1996a, b), Kolbe et al. (2002)
History	
Preparation	
Properties	
Characterization	
Structures in the crystalline state	
Spectroscopy	
Types of guest molecules	
Complexation effects in solution	
Inclusion effects in solid state	
Complex equilibria	

(continued)

Table 2.3 (continued)

General topic	References
Modified cyclodextrins and derivatives	Szejtli et al. (1978a, 1980a, e), Szejtli (1996c), Fenyvesi et al. (1982), Otta et al. (1982), Gerlóczy et al. (1983), Kandra et al. (1984), Suzuki et al. (1984), Szejtli (1983b, 1984a, 1992b), Szejtli and Kandra (1987), Szemán et al. (1987a, b, 1996), Fenichel et al. (1988), Otta et al. (1988), Szurmai et al. (1990), Jicsinsky and Szejtli (1992), Novák et al. (1993), Morva et al. (1999), Szente and Szejtli (1999), Lipták et al. (2001, 2002), Buchanan et al. (2002, 2004)
Preparation, characterization	
Properties, inclusion complexes	
Inclusion effects	
Substituted derivatives	
Cyclodextrin polymers	
Grafted polymers	
Organometallic compounds	
Fluorescent cyclodextrins	
Hydrogels/gels, beads, membranes	
Crown ethers	
Toxicology	Szejtli and Budai (1976), Szejtli and Sebestyén (1979), Szejtli et al. (1980b), Jodál et al. (1982, 1984), Gerlóczy et al. (1984, 1985, 1996), Szejtli (1987b, 1998, 1996b, 2004a, b), Verstichel et al. (2004)
Toxicity	
Biochemistry	
Degradation	
Biodegradability	
Chromatography	Zsadon et al. (1978, 1979a, 1979b, 1979c, 1981, 1983), Cserháti et al. (1983a, b, 1984, 1988, 1990a, b, 1995), Szejtli (1986b, 1987e, 2002), Szejtli et al. (1987), Alexander et al. (1988), Juvancz et al. (1988), Ujházy et al. (1988, 1989), Takeoka et al. (1990), Szemán et al. (1996, 2002), Juvancz and Szejtli (1999, 2002), Süvegh et al. (1992), Iványi et al. (2004)
Paper and thin-layer chromatography	
Gel inclusion	
Liquid chromatography	
Affinity chromatography	
Gas chromatography	
Electrophoresis	
Chemistry	Szejtli (1984b, 1986b, 1988a, 1995, 1996, 1996c, d, 1997, 2004a), Szente et al. (1987), Bakó et al. (1988, 1994), Szente and Szejtli (1998), Hinze et al. (1999)
Analytical chemistry	
Catalysis	
Stereoselective reactions	
Polymer science	
Green chemistry	
Click chemistry	

(continued)

Table 2.3 (continued)

General topic	References
Food	Szejtli et al. (1977a, 1979a, b, 1980d), Lindner et al. (1981), Szejtli (1982b, 1982c, 1984b, 2004b), Szente and Szejtli (1986, 1987a, b, 1988, 2004), Weiszfeiler and Szejtli (1988), Szente et al. (1988, 1992, 1993), Szejtli and Szente (2005)
Nutrition	
Flavors	
Aromas	
Packaging	
Tea aromatization	
Pharmacy	Szejtli (1977a, 1981, 1984c, 2004a, 2005), Szejtli et al. (1980f), Fenyvesi et al. (1984a, b, c, d, 1996a, 1999c), Habon et al. (1984b), Stadler-Szöke et al. (1984), Szente et al. (1984a, b, c, 1985), Vikmon et al. (1985, 1988, 1999), Szemán et al. (1987a, b), Weiszfeiler et al. (1988), Frömming and Szejtli (1994), Gerlóczy et al. (1999), Klokkers et al. (1999), Geczy et al. (2000), Szejtli and Szente (2005)
Drug types, drug formulation, drug-cyclodextrin complexes	
Drug delivery, controlled release of drugs	
Excipients, auxiliary substances	
Biological effects of cyclodextrins	
Limits of utilization of cyclodextrins	
Biotechnology	Szejtli (1984b, 1986a, 1989, 1990b, 1991a)
Enzymology	
Enzyme technology	
Cosmetics and toiletry	Szejtli and Szente (1979), Szejtli (1982b, c), Fenyvesi et al. (1999b, 2004)
Hygiene and personal care	
Fragrances	
Essential oils	
UV filters	
Environmental chemistry	Olah et al. (1988), Szejtli (1992a), Fenyvesi et al. (1996b, c, 2002), Molnár et al. (1999, 2002, 2005), Szente et al. (1999b), Fava et al. (2002)
Removal or enrichment of components	
Remediation	
Soil decontamination	
Wastewater treatment	
Textiles	Szejtli (1984b, 1998, 2003)
Fiber modification	
Cosmeto-textiles	

(continued)

Table 2.3 (continued)

General topic	References
Medicine	Gál-Füzy et al. (1984), Szejtli et al. (1986), Felméray et al. (1996), Szejtli (1994)
Biomedicine	
Wound healing	
Cell biology	
Agriculture and agrochemistry	Szejtli and Tétényi (1981), Szente and Szejtli (1981, 1999), Szejtli (1983a, 1985b, 1988a, c, 1996b), Szejtli et al. (1983c), Szente et al. (1990)
Physiological effects	
Pesticides	
Miscellaneous	Szejtli et al. (1980c), Bujtas et al. (1987), Szejtli (1987c, d, 1988b), Szogyi et al. (1987), Cserháti et al. (1992), Fenyvesi et al. (1992), Buchanan et al. (2001), Cserháti and Szejtli (1992)
Plastics	
Tobacco products	
Animal feeds	
Cyclodextrins in diagnostics	
Supramolecular chemistry	
Nanotechnology	
Tensides, detergents, surfactants	

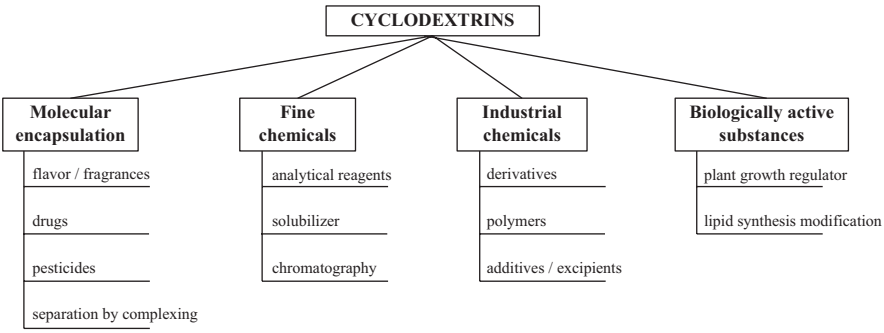

Fig. 2.10 Fields of potential applications of cyclodextrins according to Professor Szejtli. (Adapted from Szejtli 1982a, c)

Professor Szejtli was also a visionary. Since the mid-1980s, he suggested new potential markets for cyclodextrins, e.g., in biotechnology (Szejtli 1985a, 1986a, 1990b, 1991a), agriculture (Szejtli 1985b), fibers (Szejtli 1988a), and medicine (Szejtli 1988b, 1994). During the period 1990–2000, he also proposed to use cyclodextrins as active compounds in functionalized textiles, as encapsulating agents for

antioxidants, flavors, and aromas, as components of artificial enzymatic systems, as drug delivery vehicles, and as vectorizing agents.

In 2004, Professor Szejtli wrote: "The actual and potential uses of cyclodextrins in products and technologies seem to be inexhaustible" (Szejtli 2004c). Using his own results, Professor Szejtli claimed that cyclodextrins might play a significant role in cosmeto-textiles (Szejtli 2003, 2004a), functional food and therapeutic products (Szejtli 2004b), agrochemistry (Szejtli 2004a), environmental protection, i.e., in terms of removal of pollutants present in all environmental compartments, soils, waters, and air, and in other domains such as cell biology, formulation of detergents, glues and adhesives, packaging, nanotechnology, and sensors (Szejtli 2004a, c).

Professor Szejtli was among the first to introduce the concept of cyclodextrins as active and smart molecules rather than complexing molecules with expected applications in textiles, e.g., "intelligent" materials loaded with biologically active substances such as drugs, insect repellents, and antimicrobial agents, in biotechnology, e.g., biotransformation and fermentation processing, protein and peptide delivery, and vaccine production, and in cell biology (Szejtli et al. 1980i, 1982b; Szejtli 1990b, 2003).

2.4 Selected Highlights in Szejtli's Fundamentals Works

2.4.1 Historical Review

In 1957, Professor Dexter French published "the first historical survey illustrating the metamorphosis of the Schardinger dextrins" (French 1957). In this review, Dexter divided the history of Schardinger dextrins/cycloamyloses into two general periods, the discovery, between 1891 and 1935, and their maturity from 1935 to 1950. Historical milestones on cyclodextrins were also published by Thoma and Stewart (1965), Caesar (1968), and Clarke et al. (1988).

In 1998, the famous journal *Chemical Reviews* published a special issue devoted to cyclodextrins. It contained 13 chapters and is still a reference today, including the excellent introductory review by Professor Szejtli. In this paper, Professor Szejtli pursued the history of cyclodextrins written by Professor French, which was also updated 9 and 16 years later by Loftsson and Duchêne (2007) and Crini (2014), respectively.

The history as written by Professor Szejtli was divided into three major periods (Szejtli 1998): discovery 1891–1935, exploration 1935–1970, and utilization 1970 to the present day (Fig. 2.11). In the first 45 years about 50, in the second period (~35 years) about 2000, and in the third period (during the last 27 years) about 13,000 cyclodextrin-related publications have been published.

In this well-cited review (Szejtli 1998), Professor Szejtli, pointing out the misinformation on the toxicity of cyclodextrins reported by Professor French in 1957,

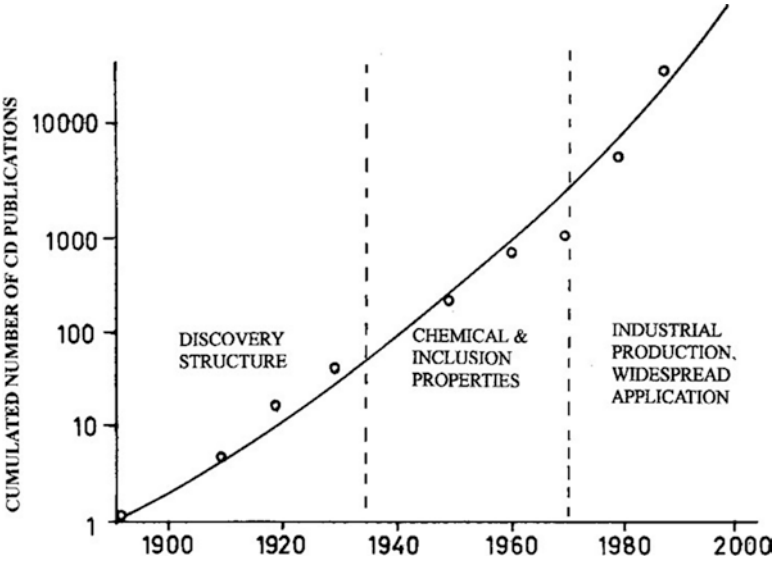

Fig. 2.11 The three stages in the development of cyclodextrin technology according to Professor Szejtli in 1998. (Source: CycloLab archives)

wrote: "Cyclodextrins can be consumed by humans as ingredients of drugs, foods, or cosmetics."

2.4.2 Preparation and Chemistry of Cyclodextrins

In the mid-1970s, Professor Szejtli showed that cyclodextrins can be produced at industrial scale by a relatively simple technology by fermentation of starch (Szejtli 1982a, 1988a), in agreement with the previous results published in the laboratory scale by Professors Freudenberg, Cramer, and French (Crini 2014). This was interesting because, at that time, cyclodextrins still remained as laboratory curiosities and were extremely expensive.

The method of preparation of β-cyclodextrin, illustrated in Fig. 2.12, was detailed in his second book (Szejtli 1988a). In the first step of cyclodextrin production, starch was liquefied at elevated temperatures. It was hydrolyzed to an optimum degree in order to reduce the viscosity of such fairly concentrated (around 30% dry weight) starch solution. After cooling the solution to optimum temperature, the cyclodextrin-glucosyl-transferase enzyme was added. The purification of the enzyme was made by affinity chromatography. In the solvent technology (Fig. 2.12), an appropriate complex-forming agent was added to the conversion mixture. If toluene was added to this system, the toluene/β-cyclodextrin complex formed was separated immediately, and the conversion was shifted toward β-cyclodextrin formation.

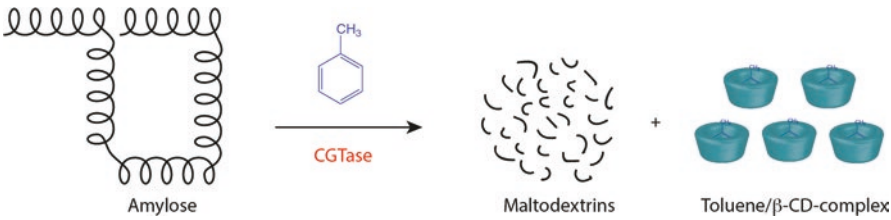

Fig. 2.12 Production of β-cyclodextrin. (Adapted from Szejtli 1988a)

If n-decanol was added to the conversion mixture, α-cyclodextrin was mainly produced, whereas with cyclohexadecenol, γ-cyclodextrin was the main product. The insoluble complexes were then filtered from the conversion mixture. The solvents were removed by distillation or extraction. The aqueous solutions obtained after removing the complexing solvent was treated with activated carbons and filtered. Cyclodextrins were finally separated from this solution by crystallization and filtration. The homogeneity and chemical purity of the industrially produced cyclodextrins exceeded 99% (Szejtli 1988a).

Rapidly, the works of Professor Szejtli not only on the production of cyclodextrins but also on their fundamentals and chemistry were acknowledged to have made an important contribution. Using his great experience on starch chemistry (Szejtli and Augustat 1966; Szejtli et al. 1967a, b, 1968) and the previous conclusions reported by Professor French and Professor Casu on the correlations between the structures of amyloses and cycloamyloses (see Crini 2014), Professor Szejtli summarized and discussed in details the steric structures of amylose and cyclodextrins (Szejtli 1969, 1971).

For a better understanding of their conformational analysis, Professor Szejtli first studied the conformation of dextrins, in particular disaccharides, e.g., maltose and cellobiose. In the maltose, the two D-glucopyranose units were linked by α-1,4 glucosidic linkage, while a β-1,4 glucosidic linkage between them resulted in cellobiose. For the calculation of the favored conformation of a disaccharide, Professor Szejtli pointed out rotations around the glycosidic (or anomeric) bonds linking the two units (dihedral angles ϕ and ψ) and the bond angle of the glycosidic oxygen atom (θ); see Fig. 2.13. It became evident that, owing to hindered rotation, for a given disaccharide, the angles have preferred values. Only the *cis* and the *trans* conformations can exist. Repeating the *cis* conformation resulted in a helical structure, e.g., for maltose, while the *trans* conformation led to a zigzag chain, e.g., for cellobiose. Later, all these results were used in the characterization of the conformational analysis of cyclodextrins and their complexes (Szejtli and Bánky-Elöd 1975a, b; Szejtli and Budai 1976; Szejtli 1977a, b, 1978).

In his various reviews, Professor Szejtli described the particular structure of cyclodextrins. The ring shape of cyclodextrins was a consequence of the C-1 conformation of the glucopyranose subunits and their α-1,4-type glycosidic linkages, in agreement with the conclusions described by Professor Casu (Crini 2014). The same structural units were found in starch.

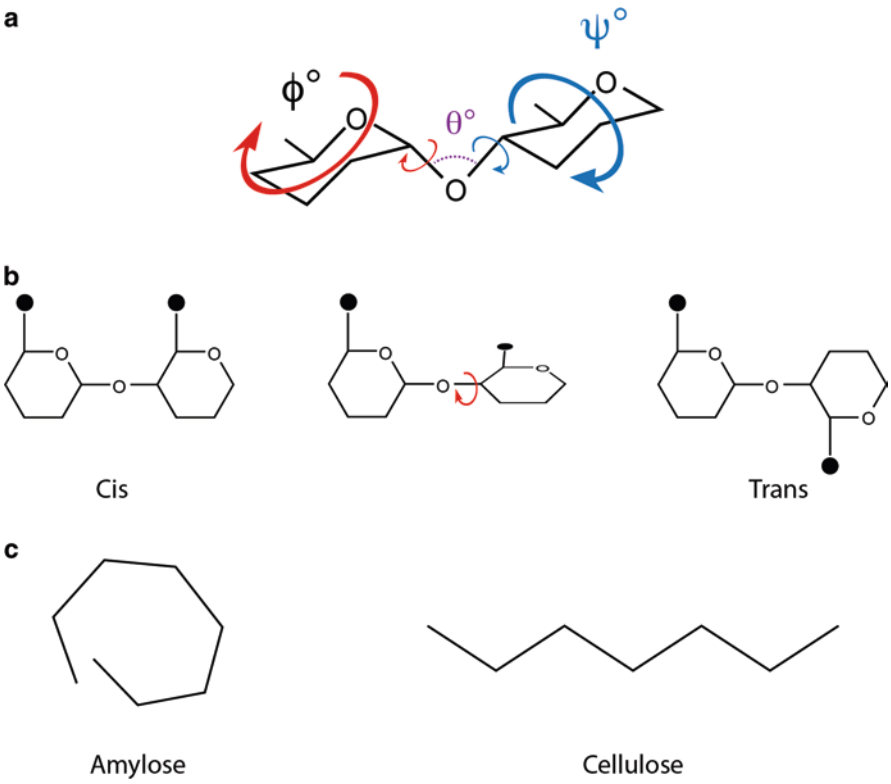

Fig. 2.13 (**a**): The ϕ, ψ-linkage conformation of disaccharides (rotation around the glycosidic bond); (**b**), the most important relative positions of the two-ring planes (only the *cis* and the *trans* conformations can exist); and (**c**), the structure of amylose and cellulose (repeating the *cis* conformation, i.e., maltose, results in a helical structure, while the *trans* conformation, i.e., cellobiose, leads to a zigzag chain. (Adapted from Szejtli et al. 1982a)

As a consequence of the C-1 conformation of the glucopyranose units, all secondary hydroxyl groups were situated on one of the two edges of the ring, whereas all the primary ones were placed on the other edge. The cavity, composed of several glucose units, was lined by the hydrogen atoms and the glycosidic oxygen bridges, respectively. The nonbonding electron pairs of the glycosidic oxygen bridges were directed toward the inside of the cavity producing there a high electron density and lending it some Lewis-base character. A schematic representation of a "cyclodextrin capsule" is reported in Fig. 2.14.

Like Professor French, Professor Szejtli pointed out the fact that a cyclodextrin molecule should be regarded rather as a truncated cone than a cylinder. The core of this structure can trap or encapsulate other substances (Szejtli 1995). Figure 2.15 illustrates the hydrophilic and hydrophobic regions of cyclodextrins.

Using the results of Professor Casu on the chemical structure of cyclodextrins obtained from infrared and NMR experiments, Professor Szejtli also indicated that

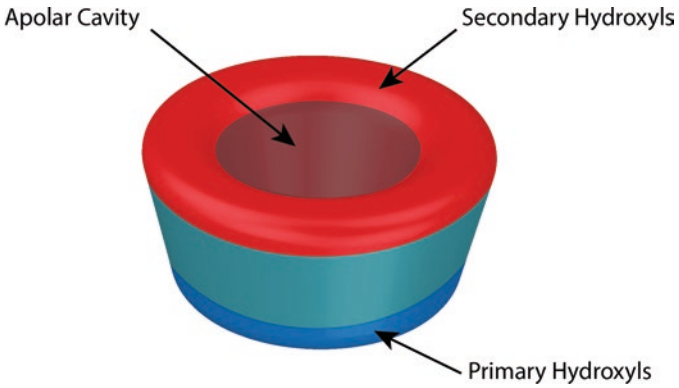

Fig. 2.14 Schematic representation of a cyclodextrin "capsule" or "torus": on the side where the secondary hydroxyl groups are situated, the diameter of the cavity is larger than on the side with the primary hydroxyl groups, since free rotation of the latter reduce the effective diameter of the cavity; rhe lining of the internal cavity is formed by hydrogen atoms and glucosidic oxygen-bridge atoms; therefore this surface is slightly apolar. (Adapted from Szejtli 1978)

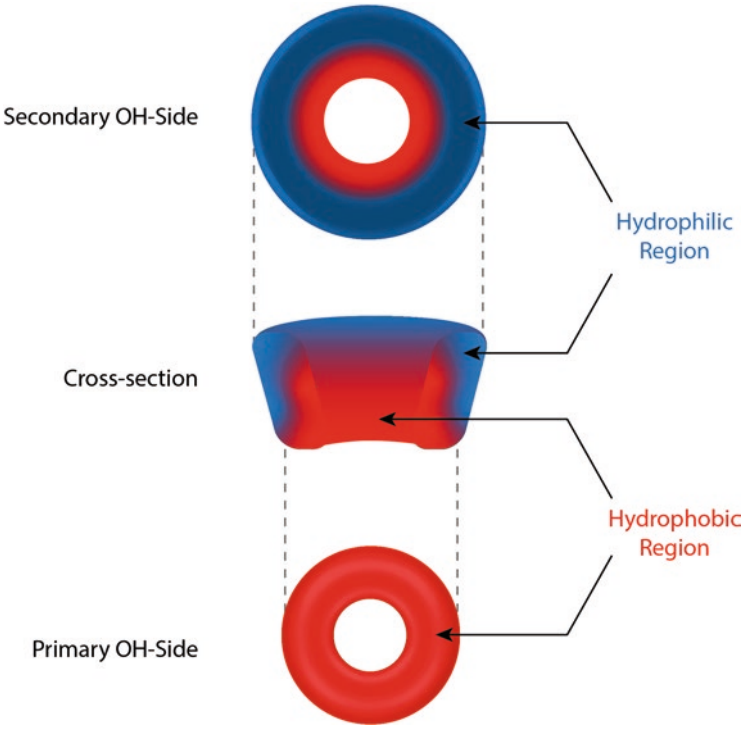

Fig. 2.15 Schematic representation of the hydrophilic and hydrophobic regions of cyclodextrins. (Adapted from Szejtli 2004a)

the structure of cyclodextrins was stabilized by the formation of hydrogen bond between C-2 and C-3 hydroxyl groups of adjacent glucose units. This phenomenon widely affected, in addition to molecular dimensions, the water solubility of cyclodextrins. The formation of a complete ring of intramolecular hydrogen bonds in β-cyclodextrin counteracted its hydration and reduced its solubility as compared to other native cyclodextrins (Szejtli 1978, 1982a, 1995).

2.4.3 Types, Formation, and Structures of Inclusion Complexes

Development of the optimal technology of producing crystalline cyclodextrin inclusion complexes required a knowledge of the crystallization process. However, the literature contained little information concerning crystallization temperatures and other parameters such as pH, concentration, and cooling rate (Saenger 1984; Connors 1997).

In 1977, Professor Szejtli studied the influence of the conditions of crystallization in such a way that the guest molecule was added to a cyclodextrin solution warmed to 60 °C (Szejtli and Budai 1977). Under vigorous stirring the solution was then gradually cooled at a rate of 0.3–0.4 °C/min, and the turbidity was recorded as a function of temperature. His results clearly showed that both cyclodextrin and the guest molecule produced well-defined individual turbidity curves from which it was possible to determine the temperature at which the crystallization started. If the crystallization temperature of the mixture differed from that characteristics of pure β-cyclodextrin under the given circumstances, the formation of an inclusion complex was probable.

The same year, Professor Szejtli studied the interaction of hydrochloric acid with β-cyclodextrin. This work was the first to report adequate kinetic data and activation parameters (Szejtli 1977b). The results showed that the first-order rate constant for the hydrochloric acid-catalyzed degradation of β-cyclodextrin increased during the reaction because the α-1,4-bonds present in the macrocycle and in linear dextrins, i.e., formed by opening of the macrocycles, were split at different rates. The activation energy for hydrolysis of the glycosidic bond of maltose was 30.5 kcal/mole, while the opening of the cyclodextrin ring was characterized with a value of 34.2 kcal/mol. At lower temperatures and higher hydrochloric acid concentrations, a rather stable crystalline acid-cyclodextrin complex was formed with excellent yield (Fig. 2.16). This complex contained 1.8 molecules of hydrochloric acid per cyclodextrin unit. After storage at room temperature for 1 year, it still retained 1 mole of hydrochloric acid, and storing the product in sealed vials for 1 year led to no change in the composition. The complex was adequate for preparing tablets for supply of gastric acid (Szejtli and Budai 1976, 1977, 1979; Szejtli 1977b). Professor Szejtli also proposed new analytical methods such as thin-layer chromatography in chemistry of cyclodextrins (Szejtli 1978).

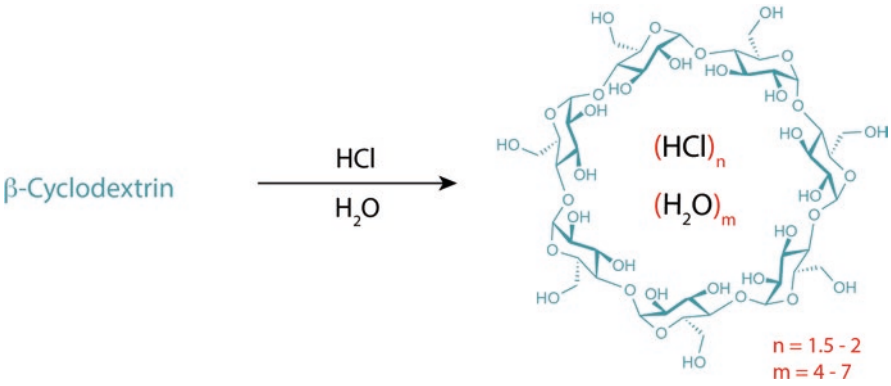

Fig. 2.16 Structure of the β-cyclodextrin-HCl complex proposed by Professor Szejtli. (Adapted from Szejtli et al. 1977b)

In the 1980s, Professor Szejtli pointed out the fact the preparation of cyclodextrin inclusion complexes was simple. Their preparation and characterization were detailed in his two books (Szejtli 1982a, 1988a). Professor Szejtli wrote: "No universal method exists for the preparation of cyclodextrin complexes; the method has to be tailor made for the guest and for the requirements: whether small-scale laboratory preparation or large-scale industrial production" (Szejtli 1982a).

The complexation was performed in homogeneous solution, or in suspension, under pressure, or by simple mixing of the components. The most common procedure was to shake an aqueous solution of cyclodextrin (cold or warm, neutral or acidic) with the guest substance or its solution (Szejtli 1987a). Water can be removed by freeze-drying or spray drying. Other methods such as kneading, slurry complexation, filtration, or heating method were also used in the formation of cyclodextrin complexes (Szejtli 1995).

To prove the formation of an inclusion complex, various methods were used, e.g., circular dichroism (Szejtli 1978, 1983b), spectroscopy optical rotatory dispersion (Szejtli 1978), powder X-ray diffraction (Szejtli 1977b, 1978), polarography (Daruhazi et al. 1982, Szejtli 1982a), thin-layer chromatography (Szejtli 1978, 1982b), gas chromatography (Szejtli 1982c), UV-visible spectroscopy (Szejtli et al. 1978b), nuclear magnetic resonance spectroscopy (Szejtli 1983b), infrared spectroscopy (Szejtli et al. 1978b), thermoanalysis (Szejtli 1978), mass spectrometry (Szejtli 1977a, b), and differential scanning calorimetry (Novák et al. 1993).

For instance, mass spectrometric investigations proved that from a mixture of (*O*,*O*-dimethyl *O*-(2,2-dichlorovinyl)-phosphate with β-cyclodextrin, this insecticide was completely evaporated between 50 and 120 °C, i.e., before the beginning of the decomposition of cyclodextrin. In the mass spectrum of the insecticide-cyclodextrin complex, the peaks characteristics of (*O*,*O*-dimethyl *O*-(2,2-dichlorovinyl)-phosphate appeared only above 200 °C, simultaneously with the degradation products of β-cyclodextrin, demonstrating that the insecticide was bound in the complex.

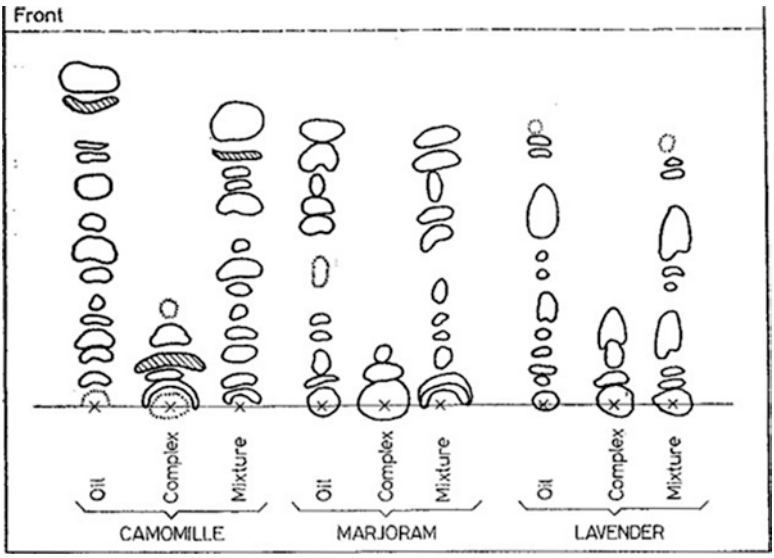

Fig. 2.17 Thin-layer chromatograms of essential oils and their mechanical mixtures and complexes with β-cyclodextrin performed by Professor Szejtli in 1978. (Source: CycloLab archives)

Figure 2.17 shows another example (Szejtli 1978). Thin-layer chromatography was useful for the verification of complex formation since this method altered the retardation factor values considerably. The values were strongly diminished, demonstrating that the complex was sufficiently stable in the solvent mixture used. The chromatograms of volatile oils and their complexes (protocol: solvent = benzene and detection = with vanillin in concentrated sulfuric acid) indicated that the value obtained was between the value of the pure guest molecule and that of the complex (Fig. 2.17).

2.4.4 The Mechanism of Formation of Inclusion Complexes

In 1954, Professor Cramer was the first to demonstrate that the main value of cyclodextrins resided in their ring structure and their consequent ability to include guest molecules inside their internal cavity (Cramer 1954, 1956; Saenger 1984; Clarke et al. 1988; Connors 1997; Szejtli 1998; Crini 2014). Professor Cramer introduced the notion of "inclusion complex." Formation of an inclusion complex was the result of an association/dissociation equilibrium between a free guest and a free host and a complex. The complex was strong when there was size complementarity between the guest and the cyclodextrin cavity (Cramer 1954, 1956).

In 1976, Professor Saenger pointed out that the complexation mainly involved hydrophobic interactions (Saenger et al. 1976). Two years later, Professor Bender

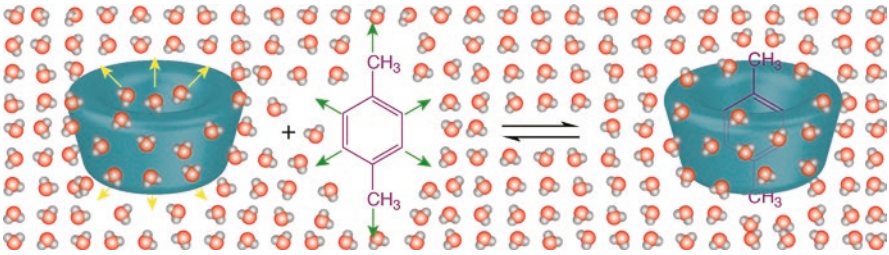

Fig. 2.18 Schematic representation of the formation of an inclusion complex between *p*-xylene, the guest, and a cyclodextrin molecule. (Adapted from Szejtli 1978)

showed that the complexation reaction involved a gain in enthalpy and a loss of entropy (Bender and Komiyama 1978).

In 1982, Professor Szejtli published a thorough state of the art of inclusion complexes (Szejtli 1982a), which was updated 2 years later by Saenger (1984). Professor Szejtli summarized and reformulated all the interpretations made on the mechanism of formation of inclusion complexes.

His three main conclusions, illustrated by a famous scheme (Fig. 2.18), were (1) the guest molecule, less polar than water, directly replaced the water molecules in the cavity; (2) the cyclodextrin molecules absorbed the energy of the water molecules retained in the cavity; and (3) the organic guest dissolved in water entered in the cavity because it had a preference for hydrophobic environment (Szejtli 1978, 1982a; Szejtli et al. 1979a). Professor Szejtli concluded that the complexation phenomenon resulted from a multitude of interactions between the three components of the system cyclodextrin-substrate-solvent leading to a state that was more thermodynamically stable overall (Szejtli 1995).

2.4.5 Inclusion Complexation Effects

Professor Szejtli showed that the various applications mainly take advantage of the different possible consequences of the encapsulation of the guest molecule within the cyclodextrin (Szejtli et al. 1979a, 1980f; Szejtli 1981, 1982b). In the 1980s, he summarized them in six points (Table 2.4). Later, Professor Szejtli also pointed out another outstanding fact: cyclodextrins were highly versatile molecules that lend themselves to being modified and used either in the dissolved form or as solids. This means that the different physical or chemical forms they can take can include particles, i.e., aggregates and microspheres, soluble or insoluble polymers, gels and hydrogels, polymers with cyclodextrins grafted on, cyclodextrin-based materials such as modified silica or organic resins, membranes, and also molecular superstructures (polyrotaxanes, etc.) or nanoparticles (Szejtli 1988a, b, 1992b, 1998). These different soluble and insoluble forms were very useful when considering chemical (Szejtli 1997), analytical (Szejtli 1997, 1998, 2002), pharmaceutical

Table 2.4 The possible consequences of the encapsulation of the guest molecule within the cyclodextrin cavity according to Professor Szejtli

1) *The modification of the physicochemical properties of the guest molecule*
Liquid compounds can be transformed into crystalline, compressible forms
Substances with low solubility in water become more soluble after complexation
The rate of dissolution of poorly soluble substances can be increased
Certain unpleasant tastes can be eliminated; smell can be covered by complex forming
The color of certain substances can be altered since inclusion can change the spectral properties of the guest
The complexed substance can be molecularly dispersed in a carbohydrate matrix
2) *The modification of the chemical activity of the guest*
Reactive substances can be protected by inclusion reducing the risks when they are mixed with other substances
Chemical reactions can be carried out selectively, the cyclodextrins playing the role of catalysts
Reactions can be promoted or suppressed
In the solid state, sublimation and volatility can be reduced to a low level
3) *The stabilization of substances sensitive to light or to oxygen*
Protection of active ingredients against oxidation, heat-promoted decomposition, or light-induced reactions
4) *The uptake of volatile substances*
Volatile drugs can be stabilized without losses through evaporation
The quantity of the volatile substance required can be reduced
Storage and handling of certain toxic substances such as pesticides can be improved
Savings can be made on the quantity of substance required owing to reduced evaporation
5) *The complexation and transport of substances*
Extraction and elimination of substances
Extraction and transport of pollutants
6) *Technical advantages*
Stable, standardized compositions, simple dosage, and handling of dry powders
Reduced packing and storage costs
Saving of energy and manpower

(Szejtli 1987b, 1988a; Szejtli et al. 1987), biotechnological (Szejtli 1990b, 1991a), or medical (Szejtli 1994) applications.

2.4.6 Cyclodextrins Derivatives

Besides being "molecular capsules," cyclodextrins were "basic materials" for the production of derivatives and polymers, biologically active substances, and reagents in analytical chemistry and diagnostics. Professor Szejtli prepared various cyclodextrin derivatives and polymers (Szejtli 1982a, 1984a, 1988a, 1998; Szente and Szejtli 1999).

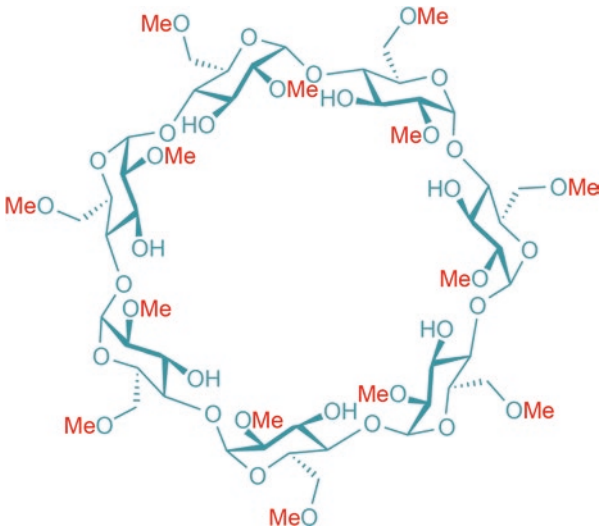

Fig. 2.19 Structure of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin or dimethyl-β-cyclodextrin, abbreviated DIMEB

Cyclodextrins can be modified by substituting one or more hydrogen atom of the primary and/or secondary hydroxyls, e.g., esters, ethers, or glycosyl-cyclodextrins, by substituting one or more primary and/or secondary hydroxyls, e.g., halogeno and aminocyclodextrins, by eliminating the hydrogen atom of the C5-CH_2OH group, or splitting one or more C2-C3 bonds by periodate oxidation. The substitution of highly reactive hydroxyl groups with either polar or apolar moieties permitted the disruption of intermolecular hydrogen bonds, and this produced cyclodextrin derivatives with anomalous increased solubility. The problems of selectivity and strategies for selective modification of hydroxyl groups have also been discussed by Professor Szejtli (Szejtli 1982a, 1984a, 1988a, 1998; Szente and Szejtli 1999).

The aim of such derivatizations may be (i) to improve the solubility of the native cyclodextrins, (ii) to improve the association between the cyclodextrin and its guest, (iii) to reduce its reactivity, (iv) to bind specific functional groups, and/or (v) to create new molecular of macromolecular structures, e.g., for chromatographic purposes.

Among the numerous cyclodextrin derivatives, heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin or dimethyl-β-cyclodextrin, abbreviated DIMEB, has been particularly studied by Professor Szejtli (Szejtli et al. 1980f, 1982a; Szejtli 1983b, 1984a). Its structure is reported in Fig. 2.19. DIMEB was prepared, using a previous protocol published by Professor Casu in 1968 (Szejtli et al. 1980a, 1983b; Crini 2014), by selective methylation of all C-2 secondary and all C-6 primary hydroxyl groups of β-cyclodextrin, while C-3 hydroxyl groups remained unsubstituted (Szejtli et al. 1980a; Lipták et al. 1982).

In 1994, a simple method of methylation of cyclodextrins by phase-transfer catalysis was proposed (Fenichel et al. 1988; Bakó et al. 1994). This reaction

proceeded in the heterogeneous phase with dimethyl sulfate, using a solvent in which cyclodextrins and bases used were poorly soluble or insoluble. However, in the presence of phase transfer catalysts, methylation proceeded with good yields. The products were a mixture of randomly methylated β-cyclodextrins containing 60–70% of DIMEB, 10–15% of heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin TRIMEB, and some mono-methylated isomers. These methylated derivatives were used as new detergents and also as solubilizing agents, e.g., to increase the solubility of hydrocortisone (Bakó et al. 1994).

Professor Szejtli also studied the complex-forming ability of partially acetylated cyclodextrins which proved to be useful for complexation of taxoid anticancer drugs, especially when applied together with hydroxypropyl cyclodextrin (Szejtli et al. 2004). On the other hand, the water-insoluble peracetylated derivatives gave the opportunity to study inclusion complex formation in organic solvents (Buchanan et al. 2001). His group participated in the development of hydroxybutenyl cyclodextrins on the analogy of hydroxypropyl derivatives (Buchanan et al. 2002, 2004), sulfate, phosphate, and amino derivatives to mention only a few (Morva et al. 1999; Mikuni et al. 2000; Kis et al. 2003).

A special HPLC column was developed for the analysis of cyclodextrin derivatives based on inclusion complex-forming ability with phenyl moieties on the surface of the stationary phase (Varga et al. 2005). This column was useful for detecting residual unreacted cyclodextrins as well as separating the isomer groups with different degrees of substitution, thus providing a fingerprint characteristic to the product and the manufacturing process. Therefore, it was later selected by the European Pharmacopoeia for official identification of hydroxypropyl-beta-cyclodextrin.

2.5 Selected Highlights in the Fields of Applications Studied by Professor Szejtli

2.5.1 Cyclodextrin in Foods

Table 2.5 describes the applications of cyclodextrins as multifunctional food ingredients in various domains (Szejtli et al. 1977a, 1979a; Dalla Bella and Szejtli 1983; Szente and Szejtli 1988, 2004). As "empty capsules," native cyclodextrins can be used either for stabilization of substances or for the elimination of undesired compounds and microbial contaminations. They also served to protect lipophilic food components or to encapsulate substances, e.g., vitamins, aroma, and flavors.

In 1977, Professor Szejtli and his collaborators patented a promising method for the stabilization of food flavors and fragrances using cyclodextrins, which was realized on industrial scale (Szejtli et al. 1977a, 1979a). The active ingredient content of complexes, e.g., benzaldehyde, was 6–15% w/w, and the complexes were very stable in dry state. Their oxygen uptake, measured by the Warburg method, was less than that of free benzaldehyde (Szejtli et al. 1979a).

Table 2.5 Cyclodextrins as multifunctional food ingredients

Domain	Applications	References
Food technology	Protectants of food ingredients, e.g., against oxidation, light-induced degradations, heat-induced changes	Szejtli et al. (1977a, 1979a), Lindner et al. (1981), Szente and Szejtli (1986, 1987a, 1988, 2004), Szente et al. (1988, 1992, 1993), Szejtli and Szente (2005)
Functional foods	To solubilize ingredients, e.g., food colorings, vitamins	
Food protection	To improve shelf life of products	
Food preservation	To modify the physical properties of foods	
Flavors/aromas	To stabilize flavors, color, vitamins	
Elimination of undesired tastes/odors	Flavors carriers	
Taste modification	To reduce cholesterol	
Production of juices	To mask or reduce undesired tastes	
Removal of substances	To suppress unpleasant odors	
Packaging materials	Elimination of bitter components of foods, beverages	
	To improve microbiological preservation during storage, e.g., as antiseptic, conserving agents Edible films	

Later, Professor Szejtli suggested practical applications of cyclodextrin-complexed flavors (Szejtli 1982b) such as in households, in the catering trade, in dietetics and hospitals, and in the tinned food and meat industry (Fig. 2.20). In this paper, Professor Szejtli pointed out the fact that Japan was the only country where the application of cyclodextrin in food products was not limited (Szejtli 1982b). Coffee flavors were also stabilized by complexation with β-cyclodextrin as reported by Szente and Szejtli et al. (1986). In contact with water, the complex-bound flavor substances were released immediately. In a previous work (Lindner et al. 1981), flavor-β-cyclodextrin complexes were used in sausages, e.g., 1 g complex was equivalent to 130–150 g and 3–100 g of onion and cumin, respectively.

2.5.2 Cyclodextrin in Cosmetics and Toiletry

The two first reviews on the potential applications of cyclodextrins in cosmetics and toiletry were published in 1982 (Szejtli 1982b, c). These applications were presented at the 33rd Starch Convention of the Arbeitsgemeinschaft Getreideforschung

1., In households

It simplifies cooking by providing a wider choice of tastes and aromas. The dispensing units (e.g. tablets) containing various aromas can be stored in a small place for a long time without risking any loss of the active ingredient.

2., In the catering trade

By the elimination of manual processing of raw materials containing aroma substances, work and storage room can be saved, transport is simple, loss on storage can be avoided and a wider variety of tastes and aromas is provided. By using proper recipes identical taste and aroma can be provided independently of the location.

3., In dietetics and hospitals

The consumption of fibrous and seed shaped aroma carrying raw materials irritating the gastro-intestinal tract can be avoided, appetizing aromas can be applied in hospitals, many - otherwise forbidden - aromas can be consumed by persons on diet, the majority of problems with their eating being caused not by the aroma itself, but its vehicle mostly of plant origin.

4., In the tinned food and meat industry

In dehydrated soups or sausages without risking microbiological contamination stable aroma products resisting environmental effects can be used in a constant composition and in a well processable form.

Fig. 2.20 The main potential fields of applications of cyclodextrin-complexed flavors suggested by Professor Szejtli in the 1980s. (Source: CycloLab archives)

at Detmold (Germany, April 21–23, 1982). During this lecture, Professor Szejtli demonstrated that "cyclodextrins can be utilized for molecular encapsulation of flavors and fragrances and for water retention improving homogeneous pure active substances."

The main advantages of cyclodextrin complexation in cosmetics and toiletry were the protection of active ingredients, e.g., against oxidation, hydrolysis, or loss by evaporation, the solubilization of the guest substances in water, e.g., increase of the rate of solubilization or avoid the use of organic solvents, the elimination or at least reduction of undesired tastes and odors, the protection against microbial contaminations, and the improvement of handling, e.g., of liquid or oily substances as powders (Szejtli 1982c). In contrast to starch, cyclodextrins were not a nutrient medium for microorganisms. In this paper, Professor Szejtli also suggested that cyclodextrin polymers can be utilized in smoke filters (Szejtli 1982c).

2.5.3 Cyclodextrin and Drugs

The first studies on the complex formation of cyclodextrins with pharmaceuticals were carried out in the middle of the 1950s in Germany, e.g., with the important contributions made by Professors Cramer and Frömming, in Japan in the 1970s, e.g., with the works by Professors Nagai and Uekama, and also in Hungary. Indeed, Professor Szejtli made a significant contribution on the use of cyclodextrins in pharmacy (Pitha et al. 1983; Szente and Fenyvesi 2016).

In 1977, Professor Szejtli, reviewing the possible applications of β-cyclodextrin in pharmaceutical industries, pointed out the enhancement of drug bioavailability by β-cyclodextrin due to the molecular encapsulation, e.g., indomethacin, hydrocortisone, progesterone, lidocaine, etc. (Szejtli 1977a). The poorly soluble drug became molecularly dispersed in a hydrophilic matrix; therefore the drug became more soluble and dissolved with an increased dissolution rate in aqueous medium. The improved solubility led to higher blood level of the drug, which was manifested also in the biological response (Szejtli et al. 1980h; Szejtli 1981; Szente et al. 1984a).

Two years later, in 1979, Professor Szejtli unambiguously proved that orally applied β-cyclodextrin was not toxic (Szejtli and Sebestyén 1979). Further metabolic studies delivered explanation for the safety of cyclodextrin consumption (Gerlóczy et al. 1982; Gergely et al. 1982; Szabo et al. 1982).

For instance, ^{14}C-β-cyclodextrin or ^{14}C-glucose were given orally to rats, and the radioactivity was measured in the blood by liquid scintillation method. The results showed that the peak of radioactivity appeared in the blood within 10 min in the case of labelled glucose, while a rather protracted and low maximum was found between 2 and 10 h in the case of labelled β-cyclodextrin. The values of respiration of $^{14}CO_2$ proved that β-cyclodextrin was metabolized in rat. 8 hours after oral administration of 313 mg/kg ^{14}C-β-cyclodextrin, a very small amount (3 μg) was detected in 1000 μg of the blood. On the basis of investigations of radioactivity distribution, it was claimed that β-cyclodextrin was excreted by the feces after high dose of cyclodextrin treatment.

During the First International Symposium organized in Budapest in 1981, Professor Szejtli stated: "Some years ago, cyclodextrins seemed to be expensive and highly toxic substances of very limited accessibility, representing more scientific curiosity than industrial tangibility. The recent years however brought about dramatic change… We are entering a new era."

At the beginning of the 1980s, several patents on highly soluble cyclodextrin derivatives including DIMEB and polymers were patented by Professor Szejtli and his collaborators (Szejtli et al. 1980d, e, 1980g, h, 1981b, 1982b). The DIMEB was an interesting substance in drug formulation due to the fact that it was very soluble in cold water and also in organic solvents (Szejtli et al. 1980g). In such aqueous solutions, many insoluble and/or poorly soluble compounds can be easily dissolved, e.g., the solubility of steroids in water increased by a factor of 40–1200; 13 mg/mL progesterone or 20 mg/mL hydrocortisone can be dissolved in a 100 mg/mL DIMEB solution (Szejtli et al. 1980g).

In 1983, Professor Szejtli proposed to use DIMEB as parenteral drug carrier (Szejtli 1983b, 1984a). The results were explained by the molecular encapsulation concept. The complexation of a drug with DIMEB allowed a considerable increase in the molecular mass of the guest, without establishing covalent bond. The consequence was a reduced diffusion rate. This behavior was interesting for specific applications such as intramuscular or subcutaneous drug injections in rats (Szejtli 1983b, 1984a), e.g., on the action of lidocaine, a local anesthetic drug was nearly doubled injecting the drug dissolved in aqueous DIMEB solution. The solubility of lidocaine increased in presence of DIMEB. An increase of 2 mol in DIMEB concentration resulted in an increase of 1 mol in the concentration of dissolved lidocaine base. Chemical stability and duration of the biological effects of drug were enhanced. Diffusion and biological elimination were also decreased on interaction with DIMEB. NMR and circular dichroic spectra clearly showed the formation of inclusion complexes as illustrated in Fig. 2.21. The same techniques were previously used to demonstrate the formation of an inclusion complex between DIMEB and vitamin D3 (Szejtli et al. 1980f, g) or vitamin K3 (Szejtli et al. 1982a).

Solutions of soluble cyclodextrin polymers were also able to enhance the solubility of substances, e.g., drugs, vitamins, pollutants, etc., that were sparingly soluble or practically insoluble in water (Szejtli 1984a; Szemán et al. 1987a, b), e.g., in a 10 g/100 mL β-cyclodextrin-epichlorohydrin polymer solution, 16 g cholic acid or 0.4 g benzene can be dissolved at room temperature; the solubility enhancement factors were more than 50 and 6, respectively. These results were also explained by molecular encapsulation (Szejtli 1984a).

In 1994, Professors Frömming and Szejtli wrote a famous monograph on the role of cyclodextrins in pharmacy, which is still considered as a reference book in the cyclodextrin community (Frömming and Szejtli 1994).

2.5.4 Applications of Cyclodextrins in Chromatography

Inclusion complexation of lipophilic guest molecules by soluble α- and β-cyclodextrin polymers, prepared by cross-linking cyclodextrins using epichlorohydrin, showed to be useful in reversed phase thin-layer chromatography, e.g., for separation of prostaglandins (Szejtli 1978, 1984b, 1985a; Cserháti et al. 1983a, 1984, 1988). The method was also used for the determination of cyclodextrin inclusion complex stability (Cserháti et al. 1983a, 1990a).

An interesting field of applications of insoluble β-cyclodextrin polymers (Zsadon et al. 1979b; Szejtli 1980), also prepared by cross-linking cyclodextrins using epichlorohydrin, was in gel-inclusion chromatography for amino acids (Zsadon et al. 1979a), alkaloids (Zsadon et al. 1981, 1983), and proteins separation (Ujházy et al. 1988, 1989) and in gas chromatography or in liquid chromatography as packings (Cserháti et al. 1983b; Szejtli 1985a). The separation was based either on selective inclusion or on specific affinity. Preparative chromatography was also interesting for separation of racemic mixtures. Figure 2.22 shows the resolution of 500 mg

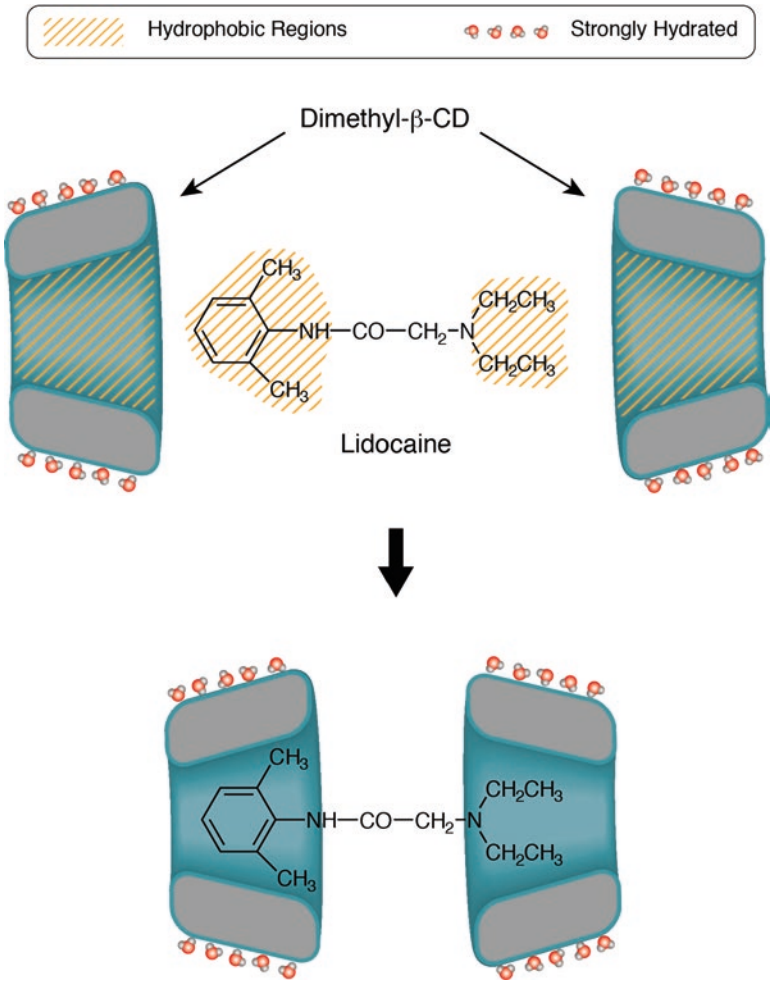

Fig. 2.21 Schematic illustration of the interaction between lidocaine and dimethyl-β-cyclodextrin DIMEB. (Adapted from Szejtli et al. 1983b)

racemic mixture of (+) and (−) enantiomers of vincadifformine on a β-cyclodextrin-polymer column (5 × 90 cm, pH 5.5, flow rate 300 mL/h, 25 °C) in one run. The relative retention volumes were 1.9–2.1 for the (+) enantiomer and 2.2–2.4 for (−) enantiomer (Szejtli 1985a, 1987e).

Later, insoluble β-cyclodextrin polymer was used as thin-layer chromatographic adsorbent, and the method was a very simple tool used to separate a wide variety of compounds with similar chemical structure (Cserháti et al. 1995). Table 2.6 summarized the known possibilities of the applications of cyclodextrins in chromatographic methods according to Professor Szejtli, "which did not implicate that no further combinations will be exploited in the future" (Szejtli 1987a, e).

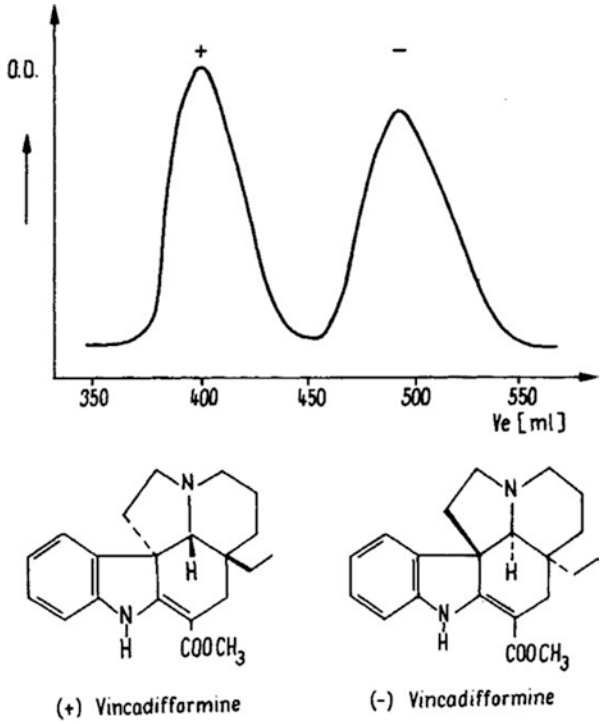

Fig. 2.22 Separation of the enantiomers of racemic vincadifformine by passing its aqueous solution through a β-cyclodextrin-polymer column. (Source: CycloLab archives)

Table 2.6 Applications of cyclodextrins in chromatographic methods (*MP* mobile phase; *SP* stationary phase)

Cyclodextrins	Thin layer	Gas-liquid	Gas-solid	Gel inclusion	High-performance liquid	Affinity	Electrokinetic
Native	MP	SP	SP		MP	MP	
Modified	MP	SP	SP		MP		MP
Soluble polymers	MP						
Insoluble polymers		SP	SP	SP			
Immobilized	SP				SP	SP	

Later, the capillary electrophoresis technique was developed for enantioseparation of racemic mixtures using various cyclodextrin derivatives as chiral selectors (Szemán et al. 1996; Iványi et al. 2004). Professor Szejtli has recognized the importance of this, at that time novel, technique. CycloLab was among the first in Hungary

to purchase such an equipment. Professor Szejtli also observed the business opportunities in selling cyclodextrin derivatives for chiral separations.

2.5.5 *Cyclodextrin in Catalysis*

Cyclodextrins and their derivatives had an enzyme-like activity (Bender and Komiyama 1978). Considerable reaction rate enhancements, stereoselective effects, and other catalytic phenomena can be accounted to the cyclodextrins. Inclusion catalysis revealed several characteristics of enzyme-catalyzed reactions, e.g., saturation limit, competitive inhibition, and unproductive bonding. The correlation between the acceleration of the reaction rate and cyclodextrin concentration was not linear; it approached asymptotically the maximum value. This saturation feature was characteristic of such reactions in which the rate-determining step was preceded by complex formation.

Professor Szejtli showed that cyclodextrins can accelerate or decelerate various kinds of reactions, e.g., oxidation, hydrolysis, decarboxylation, nitrosation, and isomerization (Szejtli 1984a, 1985a, 1988a). The reaction rates depended on the cyclodextrin used and the kind and stability of the inclusion compound formed. His conclusions were in accordance with those previously reported by Bender and Komiyama (1978). Professor Szejtli described cyclodextrin-catalyzed reactions in details in his second book *Cyclodextrin Technology* (Szejtli 1988a).

Figure 2.23 shows a schematic representation of selective chlorination of anisole in presence of soluble α-cyclodextrin polymers (Szejtli 1984a, 1985a). 99% p-isomer was obtained in presence of cyclodextrin polymer, in agreement with the results previously published by Breslow and Campbell (1969).

In 1990, Professor Szejtli indicated that organic ligand containing coordination metal ion complexes and the organometallic compounds in which the metal atoms were covalently bound can form regular inclusion complexes with cyclodextrins (Szejtli 1990a).

Metal ions can be complexed with cyclodextrins in three ways as reported in Fig. 2.24: (a) the metal reacted with the hydroxyl groups of the cyclodextrin

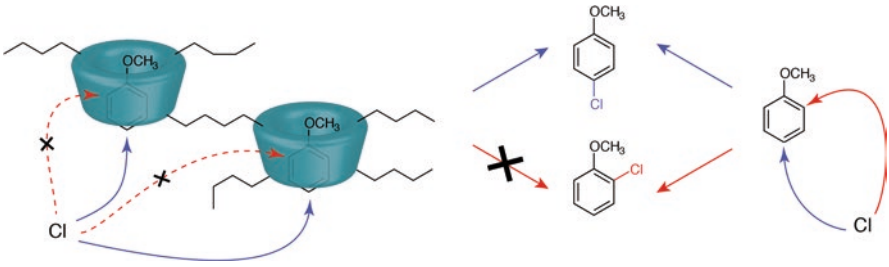

Fig. 2.23 Schematic representation of selective chlorination of anisole in presence of α-cyclodextrin polymers. (Adapted from Szejtli 1984a, 1985a)

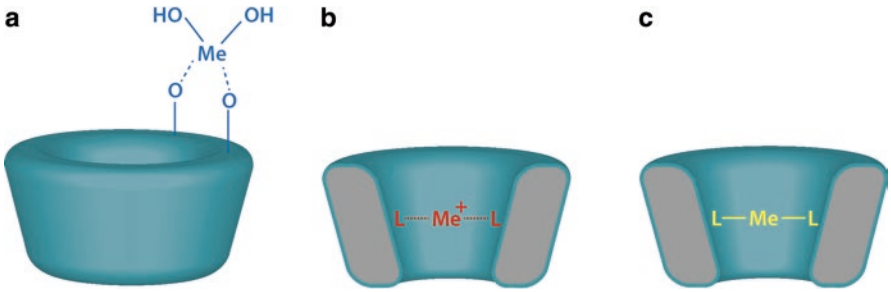

Fig. 2.24 Three types of metal-cyclodextrin complexes: (**a**) hydroxo complex, (**b**) ternary ligand-coordinated metal inclusion, and (**c**) metal-organic compound inclusion. (Adapted from Szejtli 1990a)

molecule to form a hydroxo complex; this was not an inclusion complex strictly speaking; (b) the metal forms coordination complex with organic ligands, and this coordination complex will be included into the cavity, i.e., formation of ternary complexes cyclodextrin + organic ligand + metal ion; and (c) the metal was bound covalently in a metal-organic compound, i.e., a binary complex, which will form a regular inclusion complex with a cyclodextrin molecule. These complexes were used as catalysts, enzyme models, siderophores, color, and fluorescence-enhancing reagents (Szejtli 1990a).

2.5.6 Cyclodextrin in Biotechnology

The application of cyclodextrins in biotechnology began in the 1980s (Szejtli 1986a, b; Duchêne 1987; Hedges 1998). Cyclodextrins were interesting in this domain because they did not damage the microbial cells or the enzymes. The majority of processes involved an enzyme-catalyzed transformation of a substrate in aqueous solution. In enzymic and microbiological transformations of various substrates, e.g., microbiological substrate conversion, fermentation, enhancement of vaccine production, enzymic reaction of lipids, tissue cultures, and also detoxification of industrial wastewaters, the main aims were to enhance the yield, to accelerate the conversion, to protect the microorganisms, and/or to substitute more expensive components of the medium.

In 1990, Professor Szejtli published a comprehensive review with 44 significant references on their applications in biotechnology (Szejtli 1990b). One year later, this review was updated (Szejtli 1991a). Professor Szejtli discussed the principle of intensification of the enzymatic (microbial) transformation of poorly soluble lipophilic substrates as illustrated in Fig. 2.25 (Szejtli 1991a). The cyclodextrin complexation of the substrates improved their wettability and solubility, i.e., enhanced their concentration in the aqueous phase where the reaction took places (Szejtli 1990b). In many cases, the reaction was accelerated through continuous removal of

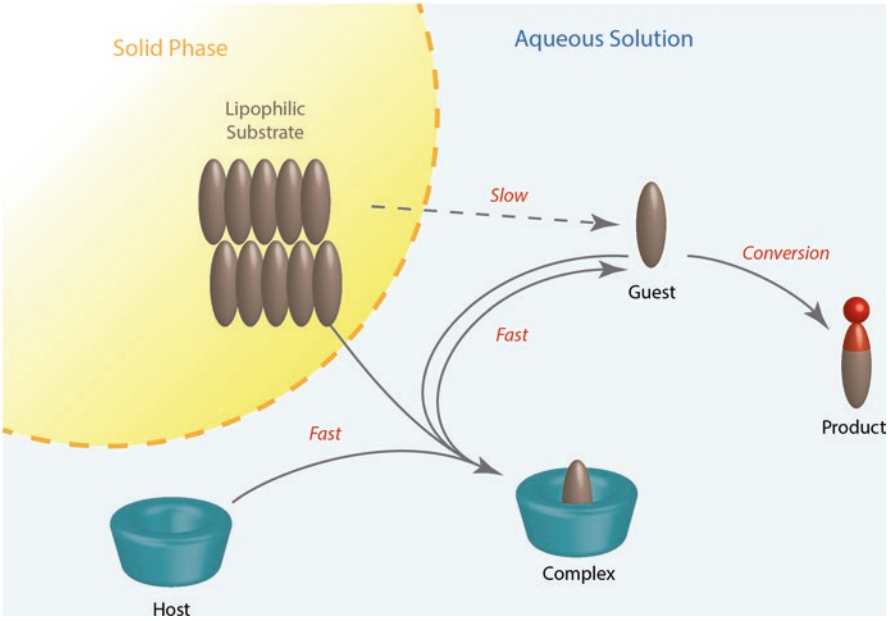

Fig. 2.25 Principle of intensification of the enzymatic transformation of poorly soluble lipophilic substrates. The cyclodextrin complexation of the substrates improves their wettability and solubility. (Adapted from Szejtli 1990b)

the inhibiting products by cyclodextrin molecular encapsulation (Szejtli 1990b, 1991a, 1996; Szejtli and Osa 1996).

2.5.7 Potential Industrial Applications

An interesting field of application of insoluble polymers prepared by cross-linking of cyclodextrins using epoxide cross-linking agents was the purification and separation processes, including isolation or concentration of products, e.g., antibiotics and aroma substances, elimination of undesired substances, purification processes, and wastewater treatment (Szejtli et al. 1978a; Zsadon et al. 1979a; Otta et al. 1982). Polymers containing cyclodextrins can bind efficiently pollutants from aqueous solutions via inclusion complexes. The same materials can also be used for the removal of substances from vapor phase (Otta et al. 1982). They can be applied in two forms: (1) as a powder or granulate, e.g., particles of irregular shape or regular beads, and (2) as column packings.

The first cellulose-cyclodextrin copolymer was patented in 1980 (Szejtli et al. 1980i, 1982b; Otta et al. 1982). Alkali-swollen cellulose fibers were reacted with cyclodextrin and epichlorohydrin. The chemically bound cyclodextrin retained its complex-forming ability and could be loaded with biologically active substances

such as drugs, insect repellents, and antimicrobial agents. These polymers were also found to be efficient adsorbents for environmental purposes (Otta et al. 1988).

Ten years later, Professor Szejtli patented a method to bind cyclodextrins chemically to fibers in order to prepare medical bandages (Szejtli et al. 1991). A cellulose fabric (2.5 g) containing chemically bound β-cyclodextrin was treated with 50 mL solution of 1% I_2 and 0.7% KI in 75% ethanol, followed by solvent removal, to give a medicated bandage. Binding cyclodextrin to fibers chemically opened up new ways for the preparation of perfumed textiles and cosmeto-textiles. The applications of cyclodextrins in the textile industry were published in 2003 (Szejtli 2003).

In 1983, at the 34th Starch Convention at Detmold, Professor Szejtli presented his results on the physiological effects of cyclodextrins on plants (Szejtli 1983a). As biologically active substances, cyclodextrins can be used as plant growth regulators. Treating cereal seeds with cyclodextrin, germination, i.e., development of shoots and roots, was retarded in the first few days as compared to the control seeds, but after some days, this initial stress effect was followed by a more vigorous growing of the new plant; the accelerated development resulted in higher green mass, enhanced ramification, more ears per plant, and higher crop yield. In several cases, a higher resistance of the cyclodextrin-treated plants to phytotoxic herbicides was also observed. The height and dry mass of 4-week-old plants developed from cyclodextrin-treated seeds under laboratory conditions were significantly higher than those of the control plants.

The most significant effects published in agrochemistry and complexation of pesticides were the increase of solubility, the stabilization of substances against rapid decomposition by sunlight, conversion of volatile insecticides into nonvolatile, long-lasting formulations, prevention of the phytotoxic effect of certain fungicides, etc. (Szejtli 1983a, 1984a, 1985a, b).

The interaction of some nonionic tensides with native cyclodextrins (Szejtli 1987c, d; Bujtas et al. 1987; Szogyi et al. 1987) and insoluble β-cyclodextrin polymer was studied (Fenyvesi et al. 1992). The results showed a reduction of the phytotoxicity of tensides after complexation with cyclodextrins (Szejtli 1987c; Bujtas et al. 1987). Cyclodextrin polymer can also bind alkylphenol polyoxyethylene glycol ethers (Fenyvesi et al. 1992) more effectively than polymer produced from linear dextran. Professor Szejtli suggested that polymer could efficiently be used for the elimination of tensides from aqueous solutions.

In 1996, the same material was proved to be effective in healing the wounds inflicted on the back of rats and in healing venous leg ulcers of human patients (Felméray et al. 1996). According to microscopic studies, cyclodextrin polymer in bead form implanted into the muscular tissue of rats did not cause inflammation cell reaction for up to 6-week observation period.

In 1999, Professor Szejtli demonstrated that cyclodextrins were ideal candidates for iodine adsorption from nuclear waste gases (Szente et al. 1999a, b). In particular, methylated α-cyclodextrin and α-cyclodextrin polymers had high adsorption capacity. Such materials could also be used in the air filtration systems.

The same year, a work on the inclusion complexes of UV filters in solution and in solid state was published (Fenyvesi et al. 1999b). The aqueous solubility of the

UV absorbers used in sunscreen cosmetics can be improved by inclusion complexation. Later, the authors demonstrated that randomly methylated β-cyclodextrin was the best solubilizing agent of UVA and UVB filters (Fenyvesi et al. 2004).

The same year, the solubility of β-cyclodextrin was studied in aqueous solutions of various organic acids (Fenyvesi et al. 1999a). The hydroxyl acids such as citric and tartaric acids were found to increase the solubility of β-cyclodextrin, while other carboxylic acids reduced it. From solubility data, the apparent complex association constants were calculated. The authors have also discovered that the inclusion complexes with hydroxyl acids as ternary components may have an outstanding solubility (Chiesi et al. 1994).

In 2004, the biodegradation of several types of cyclodextrins, e.g., acetylated α- and β-cyclodextrins and hydroxypropyl-β-cyclodextrin, under laboratory-controlled composting conditions was investigated (Verstichel et al. 2004). Fully acetylated cyclodextrins were found to be nonbiodegradable during 45 days of composting. Reducing the degree of acetylation had a positive effect on the biodegradation. The authors also showed that the incorporation of antimicrobial agents, e.g., imazalil, into cyclodextrins might open new possibilities for active packaging. The low concentration of the inclusion products in the final packaging did not affect the biodegradability of the biodegradable packaging under composting conditions.

The last paper of Professor Szejtli was published in 2005 in the journal *Journal of Inclusion Phenomena and Macrocyclic Chemistry* (Fig. 2.5) where he tried to respond to the following fact: "The increase in number of marketed drug/cyclodextrin formulations is so slow" (Szejtli 2005). Another important question was "Which cyclodextrin for what purpose?" A possible response was given in Table 2.7 (Szejtli 2005).

2.6 Conclusions

This chapter is a tribute to the immense scientific career of Professor József Szejtli. We have attempted to highlight his many scientific achievements and also provided insight into his formative years and into the importance of cyclodextrin community in his life.

Professor Szejtli has devoted his life to cyclodextrins, and he is considered to be the "Godfather of Cyclodextrins." He is distinguished not only for his contribution to chemistry, biology, and technology of cyclodextrins but also for his important contribution to the dissemination of knowledge about cyclodextrins from the end of the 1970s. Professor Szejtli was a giant among cyclodextrin chemists, an eminent scientist and visionary, a businessman, a wonderful mentor, and a warm, friendly, and generous communicator.

Professor Szejtli did attract and recruit young scientists by his own enthusiasm and oversee the everyday research at the lab, thus creating a dedicated team under his mentorship. Teaching and convincing his carefully selected young co-workers about the usefulness of cyclodextrins is probably one of the most important reasons

Table 2.7 What cyclodextrin for what purpose? (CD, cyclodextrin; SBE, sulfobutyl-β-cyclodextrin; MeCD, methylated cyclodextrin)

	Drugs/parenteral	Drugs/per os	Drugs/topical	Cosmetics	Foods	Biotechnology	Analytical chemistry	Chemical industry
αCD	+	+++	+++	+++	+	+	+	+
βCD	−	+++	+	+	++	++		+++
γCD	+	+++	+++	+++	+++	−		+++
HPβCD	++	++	+++	+++	−	++	++	++
SBE	+++	+	−	−	−	−	++	−
MeCD	+	+	+	−	−	+++	++	+++

"−": not recommended, either on account of toxic side effects or too high prices
"+": in limited number of cases
"++": can be recommended, but for the same purpose, there is better or cheaper candidate
"+++": most recommended because of existing approval, acceptable price, and technical performance

for Szejtli's ultimate success in the introduction of cyclodextrins into commercially useful applications.

His tireless efforts, dedication, and trust in the cyclodextrins helped him retain the best of his co-workers, even when the cyclodextrin product development was still in its infancy and so much unappreciated. Many of those young co-workers Professor Szejtli attracted in the early 1980s are today worldwide acknowledged cyclodextrin experts and core members of CycloLab.

Professor Szejtli has received much recognition for his immense scientific and industrial oeuvre, but more important than all the honors he has received and the prizes is the affection in which he is held worldwide.

Acknowledgments The authors thank Nadia Morin-Crini (*Université Bourgogne Franche-Comté*, France) for his critical reading of early drafts of this chapter and English corrections. Special thanks are due to Marc Fourmentin (*Université du Littoral-Côte-d'Opale*, France) for illustration graphics. For Grégorio Crini, it was a great privilege and honor to write this chapter with Éva Fenyvesi and Lajos Szente.

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Chapter 3
Professor Casu and Cyclodextrins

Giangiacomo Torri, Annamaria Naggi, and Grégorio Crini

Contents

Abstract Three years ago, Professor Benito Casu, G. Ronzoni Institute for Chemical and Biochemical Research, passed away on November 11, 2016, shortly before his 90th birthday. Professor Casu was an eminent scientist in the area of chemistry and biochemistry of polysaccharides and glycosaminoglycans.

Casu's scientific career started in the 1950s with the study of carbohydrates by innovative spectrometric techniques. Professor Casu was on the list of prestigious researchers who contributed in the 1960s to the development of cyclodextrins. At that time, there was a lack of sufficient knowledge about these molecules. Few researchers believed in the potential that these new molecules had. In the mid-1960s, Professor Casu was the first to demonstrate that infrared spectroscopy and proton

G. Torri (✉) · A. Naggi
Istituto di Chimica e Biochimica G. Ronzoni, Milan, Italy
e-mail: torri@ronzoni.it; naggi@ronzoni.it

G. Crini (✉)
Chrono-environnement, UMR 6249, UFR Sciences et Techniques,
Université Bourgogne Franche-Comté, Besançon, France
e-mail: gregorio.crini@univ-fcomte.fr

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_3

nuclear magnetic resonance were powerful methods to study the structure and conformations of cyclodextrins. He suggested a common shape of the glucopyranose rings in the chair C-1 and the presence of hydrogen bonds between the hydroxyl groups. These conclusions greatly advanced the understanding of the structure and chemistry of cyclodextrins and their properties. In 1967, Professor Casu published the first perspective view of 2,6-di-O-methylated cyclodextrin and, 1 year later, prepared cyclodextrin derivatives such as methylated and acetylated products. At the end of the 1960s, Professor Casu was among the first to verify the idea that if the guest molecule is accommodated in the cyclodextrin cavity, then the hydrogen atoms located in the interior of the cavity would be significantly shielded by the guest, whereas the hydrogen atoms on the outer surface would not be affected by the formation of the inclusion complex. In 1969, his interest extended to biological active substances such as heparin with a visit to Department of Chemistry of McGill University of Montreal, Canada, guest of Professor Arthur S. Perlin. Nevertheless, Professor Casu has continued to work on cyclodextrin, publishing important contributions on the use of methylated cyclodextrins as versatile complexing agents for the complexation of some n-alkanes and dyes, and on the interactions of cyclodextrins with glycolipids. He also studied inclusion properties of methylated cycloamyloses, demonstrating that the inclusion complexes of methylated derivatives were more stable than the corresponding complexes with the parent cyclodextrins. Professor Casu was among the first to publish general notes and reviews on cyclodextrins for a broader public. He was a prolific publisher on topics related to cyclodextrin and heparin, an enthusiastic teacher of many doctoral students and postdoctoral fellows, a genial host to visitors, and a truly caring person.

In this chapter, we would like to pay a posthumous tribute to Professor Casu, one of the pioneers in the dissemination of the knowledge of cyclodextrins in the 1960–1970s and later of heparin.

Keywords Tribute · Professor Casu · Polysaccharides · Structure · Cyclodextrin derivatives · Nuclear magnetic resonance · Infra-red spectroscopy · Awards and distinctions

3.1 Introduction

On November 11, 2016, the glycoscience community lost one of its leading figures, Professor Benito Casu (Fig. 3.1), G. Ronzoni Institute for Chemical and Biochemical Research, at the age of 89. In him, we have lost an eminent and passionate scientist, a visionary, and a colleague of great merit, particularly in the area of chemistry and biochemistry of natural substances (Crini 2014; Crini and Torri 2017; Torri and Cassinelli 2018). Gentleman Professor Casu has been a friendly and generous

Fig. 3.1 Professor Benito Casu in 2012. (Image credit: G. Torri)

communicator, an enthusiastic teacher of many doctoral students and postdoctoral fellows, a genial host to visitors, and a truly caring person.

Casu's scientific career was based on two main research axes: the first focused on oligosaccharides and polysaccharides developed essentially during the years between 1951 and 1980 and the second on biological substances during 1969–2014.

Professor Casu had many varied scientific interests: chemistry and biochemistry of starch, linear and cyclic dextrins, glycosaminoglycans, mechanism of action of biologically active substances, structural analysis of carbohydrates, and their interactions with proteins, enzymology, analytical chemistry, surfactant chemistry, etc. Professor Casu has also made a significant contribution to the development of structural modelling and NMR, infrared, and Raman techniques applied to carbohydrates (Crini 2014; Crini and Torri 2017; Torri and Cassinelli 2018). All this research was carried out, thanks to multidisciplinary and transversal collaborations developed and thanks to his willingness to involve both academic and industrial colleagues, both national and especially international. Its activities have also focused on scientific fields with direct social implications, in accordance with the principles dictated by the founder of the Ronzoni Institute.

At the end of the 1940s, the young student Casu first concentrated on the field of carbohydrate chemistry, e.g., investigating the structure of glucose and its chemical modification, at the University of Pavia, Italy, where he presented his PhD in 1950 (Crini 2014). In the early 1950s, Dr. Casu began his scientific career at the G. Ronzoni Institute, as research fellow in 1951, and research assistant in 1954, studying the structure of disaccharides such as maltose, oligosaccharides, e.g.,

linear and cyclic dextrins, and polysaccharides such as starch, using the then highly innovative spectrometric techniques (Reggiani and Casu 1957; Crini 2014).

In the mid-1950s, Professor Casu investigated in details the structure and conformation of the two components of starch, i.e., amylose and amylopectin. At that time, the studies on amylose conformation were even marred by hot debate between the different laboratories. At the same time, Professor Casu studied the structure, chemistry, and inclusion properties of cycloamyloses-cyclodextrins, mainly α-cyclodextrin and β-cyclodextrin and their methylated and acetylated derivatives. Indeed, there was a lack of sufficient knowledge about their structure (Crini 2014; Crini et al. 2018). In the mid-1960s, the works of Professor Casu on the structure and the conformations of amylose and cycloamyloses, using infrared and nuclear magnetic resonance techniques, were acknowledged to have made an important contribution (Crini 2014). Significant collaborations have been put in place by Professor Casu with American, e.g., Professor Dexter French; Hungarian, e.g., Professor József Szejtli; and French, e.g., Professor Michel Morcellet, groups in the 1960s, 1970s, and 1990s, respectively.

During more than 30 years, Professor Casu occupied a central place in the scientific knowledge of cyclodextrins. His first article on cyclodextrins entitled "Infrared spectra of amylose and its oligomers" was published in 1964 in Journal of Polymer Science (Casu and Reggiani 1964). This work, supported by a grant from the US Department of Agriculture, was presented in preliminary form at the International Conference on the IR Spectra of High Polymers in July 1963 (Milan, Italy). In 1965, Professor Casu gave an invited lecture on this work at the Starch Round Table Conference, Pocono Manor, Pa., USA. From the 1970s, as Director of the Ronzoni Institute, Professor Casu mainly focused the research on heparin. However, he continued to publish several articles and reviews on cyclodextrins and worked on several International, European, and National projects related to cyclodextrins. His last article entitled "Disruption of micellar aggregates of ganglioside GM-1 by complexation with alpha-cyclodextrin" was published in 1994 in the International Journal of Pharmaceutics (Ahmed et al. 1994).

Throughout his scientific career, Professor Casu has given numerous conferences around the world, particularly in North America. He has published an impressive number of articles and patents, and his name is very often cited in the bibliographic references of articles on these topics. Until his death, Professor Casu was still Scientific Consultant of the President of the G. Ronzoni Institute (Crini and Torri 2017; Torri and Cassinelli 2018).

This chapter is a tribute to his scientific oeuvre. First, it gives an overview of his exceptional scientific career. Next, we highlight some important work on cyclodextrins published by Professor Casu.

3.2 Benito Casu, 1927–2016

3.2.1 Early Years

Benito Casu was born on March 27, 1927, in Brescia, Italy, the son of Luigi Casu and Angela Porcu. He studied chemistry at the University of Pavia where, in 1950, he earned his doctorate in carbohydrate chemistry, studying the structure of glucose and some related carbohydrates using spectrometric techniques.

In 1951, as research fellow, Dr. Casu started his scientific career with research on starch and cyclodextrins at the Physical-Chemistry Unit of the G. Ronzoni Institute, a nonprofit research foundation for chemical and biochemical research under the direction of Professor Alfredo Dansi. Two years later, Dr. Casu became a research assistant in this institute. In May 6, 1954, Benito Casu married Marta Mancini, and they have two children.

During more than 30 years, Professor Casu published several significant papers on the structure of native and modified cyclodextrins using infrared and nuclear magnetic resonance (NMR) techniques (Crini 2014).

In early 1968, Dr. Casu obtained the professorship in chemical spectroscopy. One year later, he was a Harold Hibbert Memorial Fellow (1968–1969) at the Department of Chemistry of McGill University of Montreal, Canada, guest of Professor Arthur S. Perlin, where they forged a lifelong friendship.

During this stage, Professor Casu studied polysaccharides and biological substances using innovative NMR techniques. He also had the opportunity to present several conferences in the USA, where he met Professor Dexter French (Iowa State University), one of the prestigious researchers who have contributed to the development of cyclodextrins. The two research groups then collaborated for about 10 years (Crini and Torri 2017; Torri and Cassinelli 2018). During this "American period," Professor Casu also had friendly contacts and interactions with the Professors R.H. Marchesseault, C. Dietrich, and A. Gorin.

3.2.2 Professor Casu: Director of the G. Ronzoni Institute

Professor Casu returned to Milan in 1970 and focused his work on heparin. In 1973, he became the Director of the *Istituto di Ricerche Chimiche e Biochimiche Giuliana Ronzoni* and served in this position until 1992 (Crini and Torri 2017). Professor Casu remained the scientific consultant of the board of directors of Ronzoni Institute until to 2015.

For over 20 years, under his direction, the institute underwent significant economic and scientific development. In the mid-1970s, the pioneer NMR studies on the structure and conformational flexibility of heparin as well as of the heparin active sites to antithrombin provided him an international notoriety. Through interdisciplinary and international networks and collaborations, the institute significantly

contributed to the development of both new analytical methodologies and novel heparin derivatives (Torri and Cassinelli 2018). Pleiotropic activities of heparins have been studied through the pioneering development of non-anticoagulant/anti-thrombotic heparins.

The institute also participated to numerous National, European, and International cyclodextrin-based projects, e.g., the European FAIR program 1995–1999 "Development from cyclodextrin derivatives to polymeric materials for selective transport, separation and detection of active substances" (European Commission DGXII, contract no. CT 95-0300). This project, coordinated by Professor Gerhard Wenz, also involved Wilfried König, Michel Morcellet, Bruno Perly, Jacques Defaye, David Reinhoudt, Giangiacomo Torri, Annamaria Naggi, Carmen Vecchi, Bernard Martel and Grégorio Crini, among others.

3.2.3 Professor Casu: A Friendly and Generous Communicator

Professor Casu was a warm, friendly, and generous communicator and a gifted and dedicated teacher. He was lecturer on biopolymers from 1970 to 1982 at the University of Pavia, Italy. In order to promote the exchange of scientific information, Professor Casu organized numerous symposia and workshops and encouraged collaborative works with foreign universities and laboratories and the exchange of researchers and students (Crini and Torri 2017; Torri and Cassinelli 2018). In 1996, Professor Casu organized the 18th International Carbohydrate Symposium (July 21–26, Milan, Italy) (Fig. 3.2). The main talks were published in the journal *Pure and Applied Chemistry* (volume 69, issue 9, 1997).

Professor Casu also trained numerous students, PhD, and postdoctoral students. He has always been a teacher of the highest quality and a gentleman professor who has inspired enthusiasm for research among his students and Italian and foreign colleagues, and his hospitality to visitors has been generous. His talent was also applied in academic affairs.

3.2.4 Membership

Professor Casu was a member of the Italian Chemical Society (Carbohydrate Group Coordinator, 1984–1996) and of the International Carbohydrate Organization (National Representative since 1976, President 1996–1998). Professor Casu was a member of the International Advisory Board of Carbohydrate Research (1970–1985) and Biochemical Journal (since 1973). He also served as a member of Scientific Advisory Board at Momenta Pharmaceuticals Inc. and Endotis Pharma SA.

Fig. 3.2 Eighteenth International Carbohydrate Symposium organized by Professor Casu in 1996. (Image credit: G. Torri)

3.2.5 Awards and Distinctions

Professor Casu received many distinctions and prizes, most notably the degree of Doctor in Medicine *Honoris causa* at the University of Uppsala, Sweden (1998), the gold medals of the Italian Chemical Society (1998) and of the Italian Carbohydrate Group (2003), and recognition plaques from the Italian Cyclodextrin Group (2009) and the International Union of Angiology (1990 and 2012).

3.3 Casu's Scientific Achievements

3.3.1 Professor Casu and Polysaccharides

In the early 1950s, Dr. Casu began working on carbohydrate structure and conformation using the most innovative spectrometric techniques of the time (Reggiani and Casu 1957; Crini and Torri 2017). He was the first to demonstrate that infrared spectroscopy (IR) and proton nuclear magnetic resonance (^{1}H-NMR) were powerful methods to study the structure and conformations of disaccharides, oligosaccharides, and polysaccharides, including starch and its linear and cyclic derivatives (Crini 2014; Crini and Torri 2017). All his results were summarized in the 1980s in two comprehensive reviews (Casu 1982, 1985a).

In 1964, Professor Casu studied infrared spectra of starch derivatives. This work was supported by a grant from the US Department of Agriculture. Professor Casu reported infrared spectra of amylose, cycloamyloses, and amylodextrin and assigned

the main individual bands (Casu and Reggiani 1964). The IR spectra were taken with a Perkin-Elmer model 125 spectrophotometer. In this paper, he suggested for the first time a common shape of the glucopyranose rings, in the chair C-1, in all the starch derivatives studied, and the presence of hydrogen bonds between the hydroxyl groups (Crini 2014). The same year, Professor Casu also published hydroxyl proton resonances of sugars in water and dimethyl sulfoxide solutions in order to characterize the structural factors which affected ring vibrations in infrared data and to clarify the significance of their shifts ongoing from cyclic to linear structures (Casu 1964; Casu et al. 1964). Later, he detailed NMR spectra and conformation of glucose and some related carbohydrates in the same conditions (Casu et al. 1965b, 1966, 1967, 1968b).

In 1965, an IR spectrophotometric procedure was developed for determining water in carbohydrates (Casu et al. 1965a). The method was based on the measurement of the intensity of 1655 cm^{-1} band of water in a solution of the hydrated sugar in dimethyl sulfoxide. This method was particularly interesting when unsubstituted carbohydrates contained crystallized water. The average percent difference between the results obtained by the IR versus the usual oven-drying method was find to be about ±1%. One year later, his results clearly demonstrated that the amylose macromolecule had a flexible structure, with a helical pattern, which could take various conformations through rotation of the monomeric blocks around the glucosidic linkages (Casu and Reggiani 1966). Both IR and NMR spectra showed that the C1-H bond was equatorial and C1-O axial, also confirming the C-1 chair conformation of the glucopyranose units (Casu and Reggiani 1964, 1966). Professor Casu also showed the existence of intermolecular hydrogen bonds contributing to the stabilization of the helical structures. At that time, these works were acknowledged to have made an important contribution to this topic (Crini and Torri 2017; Crini et al. 2018). Professor Casu obtained similar results when studying the native cycloamylose molecules, particularly cyclohexaamylose or α-cyclodextrin, with the first IR and ^{1}H-NMR spectroscopic studies (Casu and Reggiani 1964, 1966). The cycloamylose samples were prepared by Professor French.

3.3.2 Professor Casu and Cyclodextrins

Professor Casu was also on the list of prestigious researchers, such as Professors Dexter French, Friedrich Cramer, Myron Lee bender, József Szejtli, and Wolfram Saenger, who contributed in the 1960–1970s to the development of cyclodextrins (Crini 2014). Few researchers at that time believed in the potential that these new molecules had (Szejtli 1982, 1988; Crini 2014; Crini et al. 2018).

Professor Casu showed that IR and ^{1}H-NMR spectroscopy were powerful methods to study the conformations of not only amylose and linear dextrins but also cyclodextrins. In the middle of the 1960s, he investigated for the first time the NMR spectra of cyclodextrins (Casu 1964, 1968a, b), and his conclusions greatly advanced the understanding of the structure and chemistry of cyclodextrins and their

properties (Crini 2014; Crini et al. 2018). For instance, Professor Casu demonstrated three important characteristics (Crini 2014): (1) all secondary hydroxyl groups were situated on one of the two edges of the cyclodextrin ring, whereas all the primary ones were placed on the other edge; (2) the cavity was lined by the hydrogen atoms and the glycosidic oxygen bridges, respectively; and (3) the C-2 and C-3 hydroxyl groups of the adjacent glucopyranose units formed hydrogen bonds which stabilized the shape of the cyclodextrin molecule. Later, Professor Szejtli has shown that these characteristics had a significant influence on the solubility of cyclodextrins in water (Szejtli 1982, 1988).

Professor Casu reported the infrared spectra of several cycloamyloses (Fig. 3.3) and assigned the main individual bands (Fig. 3.4). He detailed the spectra of hydrates of cyclohexaamylose where he observed the reduced splitting and the broadening of the bands in the dehydrated samples with respect to the hydrated forms (Casu and Reggiani 1964; Casu et al. 1965a). Professor Casu concluded that "it was not easy to explain the shift of the frequencies of the ring vibrations on going from cyclohexaamylose to cycloheptaamylose to amylodextrin and amylose in terms of the conformation of glucopyranose rings" (Casu et al. 1965a). He suggested that "the configuration of the ring sequences and the bulkiness of the chains certainly affected ring vibrations" (Crini 2014). He also suggested the existence in water of hydrogen bonds between the secondary hydroxyl functions (Casu et al. 1965a).

In 1966, Professor Casu, studying the IR spectra of cycloamyloses in the amorphous solid phase and in aqueous and dimethyl sulfoxide solutions (Fig. 3.5), showed that the C1-H bond was equatorial and the C1-O bond axial, and this was consistent with the C-1 conformation of the glucopyranose (Casu and Reggiani 1966). The same year, Professor Casu published the first NMR spectra of cycloamyloses (Fig. 3.6). Comparing the spectra of maltose and cycloamyloses, "an interesting and curious downfield displacement of the non-anomeric hydroxyl signal below 5" was evident (Casu et al. 1966). Professor Casu also showed that ^{1}H-NMR spectroscopy was applicable to quantitative analysis of concentrated solutions of mixtures of cyclodextrins in dimethyl sulfoxide (Casu 1966, 1967; Casu and Reggiani 1966; Casu et al. 1966).

Using NMR of α-cyclodextrin in DMSO-d_6 through hydrogen-deuterium exchanges of cyclodextrins, Professor Casu also demonstrated that the D-glucopyranose units in cyclodextrins were in the C-1 chair conformation and the primary and secondary hydroxyl groups had similar conformation to those in the crystalline state (Casu 1966; Casu and Reggiani 1966). Both NMR and IR spectra through hydrogen-deuterium exchanges of cyclodextrins also first showed the existence in water of hydrogen bonds between the secondary hydroxyl functions, which brought about a slight chemical shift in the protons of these functions (Casu 1966; Casu and Reggiani 1966). Later, Professor Casu determined the value of the deuteration equilibrium constant of the same functions (Casu 1967; Casu et al. 1968a). The equilibrium constant for the secondary hydroxyl groups was 0.75 in α-cyclodextrin and 0.65 in β-cyclodextrin, both much less than the corresponding value for amylose, i.e., 0.85. This clearly indicated that intramolecular hydrogen bonding rendered the secondary hydroxyl groups in cyclodextrins more resistant to

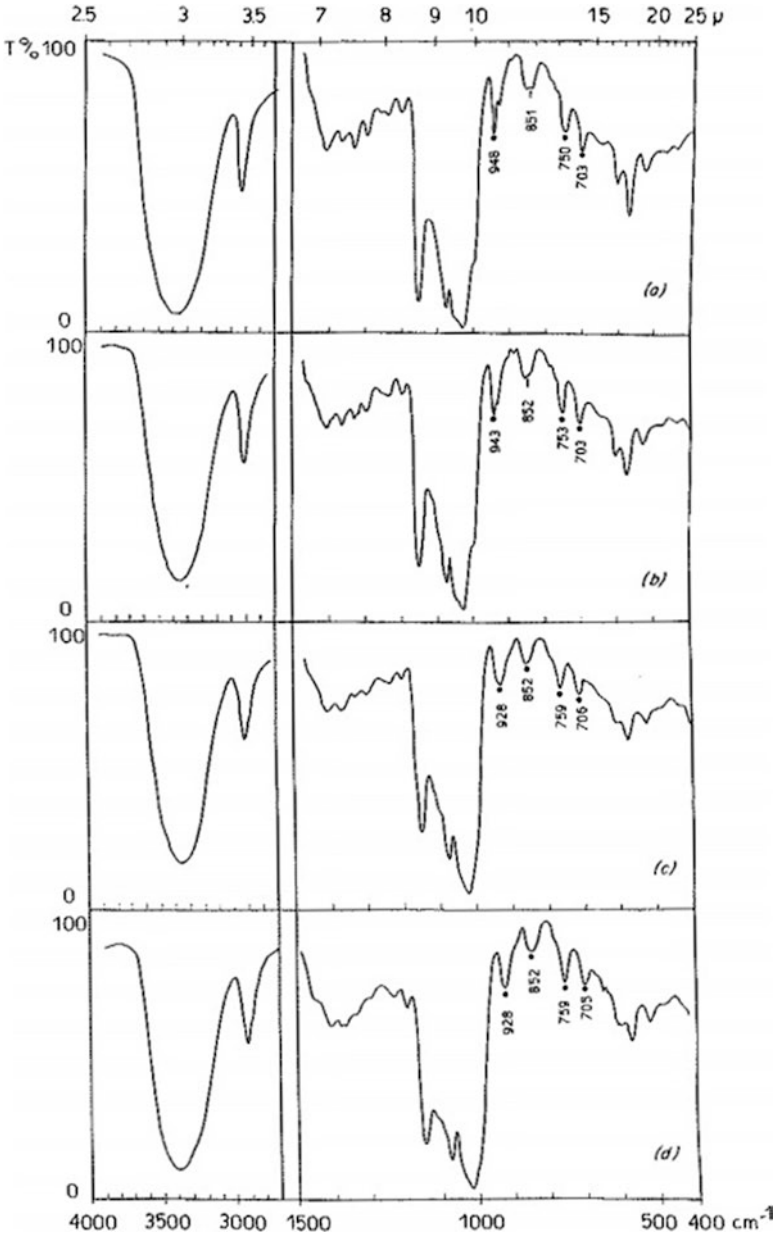


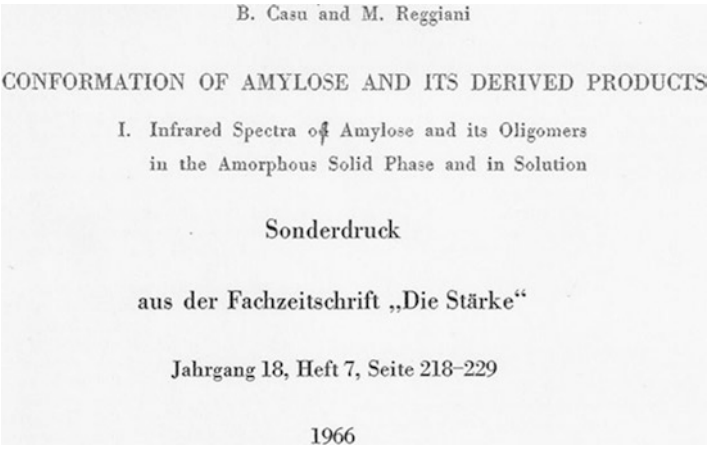
Fig. 3.3 Infrared spectra of amorphous samples performed by Professor Casu in 1964: (**a**) cyclohexaamylose, (**b**) cycloheptaamylose, (**c**) amylodextrin, and (**d**) amylose. (Source: Ronzoni Institute archives)

Frequency, cm.$^{-1}$				
Cyclo-hexa-amylose	Cyclo-hepta-amylose	Amylo-dextrin	Amylose	Tentative assignment
1445	1445	1450	1450	CH_2 bending
1405	1408	1410	1409	O—H in-plane bending
1363	1364	1370	1368	C—H bending
1330	1329	1330	1335	C—H bending
1293	1297	1300	1300	C—H bending
1260	1258			O—H in-plane bending
1237	1236	1234	1234	O—H in-plane bending
1199	1199	1200	1197	O—H in-plane bending
1151	1152	1150	1148	Coupled C—O (bridge) as stretching/O—H bending
1074	1074	1076	1075	C—O stretching/C—C stretching
1028	1025	1019	1018	C—O stretching/C—C stretching
948	943	928	928	Ring vibration
934	936			Ring vibration
856	856	852	852	C_1 group vibration
842	845			C_1 group vibration
750	753	759	759	Ring breathing vibration
703	703	706	705	Ring vibration
650	650	650	650	O—H out-of-plane bending
605	605	605	605	Ring vibration
570	574	575	573	Ring vibration
527	527	525	525	Ring vibration

Fig. 3.4 Infrared frequencies of amorphous cyclohexaamylose, cycloheptaamylose, amylodextrin, and amylose in the 1500–400 cm^{-1} range assigned by Professor Casu in 1964. (Source: Ronzoni Institute archives)

hydrogen exchange. All these results, presented for the first time at a conference invited to the 10th Congress of the Italian Chemical Society (Padova, Italy, June 1968), were "relevant" according to Professor Szejtli, since most of the reactions in which cyclodextrins were involved were carried out in solution, mostly in water (Szejtli 1982, 1988).

Another interesting fact was that the hydrogen bonds in β-cyclodextrin were also stronger than in α-cyclodextrin (Casu 1966; Casu et al. 1968a, b). On raising the temperature, the hydroxyl signals shifted to higher fields, which was indicative of a weakening of the hydrogen bonds. At the same time, the signals for the anomeric protons remained practically unchanged. These results were in accordance with the presence of intramolecular hydrogen bonding in cyclodextrins previously proposed by Hybl et al. (1965), on the basis of X-ray crystallography data. Two years later, Cramer's group also published similar results using optical rotator dispersion spectroscopy (Cramer and Hettler 1967; Cramer et al. 1967). Later, Takeo and Kuge (1969), investigating the NMR spectra of β-cyclodextrin and γ-cyclodextrin (DMSO-d_6 at 25 °C and 80 °C), showed that hydrogen bonds were stronger in γ-cyclodextrin than in β-cyclodextrin, in agreement with Casu's results.



B. Casu and M. Reggiani

CONFORMATION OF AMYLOSE AND ITS DERIVED PRODUCTS

I. Infrared Spectra of Amylose and its Oligomers in the Amorphous Solid Phase and in Solution

Sonderdruck

aus der Fachzeitschrift „Die Stärke"

Jahrgang 18, Heft 7, Seite 218–229

1966

Fig. 3.5 First page of the article of Professor Casu published in 1966 where he described the infrared spectra of cyclodextrin in the amorphous solid phase and in water and dimethyl sulfoxide solutions. (Source: Wissenschaftliche Verlagsgesellschaft MBH., Stuttgart, Germany; with permission of Pergamon Press Ltd.)

In the mid-1960s, Professor Casu also studied the formation of inclusion complexes using NMR, infrared, and UV techniques (Casu 1966, 1968a; Casu and Rava 1966). These results were presented at the *Consiglio Nazionale delle Ricerche*, Rome, Italy, in July 1966. At that time, NMR investigations of the complexes were technically difficult due to the low solubility of the products in D_2O (Higuchi and Connors 1965; Demarco and Thakkar 1970; Wood et al. 1977; Szejtli 1982, 1988; Crini 2014). Professor Casu was among the first to verify the idea that "if the guest molecule is accommodated in the cyclodextrin cavity, then the hydrogen atoms located in the interior of the cavity, i.e. C3-H and C5-H, will be significantly shielded by the guest," whereas "the hydrogen atoms on the outer surface, i.e. C2-H, C4-H and C6-H of the glucose unit, will not be affected by the formation of the inclusion complex" (Casu and Rava 1966). It was interesting to note that, at that time, only X-ray diffraction data proved that the incorporated guest was located really in the interior of the ring molecule (Takeo and Kuge 1969, 1970; Szejtli 1982).

Professor Casu also was the first to show that the acid dissociation constants of substituted benzoic acids included in cyclodextrins gave a linear correlation with Hammett's substituent constants (Fig. 3.7). The stability of the complex became higher with the increase of the electron donor character of the substituents of the included guest (Casu and Rava 1966). One year later, Professor Cramer published similar conclusions (Cramer and Hettler 1967; Cramer et al. 1967). Professor Casu, studying the interactions between dyes and α-cyclodextrin (Fig. 3.8), showed that complex formation with cyclodextrin altered the original UV absorption spectrum of the guest molecule (Casu and Rava 1966). This result was in agreement with the previous conclusions reported by Cramer's group (Cramer 1952, 1954; Cramer and

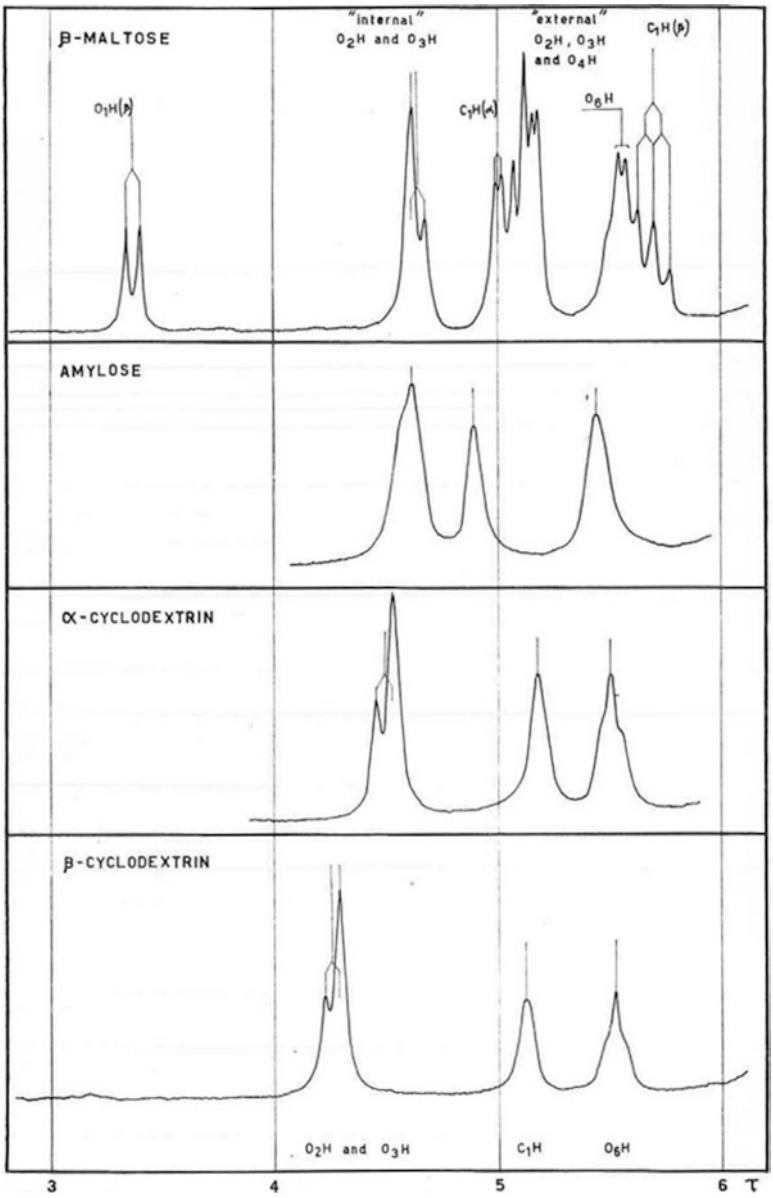


Fig. 3.6 The first NMR spectra of β-maltose, α-cyclodextrin, and β-cyclodextrin in dimethyl sulfoxide at 28 °C performed by Professor Casu in 1966 using a 100 MHz spectrometer. (Source: Ronzoni Institute archives)

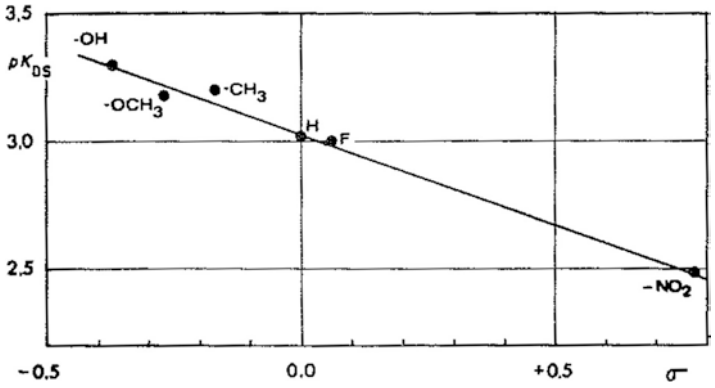


Fig. 3.7 Relationship between the dissociation constants of substituted benzoic acids included in α-cyclodextrin and the Hammett's substituent constants proposed by Professor Casu in 1966. (Source: Ronzoni Institute archives)

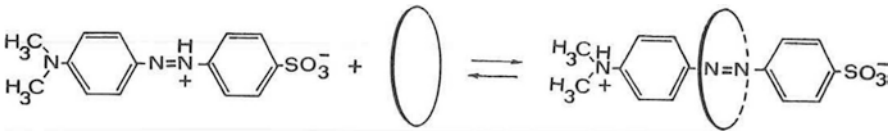


Fig. 3.8 Inclusion complex between methyl orange dye and α-cyclodextrin proposed by Professor Casu in 1966. (Source: Ronzoni Institute archives)

Henglein 1956) and by French's group (Thoma and French 1959, 1960; James et al. 1959). The intensity at the absorption maximum was considerably changed with the increase of α-cyclodextrin concentration. Professor Casu suggested that molecular encapsulation was "an interesting tool to remove dyes from aqueous solution" (Casu and Rava 1966).

In 1967, Professor Casu published the first perspective view of 2,6-di-O-methylated cyclodextrin (Casu et al. 1967). When deuterium replaced a hydrogen-bonding proton, the resulting D-bond was weaker than the original H-bond if this H-bond was strong, while the contrary was valid for weak H-bonds. The data showed that the NMR signals of the corresponding hydroxyl groups occurred at field higher than that of the O_2-H/O_3-H signals of amylose. The existence of an intramolecular H-bond was strongly substantiated by the concentration and solvent independence of the NMR and IR OH absorptions. However, this internal H-bond was not particularly strong. If it was regarded as somewhat intermediate between the "strong" and the "weak" H-bond, no substantial preferences of H of D were expected for the oxygen at C-3 of di-O-methylated cyclodextrins. Professor concluded that "more accurate results will certainly shed light on this facet in the near future when NMR instruments with higher resolution and sensitivity will be available" (Casu et al. 1967).

Later, Professor Casu prepared cyclodextrin derivatives such as methylated (Casu 1968a; Casu et al. 1968c) and acetylated (Casu et al. 1970) products. This work was further supported by a grant from the US Department of Agriculture. The

results showed that partial methylation increased solubility, due to the disruption of the hydrogen bond system. The solubility of a derivative containing seven methyl groups increased, e.g., from 1.8 g/100 mL to 6.7 g/100 mL at 25 °C. Later, Professor Casu studied inclusion properties of methylated cycloamyloses, demonstrating that the inclusion complexes of methylated derivatives were more stable than the corresponding complexes with the parent cyclodextrins (Casu et al. 1968c, 1974a, b, 1979). All these results were presented at an invited plenary lecture at the 7th International Symposium on Carbohydrate Chemistry (Bratislava, August 5–9, 1974). During this conference, Professor Casu met Professor Szejtli for the first time. They then spent a "pleasant evening" discussing these methylated compounds.

A year later, Professor Szejtli invited Professor Casu and Professor Reggiani (Director of the G. Ronzoni Institute) to Budapest for a seminar to present their results on methylated cyclodextrins. The following years saw the emergence of a fruitful and friendly collaboration between their two groups (Crini 2014). The experimental protocols for methylated cycloamyloses, detailed by Professor Casu, were repeated in the 1980s by Professor Szejtli (Szejtli et al. 1980; Szejtli 1982). Since then, these derivatives have had a tremendous development.

In 1979, methylated cyclodextrins were used as versatile complexing agents for the complexation of some n-alkanes and dyes (Casu et al. 1979). Professor Casu's latest work on cyclodextrins was carried out in the late 1980s, publishing four important articles on the interactions of cyclodextrins with glycolipids (Casu et al. 1988, 1990, 1992; Ahmed et al. 1994).

3.3.3 Professor Casu: A Pioneer in the Dissemination of the Knowledge of Cyclodextrins

Professor Casu was among the first to publish general notes and reviews on cyclodextrins for a broader public (Crini 2014; Crini et al. 2018). He is distinguished for his important contribution to the dissemination of knowledge about these substances (Casu 1966, 1968a, b, 1981, 1980, 1981, 1982, 1986, 1987; Casu and Rava 1966; Casu et al. 1974a, b, 1979, 1988).

3.3.4 Professor Casu: A Pioneer of Glycosaminoglycan Research

In 1969, Professor Casu visited the McGill University Department of Chemistry at Montréal, for 1 year as a guest of Professor Perlin. This laboratory was prominent in pure and applied carbohydrate chemistry (Crini and Torri 2017). Professor Casu pursued his studies on the structure of carbohydrates using NMR techniques (Perlin and Casu 1969; Perlin et al. 1970a). His sound collaboration with Professor Perlin

was compiled in an excellent monograph entitled *Spectroscopic Methods* published by Academic Press in 1982 (Perlin and Casu 1982). During this stage in Canada, Professor Casu was also introduced to biologically active natural substances such as heparin (Perlin et al. 1969, 1970b).

After this experience, Professor Casu returned to Milan and abandoned his research on cyclodextrins in the mid-1970s, although he continued to publish several articles on cyclodextrins (Crini and Torri 2017). Indeed, he focused his work on heparin, which earned him greater international visibility for his contribution to the chemistry and biochemistry of glycosaminoglycans (Casu 1993, 1994, 2005; Casu and Torri 1999; Petitou et al. 2003; Harenberg and Casu 2009; Guerrini et al. 2009).

Professor Casu is also recognized as one of the pioneers in glycobiology and glycochemistry and in the dissemination of the knowledge of heparin (Casu 1985b, 1986, 1989, 1993, 1994, 2005; Casu and Torri 1999; Casu and Lindahl 2001; Casu et al. 2001, 2015; Casu and Naggi 2003; Petitou et al. 2003; Harenberg and Casu 2009; Guerrini et al. 2009). He introduced and experimentally validated the concept that the unusual conformational properties of iduronic acid residues are determinant in protein binding and associated biological activities of glycosaminoglycans (Casu et al. 1986).

The 1980s saw the emergence of numerous scientific research collaborations on heparin that almost always led to interpersonal relationships between Professor Casu and eminent scientists working in this field (Torri and Cassinelli 2018). We mention a few of them because it is impossible to establish an exhaustive: e.g., the collaborations with R. Rosenberg, D. Atkins, J. Scott, E. Conrad, and J. Vercellotti, the one with the NIBSC of London in the person of E. Johnson, and mostly the *Connection Française* with J. Choay, D. Ferro, G. Gatti, J. Fareed, M. Petitou, and P. Sinaÿ.

Finally, we would like to mention the one that marked subsequent significant developments in the non-anticoagulant activities of heparin and was based on the deep mutual esteem in which Professor Casu and Professor Ulf Lindahl held each other (Torri and Cassinelli 2018). Under his direction, the Ronzoni Institute's research units have acquired a high reputation in this field, contributing, among other things, to the study of the binding mechanism of heparin to antithrombin, to the development of heparin-based drugs and new active derivatives (Casu and Lindahl 2001; Casu et al. 2001; Casu and Naggi 2003), and to the analytical insights (Guerrini et al. 2008, 2010).

The following years saw the emergence of fruitful collaborations with J. Harenberg, R. Sasisekharan, I. Vlodavsky and G.R. Sanderson, among others. G.R. Sanderson, J.R. Vercellotti, R. Laine, M. Iacomini, M. Hricovíni, G. Crini (Fig. 3.9), E.A. Yates, G. Sassaky, and C.K. Larive spent an enriching sabbatical year with Professor Casu. More than a hundred foreign researchers have been trained by Professor Casu through numerous International and European research projects that he has coordinated.

Fig. 3.9 Professor Casu with Dr. Crini at an Italian-French seminar on polysaccharides (Milan, Italy, 2010), organized by Dr. Torri, celebrating 15 years of friendly collaboration between the two laboratories. (Credit image: G. Crini)

3.4 Conclusion

Professor Benito Casu was a giant among carbohydrate chemists and biochemists, a pioneer in the dissemination of the knowledge of cyclodextrins during more than 30 years (Table 3.1), a pioneer of glycosaminoglycan research during 40 years, a gifted and dedicated teacher, and a warm, friendly, and generous communicator. Gentleman Professor Benito Casu will remain a mentor and a guide for all the researchers involved in the carbohydrate field.

We conclude with two citations of Professor Benito Casu: (1) "Cyclodextrins have been a source of fascination for over a hundred years as the heart of these molecules is easy to penetrate although they are hard to crack (Milano, 1993); 2) "*La ricerca intesa come strumento di conoscenza e non come oggetto di competizione e strumento di potere*," i.e., "Research as a tool of knowledge and not as a matter of competition and power tool" (Montalcini, Elogio dell' imperfezione).

Table 3.1 Recap of the main results of Professor Casu on cyclodextrins

Year	Result
1964	Infrared spectroscopy is a powerful method to study the conformations of cycloamyloses The first infrared spectra of four different hydrates of cyclohexaamylose/α-cyclodextrin Cyclic oligomers of amylose can occur in a variety of crystalline forms: eight crystalline modifications of cyclohexaamylose are published Spectral differences between amorphous amylose, cycloamyloses, and amylodextrin are limited to small frequency displacement of some bands The first suggestion on the fact that the glucopyranose rings in a cyclodextrin molecules possess the C1 chair conformation from spectroscopic data
1965	An infrared spectrophotometric procedure is developed for determining water in carbohydrates Proton nuclear magnetic resonance is also a powerful method to study the conformations of cycloamyloses The first NMR spectra of α-cyclodextrin and β-cyclodextrin NMR data demonstrate that (i) the D-glucopyranose units in cyclodextrins and in maltose possess the C1 chair conformation; (ii) β-cyclodextrin possesses a perfect rigid structure; (iii) the secondary hydrogen bond belt in α-cyclodextrin is incomplete; and (iv) the primary and secondary hydroxyl groups have a similar conformation in both the dissolved and the crystalline state The first suggestion on the existence in water of hydrogen bonds between the secondary hydroxyl groups
1966	The hydrogen bonds in β-cyclodextrin are stronger than in α-cyclodextrin Temperature strongly affects the presence of hydrogen bonds The complete oxidation of all primary hydroxyl functions of α- and β-cyclodextrins is reported Using chemical experiments and NMR data, the existence in water of hydrogen bonds between the secondary hydroxyl groups is demonstrated Intramolecular hydrogen bonding renders the secondary hydroxyl groups in cyclodextrins more resistant to hydrogen exchange The chemical shift and splitting of C_1-H signals of cyclodextrins and amylose in DMSO strongly substantiate the C1 chair conformation C1 chair units are consistent with strong intramolecular H-bonding between O_2-H and O_3-H hydroxyls The strongest intra H-bonding of β-cyclodextrin compared to α-cyclodextrin can arise either from different values of the glycosidic angles or from a slightly different rotation of the glucose units about the glycosidic bond The acid dissociation constant of p-substituted benzoic acids complexed by cyclodextrins give a linear correlation with Hammett's substituent constants The stability of the complex becomes higher with the increase of the electron donor character of the substituents of the included molecule

(continued)

Table 3.1 (continued)

Year	Result
1967	The isotopic hydrogen-deuterium exchange provides valuable information on the conformation of glucose and polyglucoses in solution The O_2-H and O_3-H protons of β-cyclodextrin are less exchangeable than those of α-cyclodextrin and consistently more resistant to exchange than those of maltose and amylose The coupling constants are dependent essentially on the conformation of the glucopyranose units; the chemical shifts are influenced by the magnetic anisotropy of the C-O and C-C bonds of the adjacent units A new method is proposed for methylation of cyclodextrins in solution using DMF or DMF-DMSO mixture in the presence of BaO The first perspective view of 2,6-di-O-methylated cyclodextrin is published The first evidence that O-methylation does not appreciably modify the C1 conformation of the D-glucopyranose units of cyclodextrins and amylose The first suggestion that ^{1}H-NMR spectroscopy is applicable to quantitative analysis of concentrated solutions of mixtures of cyclodextrins in dimethyl sulfoxide
1968	A detailed study using NMR spectroscopy on the effect of temperature on the hydrogen bonds On raising the temperature, the hydroxyl signals shift to higher fields, which is indicative of a weakening of the hydrogen bonds; at the same time, the signals for the anomeric protons remain practically unchanged A detailed study of hydrogen-deuterium exchange on the hydroxyl groups in dimethyl sulfoxide by NMR spectroscopy demonstrates that the equilibrium constant for the secondary hydroxyls is 0.75 in α-cyclodextrin and 0.65 in β-cyclodextrin, both much less than the corresponding value for amylose, i.e., 0.85: this also confirms that intramolecular hydrogen bonding renders the secondary hydroxyl groups in cyclodextrins more resistant to hydrogen exchange The degree of substitution of partially methylated cyclodextrins is determined using NMR spectroscopy First detailed discussion of the conformation of O-methylated cyclodextrins and amylose
1970	The spin-spin coupling constants of the ring protons confirmed the C1 conformation for the D-glucopyranose units in cyclodextrin molecules First detailed discussion of the conformation of acetylated cyclodextrins β-cyclodextrin triacetate has a quasi-eclipsed chain conformation
1974	The inclusion complexes of methylated cyclodextrins are more stable than the corresponding with the parent cyclodextrin Methyl groups introduced during the modification of cyclodextrins by methylation are not expected to obstruct the macrocycle cavities
1979	Methylated cyclodextrins form crystalline complexes with homologous n-alkanes, the stability of which depends on the size and shape of the guest molecule Methylated cyclodextrins are used as stationary phases
1982	The analysis of coupling between ^{13}C and ^{1}H across the glycosidic bridges appears the most promising approach for evaluating inter-residue torsional angles High-resolution NMR spectra of solid samples: these spectra are of obvious interest for direct comparison with spectra in solution

(continued)

Table 3.1 (continued)

Year	Result
1988	A comprehensive study of the interaction of cyclodextrins with neutral glycolipids Cyclodextrin molecules are able to form inclusion complexes with long hydrophobic chains of surfactant molecules The NMR spectra of cyclodextrin change in the presence of the glycolipid not only with shifts of the H-3 and H-5 signals, those usually affected by formation of inclusion complexes, but also with involvement of other signals, e.g., shift of H-2 and H-4 groups
1990	The first demonstration that α-cyclodextrin can disrupt the microaggregates of alkylglycosides in aqueous solutions: the NMR parameters sensitively reflect the interaction of cyclodextrins with these amphiphilic molecules Cyclodextrins can control the aggregation and surfactant properties of amphiphilic substances
1992	Further evidence that cyclodextrins can disrupt micellar aggregates of glycolipids are obtained through ultrafiltration experiments
1994	Confirmation that micellar aggregates of glycolipid can be disrupted by the formation of inclusion complexes only with α-cyclodextrin β-cyclodextrin gives weaker complexes with glycolipid but does not produce any significant disaggregation effects Fully methylated β-cyclodextrin and hydroxyethyl-β-cyclodextrin are also ineffective

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Chapter 4
History of Cyclodextrin Production in Hungary

Éva Fenyvesi, Gábor Seres, and Lajos Szente

Contents

Abstract The research on cyclodextrin started at the beginning of the 1970s at Cyclodextrin Research Laboratory of Chinoin Pharmaceutical and Chemical Works Co. Ltd. in Hungary. Professor József Szejtli, the leading scientist of the field, soon recognized the importance of production. According to his estimations, market demands were likely to reach 1000–2000 tons per year. In early times, cyclodextrins were available on the market only as fine chemicals in few gram quantities. Cyclodextrins were produced by enzymatic degradation and subsequent cyclization of starch, forming a mixture of acyclic and cyclic dextrins. The converting enzyme, cyclodextrin glucosyltransferase, could be found in some strains of soil microorganisms. The industrial scale production of enzyme possessing high cyclizing activity was an essential demand for the high capacity cyclodextrin production. It was also aimed to develop an appropriate starch conversion technology capable to produce alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin at high yields by the means of processed enzyme.

É. Fenyvesi (✉) · L. Szente
CycloLab Cyclodextrin Research & Development Ltd, Budapest, Hungary
e-mail: fenyvesi.e@cyclolab.hu; szente@cyclolab.hu

G. Seres
Berlini Park Research and Development Centre, Budapest, Hungary
e-mail: seres@mail.iif.hu

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_4

Development of both enzyme fermentation and starch conversion technology was started simultaneously around the mid of the 1970s, in the microbial and processing laboratories of Chinoin, respectively. The researcher had to tackle (i) selecting the microorganism producing cyclodextrin glucosyltransferase enzyme; (ii) building up analytical methods for cyclodextrin glucosyltransferase enzyme activity; (iii) optimizing the conditions for cultivation; (iv) separating the enzyme from culture medium; (v) purification and characterization of the enzyme; (vi) selection of starch and optimization of hydrolysis by alpha-amylase; (vii) optimizing the enzymatic conversion of starch to the mixture of cyclic and acyclic maltodextrins; (viii) optimizing the conditions for the desired ratio of alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin in the conversion mixture; (ix) developing an alpha-cyclodextrin-specific conversion pathway; (x) developing a gamma-cyclodextrin-specific conversion pathway; (xi) developing analytical techniques for characterization of the composition of the conversion mixture; (xii) separating cyclodextrin(s), purification, and crystallization; (xiii) scaling up the production; and (xiv) developing an immobilized enzyme.

As a result of substantial development, the first 100 kg beta-cyclodextrin was produced in 1978. Parallel to the development of the cyclodextrin production, the technologies for the preparation of some cyclodextrin derivatives were also scaled up: hydroxypropyl-beta-cyclodextrin as a parenteral drug carrier and cyclodextrin bead polymer for wound healing were selected for industrial production.

This chapter gives the details on how the development of the production technologies proceeded and how the difficulties were overcome until the final technologies were documented and the industrial production realized.

Keywords History · Production · Enzyme production · Native cyclodextrins · Cyclodextrin derivatives · Cyclodextrin polymer · Industry

4.1 Introduction

Cyclodextrin research in Chinoin Pharmaceutical and Chemical Works Co. Ltd., one of the biggest pharmaceutical companies in Hungary and Central Europe, started after Professor József Szejtli established the Biochemical Research Laboratory in 1972. The radical development of cyclodextrin processing began after 1975 and continued in close collaboration with the Biotechnology Development Department of the factory. The first cyclodextrin-related research paper on achievements of laboratory was published in 1975. Also in this and subsequent years, the authors of this chapter were involved in the cyclodextrin research to witness or participate in research and development of cyclodextrin production.

In the mid of the 1970s, it was generally accepted that (i) cyclodextrins were interesting compounds able to molecularly encapsulate various organic materials; (ii) cyclodextrins were toxic, hindering practical utilization; and (iii) cyclodextrin production was complicated and expensive; therefore large-scale applications were

not conceivable. There were only a few, including Professor Szejtli, who did not believe in these statements. He was sure in that times that oligosaccharides, like cyclodextrins, cannot be toxic and their production should be economical in large scale. It was clarified later that the toxicity was concluded based on erroneous experiments using unpurified cyclodextrins.

In the time 1975–1976, cyclodextrins were available in small quantities, mainly as fine chemicals produced on laboratory scale. According to common procedure, a cyclodextrin glucosyltransferase enzyme was added to a dilute solution of gelatinized starch, and the enzymatic degradation was allowed to proceed for a sufficient time. The main drawback of this procedure was that acceptable conversion was achieved only at low substrate concentration owing to high viscosity of >5% potato starch solution which limits the enzyme reaction. The viscosity was reduced by means of hydrolyzing starch to small fragments resulting an average dextrose equivalent (the amount of reducing sugars present in a sugar product, expressed as a percentage on a dry basis relative to dextrose) of <20. This preliminary procedure allowed to use 30% substrate concentration resulting in cyclodextrin yields high enough for scaling up the process to industrial level (Armbruster and Kool 1969). The pre-hydrolysis performed either by acidic hydrolysis (Armbruster and Mukhtar 1968) or by α-amylase resulted in water-soluble starch fractions with reduced tendency for retrogradation. After the partial hydrolysis, the starch was converted to cyclodextrins by cyclodextrin glucosyltransferase. Utilizing the outstanding inclusion complex-forming ability of cyclodextrins and the low solubility of resulting complexes, various apolar precipitating agents, such as toluene, trichloroethylene, and bromobenzene, were recommended for selective beta-cyclodextrin formation (Armbruster and Kool 1969; Armbruster 1970).

It was already known that the cyclodextrin yield could be highly enhanced by applying these complexing agents in the cyclodextrin glucosyltransferase-catalyzed starch conversions. Cyclodextrin reaction products could be collected from the enzyme-catalyzed reaction mixture by precipitation, inclusion complex formation, and crystallization (Table 4.1) (Armbruster and Kool 1969). Figure 4.1 refers to the general principle of cyclodextrin production. It was also recognized that using an appropriate complexing agent, the conversion equilibria could be shifted toward the production of desired cyclodextrin. For instance, long alkyl chain alcohols were found useful for production of alpha-cyclodextrin as dominant cyclodextrin component (Armbruster and Jacaway 1969) (Table 4.1).

Optimizing the reaction conditions, 100% pure alpha-cyclodextrin or beta-cyclodextrin was obtained by applying a selective precipitant, 1-decanol or toluene, respectively (Armbruster and Jacaway 1969). Figure 4.2 shows the Schardinger β-dextrin (beta-cyclodextrin) marketed as cyclohexane complex and purchased from Sigma, at the end of the 1970s.

Because of the growing interest for cyclodextrin production, the focus was directed to isolation and purification of cyclodextrin-producing enzymes. Before the 1970s, only few bacteria, i.e., *Bacillus macerans*, *Bacillus circulans*, and *Bacillus polymyxa*, were described as appropriate cyclodextrin glucosyltransferase enzyme sources. According to the patent of Armbruster and Kool (1969), maximum

Table 4.1 Effect of precipitating agents present during enzymolysis on the conversion yield (potato starch concentration, 33.3 g/100 mL; pre-hydrolyzed until 1.9 dextrose equivalent) (Armbruster and Kool 1969; Armbruster and Jacaway 1969)

Precipitant	Cyclodextrin yield	Percent of cyclodextrin type within the cyclodextrin mixture	
	after 4 days	Alpha-cyclodextrin	Beta-cyclodextrin
None (control)	10	No data	No data
p-Cymene	50	0	100
Tetrachloroethane	47	38	62
Benzene	47	0	100
Toluene	45	0	100
Cyclohexane	41	0	100
1-Butanol	24	0	100
1-Octanol	58	53	47
1-Octadecanol[a]	79	82	18

[a]After 7 days of conversion

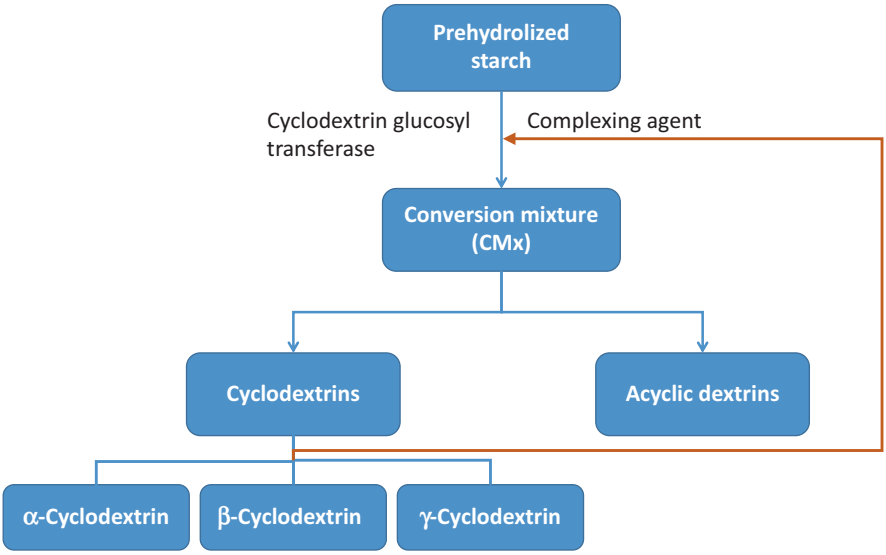

Fig. 4.1 Flow chart of cyclodextrin production: pre-hydrolyzed starch is converted to a mixture of cyclic and acyclic dextrins at a high yield in the presence of a complexing agent, which can be recycled and the cyclodextrins crystallized

yields of cyclodextrin were obtained within 2–7 days at 50 °C and a pH of about 7 when the enzyme dosage ranged between 100 and 1000 Tilden-Hudson units per 100 grams of starch.

A few other cyclodextrin-producing bacterium strains were reported later, e.g., *B. megaterium* and *B. stearothermophilus* were recognized as good enzyme producers (Shiosaka 1973; Okada and Kitahata 1975). For purification of enzyme, various

Fig. 4.2 The Schardinger β-dextrin (beta-cyclodextrin) marketed as cyclohexane complex and purchased from Sigma (CycloLab archive)

multistep processes including precipitation, adsorption on starch, and gel filtration were developed (Okada and Kitahata 1975). Later, an alkalophilic and thermostable cyclodextrin glucosyltransferase derived from *Klebsiella pneumonia*e with a considerably high initial cyclization rate especially on long-chain maltodextrin was reported (Bender 1977).

The first Japanese patents described processes using trichloroethylene, chloroform, and bromobenzene as appropriate beta-cyclodextrin precipitation agents in potato starch conversion (Okada and Tsujama 1974; Horikoshi 1975; Horikoshi and Nakamura 1979). The other Japanese technologies applied strict control on maltose and glucose concentration (Suzuki et al. 1975) and used ion-exchange resin for separation of cyclodextrins from glucose and other linear dextrins with reducing end groups in conversion mixture (Suzuki et al. 1975; Yoritomi and Yoshida 1976). At the beginning of the 1980s, the latter technologies led to the early approval of cyclodextrins as enzymatically modified starch for food and pharmaceutical use by the Japanese Food and Drug Administration Agency (Nagai 1982). Szejtli (1988, 1990) reviewed the various cyclodextrin-producing technologies.

4.2 History of Hungarian Cyclodextrin Production

The cyclodextrin research at Chinoin Pharmaceutical and Chemical Works Co. Ltd. started in 1975. As a world-known outstanding expert of carbohydrate chemistry, Professor Szejtli received the background including a new laboratory and annual budget for this research. The management of the factory supported his initiative for the cyclodextrin production. According to Chinoin marketing experts, it seemed to be a massive beta-cyclodextrin demand in world market, in not too distant future. Cooperation agreement between the Biochemical Research Laboratory (this was the name of the cyclodextrin research laboratory headed by Professor Szejtli) and

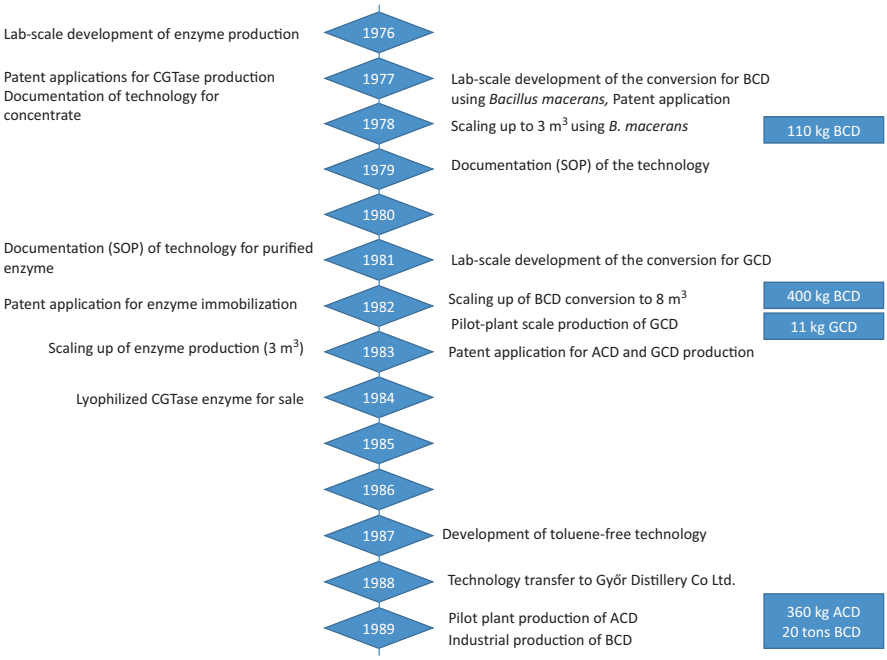

Fig. 4.3 Chronology of technology development for production of alpha-cyclodextrin (ACD), beta-cyclodextrin (BCD), and gamma-cyclodextrin (GCD) and cyclodextrin glucosyltransferase (CGTase)

the Fermentation Factory Group of Chinoin including Biotechnology Development Department was signed in 1976. Further, both cyclodextrin glucosyltransferase preparation and cyclodextrin production proceeded in close cooperation of research and development members. Milestones of the technology development are summarized in chronological order in Fig. 4.3.

4.2.1 Development of Enzyme Production

Selection of a Cyclodextrin Glucosyltransferase Enzyme-Producing Microorganism and Optimizing the Cultivation Conditions

Cyclodextrin glucosyltransferase is a unique enzyme, which reacts with starchy substrates with three action mechanisms: cyclizing, transglucosylation (coupling and disproportionation), and hydrolyzing. It should be noted that cyclodextrin glucosyltransferases always produce alpha-cyclodextrin as primary cyclization product, which is transformed into beta-cyclodextrin and gamma-cyclodextrin in parallel due to coupling and cyclization reactions proceeding mainly in late stage of starch conversion.

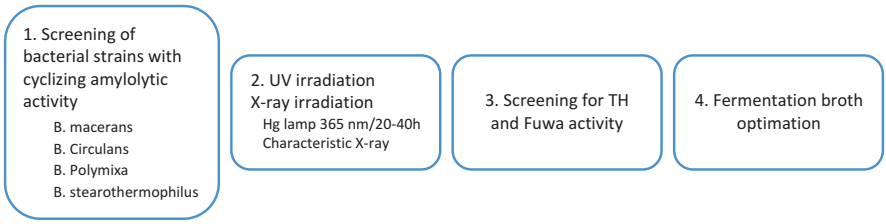

Fig. 4.4 Development steps for enzyme production by fermentation (screening methods, Tilden-Hudson (TH) method and Fuwa method for enzyme activity measurements; see section "Measuring of Enzyme Activity")

The research started with selecting the proper bacteria expressing the desired enzyme able to produce cyclodextrins with highest activity and productivity. Various *B. macerans*, *B. circulans*, *B. stearothermophilus*, and *B. polymyxa* strains were screened for the best cyclodextrin glucosyltransferase, which converts starch into the preferable beta-cyclodextrin in the maximal ratio. The following parameters had to be optimized: (i) cultivating circumstances of an industrial strain; (ii) ingredients of culture medium; (iii) screening of various amino acid nitrogen sources; and (iv) fermentation parameters such as determination of optimal pH, cultivation temperature, and oxygen uptake.

Hundreds of experiments were carried out to find optimal conditions for cultivation of these bacteria. Mutagenic stimulation by either UV or X-ray irradiation was also intensively applied. It was crucial also to select an optimal cultivation medium. Finally, selection among various carbon sources led to a recognition that oat bran was the best nutrient for culturing. The main steps in laboratory development of cyclodextrin glucosyltransferase enzyme (1976–1982) are summarized in Fig. 4.4.

Measuring of Enzyme Activity

In very early times, in correspondence with the actual literature sources, cyclodextrin glucosyltransferase activity was measured by the earliest Tilden-Hudson method (Tilden and Hudson 1942). This simple procedure was based on visual observation of primary enzyme attack, i.e., alpha-cyclodextrin production from soluble starch substrate. The enzyme-catalyzed metamorphosis of starch-iodine-enzyme mixture can be visualized under microscopic investigation. The reaction endpoint relates to the time required for disappearance of the blue color of initial starch-iodine complex and the appearance of characteristic dichroic needle-like alpha-cyclodextrin crystals. One Tilden-Hudson (TH) unit is the amount of enzyme required to convert 30 mg of starch in 30 min at 40 °C to the brown-violet stage. The disadvantages of Tilden-Hudson method are the individual uncertainty in microscopic observation and that it only detects an unwanted property: initial alpha-cyclodextrin cyclisation rates can be seen only and gives no direct information on

beta-cyclodextrin producing ability of the enzyme. Additionally, other carbohydrase enzymes can disturb the measurement.

In the later conversion stage, cyclodextrin glucosyltransferase promotes decylization and transferring glucosyl moieties to the initially produced alpha-cyclodextrin, resulting in the formation of higher degree of polymerization beta- and gamma-cyclodextrins in the conversion mixture. The methods of Fuwa (1954) and Kitahata et al. (1974) for determination and screening of cyclodextrin glucosyltransferase activities characterized this second step. The reaction mixture containing soluble starch and the enzyme in a pH 5.5 buffer was incubated at 40 °C for 10 min. Thereafter, aliquot of this mixture was added to iodine in potassium iodide solution and diluted with distilled water. As zero control, aliquot of this reaction mixture was also added to the iodine solution before the incubation. Absorbance was measured at 660 nm. According to Fuwa (1954), the enzyme activity is defined as the amount of enzyme that produced a difference in absorbance of 1.0 unit per min under the described conditions. According to the later published and generally accepted Kitahata method, one Kitahata unit corresponds to 1% decrease in light absorption in 1 min (Kitahata et al. 1974). Because this assay refers to time-lapsed secondary stage of enzyme starch conversion, it fulfills the development requirements for not only beta-cyclodextrin but gamma-cyclodextrin formation, too. To match the early-published data, it was postulated that one Tilden-Hudson unit activity corresponds to approximately 3 Kitahata units.

To detect parallel both recycling and glucosyl coupling enzyme activity, a method utilized in presence of alpha-methyl glucoside acceptor was also developed. The reaction product of hydrolysis by hog pancreatic alpha-amylase (maltose) can easily be measured by any conventional reducing sugar determination method. The main advantage of this method is that the cyclodextrin glucosyltransferase enzyme action is not disturbed by the presence of common hydrolytic enzymes, because these enzymes are unable to split alpha-cyclodextrin substrate (Thoma and Stewart 1965).

A similar rapid method for determination of cyclodextrin glucosyltransferase activity was elaborated in the Chinoin Biotechnology Development Laboratory by further development of Thoma's activity assay (Péterfi and Seres 1982). This method was based also on general glucosyltransferase mechanism: the forming enzyme splits alpha-cyclodextrin substrate, and –in the presence of hog pancreatic amylase – the resulting linear fragment is coupled to the C-1 terminal of *p*-nitrophenyl-beta-D-glucoside acceptor. The resulting mixture of saccharides can easily be detected as reducing sugars by any conventional method measuring reducing ability, by dinitrosalicylic acid assay in this case.

A reliable cyclodextrin glucosyltransferase activity measuring method, which is based on direct determination of nascent cyclodextrins by means of high-performance liquid chromatography, applies a polymer-based reverse phase column equipped with a refractive index detector. The advantage of this assay is that enzyme activity is expressed in SI system in units of micromoles cyclodextrin/g substrate, in accordance with later regulations of Enzyme Commission (Sato 1985).

Because of the simplicity of Kitahata method, and due to its wide representation in overall process technology documentation, the proposed more specific and

Fig. 4.5 Labsys80 computer used for calculating enzyme activity (CycloLab archive)

accurate glucosyl transfer methods were not introduced into Chinoin practice, and in the lack of any equipment, high-performance liquid chromatography-based activity method was not applied either. A basic language computer program was compiled later for quick calculation of Kitahata unit values and immersing results directly into the newly established technology database of Chinoin (Seres 1986). Figure 4.5 shows the computer used for these calculations.

Separation of Enzyme from Culture Medium and Purification

Summarizing the forthcoming data of enzyme purification technologies described in the literature, it was concluded that the technology based on multistep precipitation, sorption on starch, and chromatography was expensive, complicated, and time-consuming (Kobayashi et al. 1978).

Initially, researchers had to develop an independent and patentable cyclodextrin glucosyltransferase-producing bacterial strain. After numerous isolation and screening efforts, an appropriate soil microorganism *Bacillus macerans* strain – isolated from putrid potato – proved the best enzyme-producing source. Unfortunately, this strain was covered by an American patent (Armbruster and Mukhtar 1968). So, profound X-ray and UV light mutagenic treatments were needed to isolate a taxonomically different new bacterial strain. The resulting new mutant was characterized and patented thereafter.

The first documentation filed in 1976 referred to the preparation of a crude enzyme powder of independent *B. macerans* mutant industrial strain and involved the instructions for laboratory-scale preparation. It was not easy to work out a process, because of permanent industrial aim to develop a simple, economical, and relatively not time-consuming procedure, robust and reproducible enough and suitable for continuous manufacturing. The problem was that fermentation liquor always contained other hydrolytic amylases synthetized in final stage of cultivation. These hydrolytic enzymes interfered with cyclodextrin glucosyltransferase and reduced randomly the yield of cyclodextrins. Therefore, continuous efforts were made, and an outstanding attention focused to the development of a hydrolytic factor proof enzyme isolation and purification technology. The objective was inserting

a fractional salting out step into the downstream enzyme processing. This fractional precipitation was carried out using ammonium sulfate. In this way, the alpha-amylase contamination of final product could be reduced. A combined purification procedure involving gel filtration and isoelectric focusing was applied to get a fine enzyme preparation and for physicochemical characterization of our new *B. macerans* mutant enzyme (Seres 1984). As a result of these investigations, the molecular weight was found 79 kDa, and two isomeric forms were proved (Seres 1986 and Table 4.2).

In the early 1980s, a new and innovative enzyme purification method was worked out in cooperation of the Chinoin researchers (Seres's team) with research members (Professors E. László, Á. Hoschke, and B. Bánky) of Agrochemical Department of Budapest University of Technology. This ingenious chromatography procedure was based on the specific key-lock enzyme substrate affinity property. Alpha-cyclodextrin was immobilized on an agarose gel matrix at first, to get an immobilized affinity chromatography stationary phase. When passing the crude cyclodextrin glucosyltransferase concentrate through this alpha-cyclodextrin-agarose gel column, cyclodextrin glucosyltransferase enzyme was selectively affixed to its covalently bound substrate. After completely washing off the unbound constituents, the enzyme could be eluted by concentrated solution of alpha-cyclodextrin substrate (Fig. 4.6). The technology was scaled up to 250-cm^3 volume affinity column, which allowed to load 1.5–2.0 mega-Kitahata unit crude enzyme concentrate in a single cycle,

Table 4.2 Specification of cyclodextrin glucosyltransferase

Name	Cyclodextrin glucosyltransferase alpha-(1–4)-glucan-4-glucosyltransferase E.C.2.4.1.19
Appearance	White powder
Gross activity	10.000 Kitahata units/vial
Ingredients	Protein content minimum 40% of dry material (Lowry method 1951)
	The preparation also contains alpha-cyclodextrin and maltooligosaccharides as stabilizers and sodium phosphate in order to maintain the pH of the dissolved material at 7.0
Stability	At least 1 year when stored at 4 °C
	The solid preparation can lose <5% of its activity within 1 month when stored at 25 °C
Solubility	The vial content is fully soluble in 1.0–3.0 mL distilled water
Molecular weight	79 kDa
Michaelis-Menten constant for soluble amylose as substrate	5.7 mg/mL (Stavn and Granum 1979) 3.9 mg/mL (De Pinto and Campbell 1968)
Isoelectric point (pI)	Two bands by agarose gel isoelectric focusing: pI = 4.45 and pI = 4.65
pH optimum	5.9
Operating pH interval	5.0 < pH < 8.0
Operating temperature optimum	60 °C

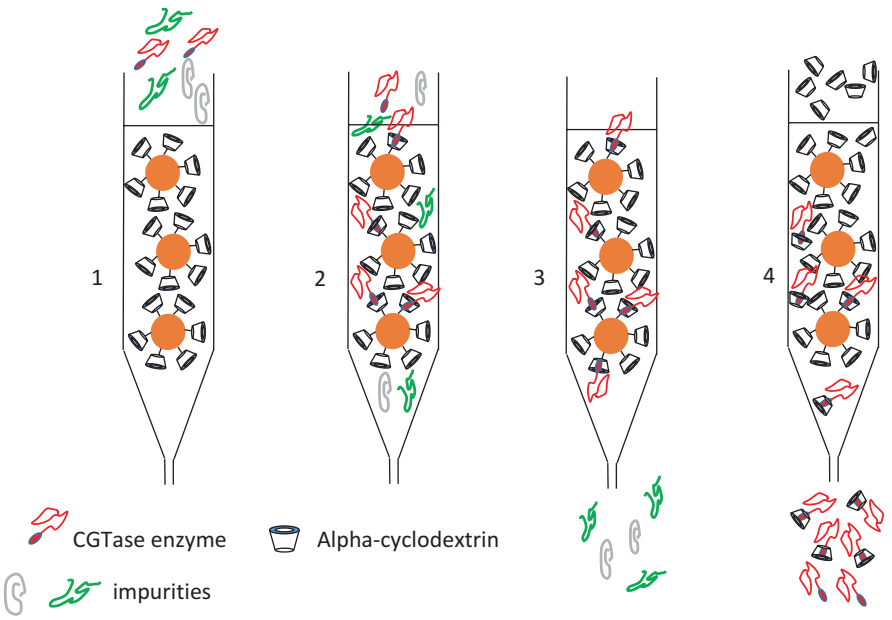

Fig. 4.6 Four steps for purification of cyclodextrin glucosyltransferase (CGTase) enzyme by affinity chromatography: 1. sample introduction; 2. adsorption of cyclodextrin glucosyltransferase on alpha-cyclodextrin substrate bound to column packing; 3. removal of impurities such as other proteins, low molecular weight compounds, and inorganic salts; 4. retrieval of cyclodextrin glucosyltransferase by selective elution with alpha-cyclodextrin-containing buffer

resulting in a highly purified enzyme product, with 78–94% overall yield. The chromatography was carried out at 5–7 °C to avoid enzyme decomposition. The time requirement of one affinity adsorption-desorption cycle was typically 26–30 h (Seres et al. 1980).

The affinity-chromatography-based enzyme processing can be summarized in three main steps:

Step 1: Preparation of affinity chromatographic sorbent (occasional) – sepharose-6B agarose gel was reacted with 1,4-butanediol diglycidyl ether, and alpha-cyclodextrin was added to be bonded; approximately 10 μmol alpha-cyclodextrin/g wet gel was immobilized by this method; the resulting affinity sorbent was quite stable and reusable many times and possessed high binding affinity toward cyclodextrin glucosyltransferase.

Step 2: Laboratory-scale concentration of enzyme via affinity chromatography – initially, the crude fermentation liquor filtrate was concentrated to 1/10 in volume, and its pH maintained to slightly acidic (pH 6); this filtered concentrate was passed through the cooled chromatographic column filled with the special affinity chromatographic absorbent; loading about 2000 mL of filtrate corresponding to 200,000 Kitahata units with 100 mL/(cm^2*h) linear flow velocity, the whole cyclodextrin glucosyltransferase content was bound to the affinity stationary

phase; the unreacted proteins, pigments, and further organic and inorganic ingredients could be removed by washing the column with water and diluted sodium chloride solution thereafter; the column effluent contained unreacted hydrolytic enzyme constituents, except for cyclodextrin glucosyltransferase active ingredient.

Step 3: Elution and freeze-drying of purified product – the cyclodextrin glucosyltransferase enzyme bound to the column was eluted by 1% alpha-cyclodextrin-containing buffer; the resulting column effluent was a concentrated solution having high (2 Kitahata units/100 mg protein) cyclodextrin glucosyltransferase activity. This alpha-cyclodextrin-containing enzyme solution was diluted with buffer to 10^4 Kitahata units/mL, filtered through a 0.2 μm pore size membrane filter, and dispensed into sterile glass lyophilization vials to obtain a uniform filling quantity of 10^4 Kitahata units/vial via freeze-drying; finally, the vials were closed under vacuum and labeled.

At the time of these technology developments, Hungary belonged to the Soviet block, and any sophisticated equipment, for example, automatic chromatography instrument (Pharmacia) or any HPLC analytical system, was embargoed. The spare parts of the chromatographs needed for automation of affinity chromatography and protein purification were purchased in the Western countries by the researchers as tourists and personally imported, violating the embargo. Finally, a chromatograph was constructed by Chinoin's researchers, who developed also an elution control program to obtain the equipment useful for attention-free, semi-automatic enzyme production.

For pilot plant scale-up, affinity chromatography parameters were optimized: elution rate, temperature of binding, selection of buffer (acetate or phosphate), pH, volume of buffer, volume of column packing, and enzyme load. Based on these experiments, the optimized operation parameters were established, and the documentation of instructions for laboratory-scale production submitted in 1985. The column packing had the capacity to bind as much as 500 mg enzyme related to 1 mL gel bed volume from 100 to 1000 mL culture broth in one cycle (Szejtli et al. 1980a).

The industrial cyclodextrin glucosyltransferase manufacturing started at Chinoin Fermentation Plant in 1981, with the selected best mutant strain of *B. macerans*. Both inoculation and fermentation culture media consisted of oat flake and corn steep liquor as appropriate carbon sources. The essential nitrogen was applied in ammonium sulfate form. To ensure an optimal enzyme-stabilizing environment, pH of the oat-flake-containing fermentation broth was maintained to near neutral, with addition of potassium bisphosphate and calcium carbonate. The main fermentation was carried out at 37 °C, for 2 days. The fermentation liquor was filtered on a rotary vacuum drum filter and concentrated to its 1/10 volume in vacuum evaporators. The macromolecular enzyme fraction of resulting concentrate was salted out with ammonium sulfate, filtered, and dried. The industrial process technology, suitable for enzyme production in 10–100 mega Kitahata unit range in 3 m^3 batch volumes, was realized in 1982. An amount of 150 mega Kitahata unit crude enzyme powder

was processed this year, barely enough for producing about a 100 tons beta-cyclodextrin quantity.

The Chinoin's cyclodextrin glucosyltransferase product was a highly purified preparation isolated from *B. macerans* fermentation liquor and concentrated by about 200-fold related to its original specific activity by affinity chromatography (Seres and László 1982). The enzyme was available as a white odorless freeze-dried powder shipped in 5 mL vials under reduced pressure.

In 1984 and 1985, 500 and 600 vials were sold as fine chemical via LucernaChem AG. At that time only Chinoin and Amano Pharmaceutical Co. (Japan) produced this enzyme in purified form. Specification of the purified enzyme manufactured by Chinoin Pharmaceutical and Chemical Works Co. Ltd. was set up (Table 4.2).

At this time, the management of Chinoin was considering purified enzyme production for sale. As part of new economical era, a special new firm formation, so-called part-time work cooperative, the Cyclodextrin VGM was established in the factory in the late 1980s. This VGM was responsible for the affinity chromatographic manufacturing and qualification of the product, with a cooperation with Central Analytical Department of Chinoin. Due to lack of any export license, both sales and distribution of product were managed by an international cooperation between Reanal Fine Chemicals Co. (Budapest, Hungary) and LucernaChem AG (Luzern, Switzerland) (Fig. 4.7).

In the late 1980s, additional attempts were made to purify further this lyophilized cyclodextrin glucosyltransferase enzyme product by gel filtration in pilot plant scale. After separation by gel chromatography on Sephacryl-S-200, the resulting fractions were lyophilized on a Leybold-Heraeus industrial equipment (Seres and

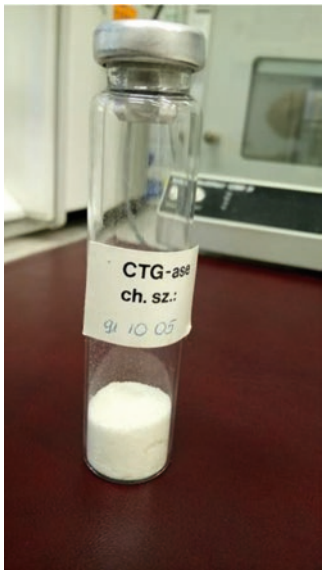

Fig. 4.7 Photograph of the exported pure glucosyltransferase enzyme product

László 1988). Because no significant enhancement in specific activity and catalytic properties was observed after purification, the extra pure enzyme was not produced for commerce.

Immobilization of the Enzyme

As a final step of developments, the cyclodextrin glucosyltransferase enzyme was immobilized on an appropriate carrier to reduce the enzyme consumption and simplify the downstream procedure. Using immobilized enzyme, the same enzyme could be utilized in several conversion cycles either in batch-wise or continuously operating technologies. To implement above development concept, experiments started in 1980 using a commercially available carrier, Eupergit-C. Common coupling studies were performed at Reanal Fine Chemicals Co. (Budapest, Hungary) by researchers with high experience in enzyme immobilization. The cyclodextrin glucosyltransferase enzyme was reacted with carbodiimide-activated polysaccharide-based carrier. Another immobilizing procedure was invented using carboxyl functional group-containing acrylic polymer backbone (Boross et al. 1986; patent application was submitted in 1982).

In contrast to activity of enzyme immobilized on cellulose, which was only 26.5 Kitahata units/g dry weight, the enzyme immobilized on polyacrylamide reached the 230–450 Kitahata units/g. Immobilization shifted the pH optimum from 5.9 to 5.5. The temperature optimum range was rather broad, between 40 and 60 °C, whereas the soluble enzyme had a relatively sharp activity peak around 60 °C. Half-life was improved considerably at all pH values and temperatures. For example, the half-life of the soluble enzyme at 70 °C (optimum pH 5.9) is only 1.0 min, while that of the immobilized enzyme was 24.3 min (optimum pH 5.5) (Ivony et al. 1983a, b). Degree of immobilization was strongly dependent on the structure of disubstituted carbodiimides (Szajáni et al. 1991).

The continuous mass transfer kinetic of semi-permeable membranes made from immobilized cyclodextrin glucosyltransferase enzyme-containing acrylic polymers was thoroughly studied by Professors E. Nagy and Cs. Sisak, researchers at Technical Chemistry Research Institute, Veszprém (MÜKKI, Hungary). Compared to dissolved enzyme, enhanced stability and reusability were an important advantage, permitting a possibility for development of continuous cyclodextrin manufacturing procedure, instead of batch-wise processes (Sisak et al. 1996). A stirred tank reactor system, operated with immobilized cyclodextrin glucosyltransferase enzyme beads, was developed. This reaction vessel was coupled to a hollow fiber ultrafiltration membrane to separate cyclodextrin from the low molecular reaction products. This laboratory system worked in recycling mode developed for months. By means of such arrangement, starch substrate inhibition and the competitive blocking effect of glucose and short-chain oligosaccharides on the cyclization reaction diminished. Moreover, the time-dependent decomposition of parent cyclodextrins could be decreased in this system. Starch degradation and formation of glycosylic cyclodextrin coproducts were also repressed. Due to the change of regime in

1989 – unfortunately – the continuous production of cyclodextrins by using immobilized enzyme has not been scaled up on process scale.

4.2.2 Production of Beta-Cyclodextrin at Chinoin

Laboratory processing: The laboratory-scale experiments for development of beta-cyclodextrin production technology started in about 1977. The fundamentals of the technology have not changed since Schardinger (1903): A cyclodextrin glucosyltransferase enzyme of *B. macerans* origin was used. It was clear, at the first occasion, that foamy, stinking, and not easy-to-handle culture liquors of *B. macerans* were not suitable for an economical high-throughput industrial manufacturing. After optimizing the fermentation, crude enzyme filtering and fractionating parameters of the downstream processing were established, and a robust and reproducible enzyme technology was documented in 1982. Compared to achievable 8.7% and 10.2% cyclodextrin yields using crude enzyme powder supply, conversion rates of beta-cyclodextrin production increased to 12.6% and 17.5% after 3- and 5-day incubation, respectively, with a semi-purified and hydrolase-free enzyme preparation (Seres et al. 1980).

Beta-cyclodextrin manufacturing technology: In the early 1980s, only Japanese firms distributed limited quantities of purified beta-cyclodextrin in the world market: (i) Celdex-N from Nihon Shokuhin Kako (a company belonging to Mitsubishi, Japan); (ii) Ringdex from Ocean Sanraku (a company belonging to Sumitomo, Japan); and (iii) Dexypearl from Ensuiko Sugar Refining Co. Ltd. Japan.

The initial concept was based on the common accepted fact that continuous precipitation of water-insoluble toluene/beta-cyclodextrin complex shifted the conversion direction toward beta-cyclodextrin production. After preliminary laboratory procedures using potato starch, corn starch was selected as raw substrate because of the higher abundance in Hungary and its lower price. Due to its shorter chain and more branched structure of corn amylopectin, reduced viscosities could be achieved after gelation of the high-starch-containing gel. This gelatinization process makes possible to prepare a concentrated (20–45 w/w %) gelatinized starch solution with considerable viscosities without any observable retrogradation of starch and provides high cyclodextrin levels in the further cyclodextrin glucosyltransferase-catalyzed conversion (Vakaliu et al. 1979). An optimal starch concentration of around 30% was found to give the highest cyclodextrin yield. Additional step was inserted into the process to hydrolyze the resulted starch gel to 1–3 dextrose equivalents. For the sake of this mild hydrolysis, an alpha-amylase of *Bacillus subtilis* origin was applied. Existing calcium ions are essential to stimulate – as cofactor – both alpha-amylase and cyclodextrin glucosyltransferase activity. The optimal pH (7.2) and the essential cofactor input were maintained with sodium hydroxide and calcium carbonate. The cyclodextrin glucosyltransferase used in this process was the own product of Chinoin.

Laboratory-scale conversion technology using corn starch and toluene complexant was developed in the late 1970s. The optimized parameters include 30 w% prehydrolyzed corn starch, 5 v% toluene, 50 °C conversion temperature, pH 6.8, and 5 days conversion time.

The scale-up of cyclodextrin conversion technology started in 1978 in the pilot plant of Chinoin (plant IX). The cyclodextrin conversion (in presence of toluene complexant) was implemented at 3 m^3 level. The preliminary pilot plant technology manual describes a cyclodextrin glucosyltransferase-catalyzed corn starch conversion leading to a high beta-cyclodextrin-containing starch degradation mixture. The downstream processing was based on a new development, namely, cyclodextrin content was separated via its soluble ethanol complex form. With 30 v/v % ethanol in the final conversion mixture, the beta-cyclodextrin and gamma-cyclodextrin are soluble; other insoluble cyclodextrins and degraded starch reaction products can be filtered off.

To realize this separation step, after filtration of final conversion mixture, the filter cake containing toluene-cyclodextrin complex was re-suspended in water; then the toluene content was eliminated by steam distillation. Beta-cyclodextrin was separated from linear starch degradants and maltodextrins in soluble ethanol complex form. For this reason, purification technology involved a step of adding twofold ethanol to the concentrate. The resulting ethanol complex solution was hot filtered, concentrated in vacuum, decolorized with charcoal, filtered, and crystallized. Using this technology 112 kg of pure beta-cyclodextrin was manufactured in 1978. The purity of resulting beta-cyclodextrin was >99.7%, and the overall yield was 33%, calculated on corn starch reference. This procedure was applied for patenting in 1977, and that patent was granted in 1980 (Vakaliu et al. 1979), based on a preliminary laboratory-scale production documentation compiled in 1977.

The high ethanol consumption, however, made the beta-cyclodextrin technology too expensive. To reduce the producing costs, a new process was elaborated at Chinoin Biotechnology Department. This concept was based on decaying the remaining unreacted dextrins derived from the high molecular weight fraction of conversion mixture. A thermostable alpha amylase of *Bacillus amyloliquefaciens* (BAN 240 L enzyme) was applied at the end of the cyclodextrin glucosyltransferase incubation period for this purpose. The resulting low viscosity conversion mixture could be filtered without difficulties. The cyclodextrin-toluene complex-containing filter cake was re-suspended in water, and toluene eliminated by steam distillation. Then the diluted material was decolorized with active carbon and hot filtered. The cyclodextrin-containing filtrate was concentrated in an evaporator thereafter. It was decolorized again with active carbon, and finally beta-cyclodextrin was crystallized. Based on initial laboratory-scale documentation, an industrial plant-scale technology was compiled by Biotechnology Department in 1979. Further experiments started in 1981 for industrial scale-up in plant Chinoin-IV in 1982.

For elimination of remaining toluene, sugar, and maltooligosaccharide traces, an additional purification procedure was inserted into the beta-cyclodextrin technology in 1981. It was realized by the application of mixed styrene divinylbenzene polymer-based Varion KS and Varion AD ion exchangers. To satisfy ongoing press for the

substantial removal of toluene and also get rid of time-consuming intermittent drying technology, conventional drying ovens were substituted by a continuous fluid dryer. Based on these developments, the industrial beta-cyclodextrin manufacturing started in plant Chinoin-II, in 1985. Pure industrial beta-cyclodextrin was produced in a robust process with high throughput and appreciable yield (38% in average). The process and the parameters of the final technology can be seen in the flow chart in Fig. 4.8.

Between 1977 and 1981, 59 industrial batches of beta-cyclodextrin were characterized by the Quality Control Department of Chinoin. The pH of 26 lots did not conform the requirements (5 > pH > 8) with pH higher than the upper limit. The batches out of specification were qualified for using as additives in fire extinguishers, meanwhile the laboratory and the producing units tried to find explanation and solution for the phenomenon. That problem was resolved by flushing the converter's connection lines with overheated steam before acid addition.

A wheat starch-based beta-cyclodextrin technology was also elaborated and documented by researchers of Chinoin Biotechnology Department in 1988. After mild alpha-amylolysis, toluene and methyl ethyl ketone as ternary cyclodextrin complexing agents were added simultaneously to partially degrade starch. Finishing the conversion, glucoamylase was used to disrupt high molecular weight dextrins. As final purification step, mixed strong anionic and cationic ion exchangers were inserted

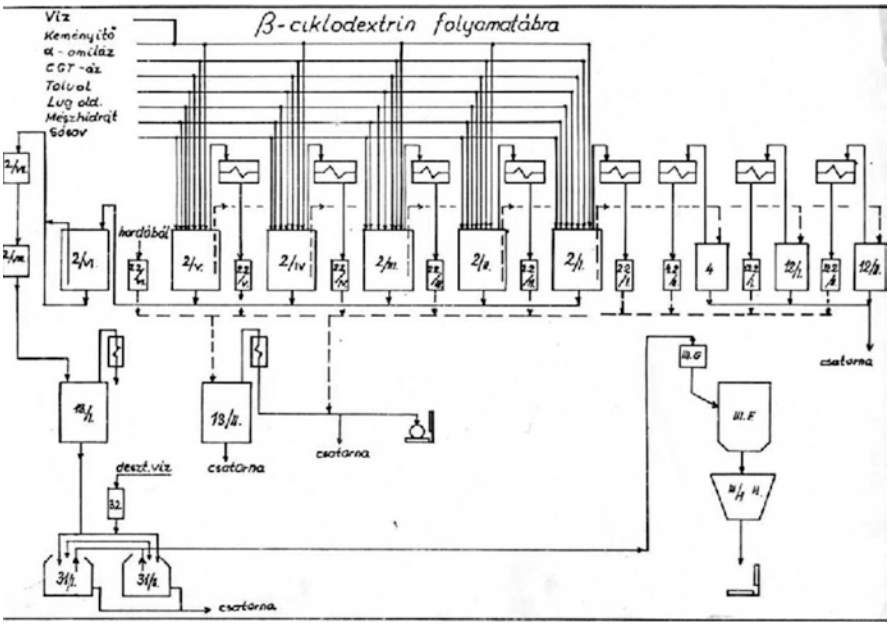

Fig. 4.8 Detailed flow chart of beta-cyclodextrin production with 5 parallel conversion units (2/I-2/V) of 3 m^3 each (copy of original flow chart in Hungarian from Chinoin archive). Inputs: water, starch, alpha-amylase, cyclodextrin glucosyltransferase, toluene, lime hydrate, hydrochloric acid

into the technology. Under these circumstances, also branched cyclodextrins of high aqueous solubility were produced from wheat starch substrate. In these branched cyclodextrins, glucosyl and maltosyl side chains were attached to glucopyranosyl units of the parent cyclodextrin via alpha-1,6 linkages. Compared with other starch sources, wheat starch produced the highest (35–40%) degree of conversion.

The conversion mixture obtained by processing pre-hydrolyzed starch using any cyclodextrin glucosyltransferase enzyme always contains negligible amounts of higher degree of oligomerization (9, 10, 11, and 12) cyclodextrins, so called large-ring cyclodextrins, moreover a series of branched cyclodextrins besides the three major (native) cyclodextrins. The solubilities of branched cyclodextrins in water, even in aqueous 80% ethanol or in aqueous 50% solutions of methanol, formaldehyde, and ethylene glycol, are extremely high in comparison with their parent cyclodextrins. Their ratio depends on the conversion time and the applied enzyme and can be strongly influenced by the reaction conditions, especially on the chemical nature of specific precipitating complexant. According to Chinoin developers, the ratio to beta-cyclodextrin can be enhanced if wheat starch and trichloroethylene or toluene is used as raw material and precipitating agent, respectively. From the crystallization mother liquors of wheat starch-based beta-cyclodextrin technology, the glucosyl beta-cyclodextrin content was recoverable at 50 °C, by the means of chromatography on Amberlite cation exchange resin (Seres et al. 1989). At that time, however, both branched cyclodextrins and large-ring cyclodextrins were considered scientific curiosities only.

Application of an immobilized cyclodextrin glucosyltransferase made possible a continuous process in a stirred reactor connected with a laboratory-sized hollow fiber membrane-equipped diafiltration cassette. Low molecular weight components, cyclodextrins, and maltooligosaccharides squeezed through the membrane, whereas unreacted amylose and amylopectin degradation products were recirculated. With continuous input of corn starch hydrolysate, benzyl alcohol was added into the reaction vessel containing cyclodextrin glucosyltransferase beads. This system was operated in steady state, for months in laboratory size; it has not been scaled up due to the lack of a suitable industrial filtration device.

Because of limited scale-up capacity, Chinoin Pharmaceutical and Chemical Works Co. Ltd. initiated negotiations with Győri Szeszipari Vállalat (Győr Distillery, Hungary) in 1985, to adopt the beta-cyclodextrin technology and scale up it in the future to 100 tons/year capacity. The original toluene-based beta-cyclodextrin technology, used in Chinoin earlier, was transformed into a large-scale manufacturing pathway in the Győr Distillery. The industrial production in 20 m^3 volume fermentors was continued over 2 years in 1987–1989 period, to produce approximately 20 tons of beta-cyclodextrin.

As a factory product subjected to Hungarian food manufacturing law, permanent problem was to reduce the toxic toluene residual solvent in the high capacity manufacturing. According to Hungarian dietary regulation, the allowable limit of toluene was 1 ppm at that time. Moreover, it was a purchaser demand to get a toluene-free product, which is utilizable safely in dietary or pharmaceutical products. To resolve this problem, a new toluene-free conversion technology was elaborated at Chinoin

Biotechnology Department, applying nontoxic benzyl alcohol as appropriate beta-cyclodextrin precipitant. This new beta-cyclodextrin conversion process using benzyl alcohol as complexant was developed in 1986–1988 period. Briefly, partially hydrolyzed corn starch was converted to cyclodextrins with in-house-manufactured industrial cyclodextrin glucosyltransferase in presence of benzyl alcohol precipitant. The non-cyclic oligosaccharide content of final conversion mixture was degraded to dextrose with glucoamylase, and the resulting mixture filtered at room temperature. After suspending filtered material in water, the precipitant content was eliminated via atmospheric pressure steam distillation. Continued with carbon decolorization and subsequent evaporation, the pure beta-cyclodextrin product was crystallized from the resulting concentrate.

Benzyl alcohol is, however, not stable under conversion-reaction circumstances. In the late conversion, benzyl aldehyde and benzoic acid oxidation products were formed in the reaction mixture. Therefore, many efforts were made to optimize conversion and steam distillation parameters to eliminate the cyclodextrin-benzaldehyde complexes. Additional experiments were focused on replacement of the original corn starch to its fiber-free corn starch grease form. Later corn starch was replaced with cheap wheat corn grinder, but because of its relatively high protein content, it was not proved an appropriate substrate. Due to change of regime, these technology variations were not realized in the process-scale manufacturing.

4.2.3 Production of Alpha-Cyclodextrin and Gamma-Cyclodextrin

The other two cyclodextrins, i.e., alpha-cyclodextrin and gamma-cyclodextrin, can be isolated from the conversion mixture by subsequent and combined application of bromobenzene and trichloroethylene according to method of French et al. (1949). The resulting products are of low purity materials, often contaminated by a toxic residual solvent (Armbruster and Jacaway 1969). Starch conversion was conducted in the presence of any aliphatic compounds having >8 carbon chain length, e.g., n-decanal resulted in mainly alpha- and beta-cyclodextrin-containing potato starch conversion mixture. Bromobenzene was applied by Bender (1984) for the special purpose to obtain a gamma-cyclodextrin-enriched conversion mixture. After removing bromobenzene by distillation, the linear dextrin fraction was precipitated by methanol, beta-cyclodextrin was removed by crystallization, and the residual solution was treated again with bromobenzene to obtain a product with 90% gamma-cyclodextrin and 10% beta-cyclodextrin composition. The final purification step was a crystallization in pyridine-methanol solvent mixture to get a gamma-cyclodextrin product of 98–99% purity.

Another method for separation of alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin from the conversion mixture was based on chromatography using ion-exchange columns (Okada et al. 1980). The main advantage of this

method was elimination of the total quantity of organic precipitant; therefore no toxicity issues arose. On the other hand, the low capacity and high energy consumption required for the concentration of diluted solutions of cyclodextrins are drawbacks hindering the industrialization of this technology.

In consequence of the expensive multistep precipitation processes and chromatography, moreover the lack of industrial processing, both alpha- and gamma-cyclodextrins were available only as fine chemicals in the 1970s–1980s. In the conversion step, various polycyclic compounds were applied as precipitating agent. For instance, in 1982 gamma-cyclodextrin was available as fine chemical only purchased with a price of 1800 $/kg from Nihon Shokuhin Kako and 2740 $/kg from Senn Chemicals (Fig. 4.9). The high price of the gamma-cyclodextrin was the consequence of the special producing technology using a galaxolide-containing expensive musk oil, which is a common component in luxury perfumes.

Before elaboration of selective conversion technologies, in the early times, researchers focused on isolation of alpha- and gamma-cyclodextrin by-products, which originated from beta-cyclodextrin conversion. Primary efforts were taken to achieve remaining cyclodextrin content of crystallization mother liquors of beta-cyclodextrin manufacturing. This concentrated solution typically contained 3–5% alpha-cyclodextrin, 2% beta-cyclodextrin, and 6–10% gamma-cyclodextrin. Adding xylene precipitant to mother liquor, the beta-cyclodextrin and gamma-cyclodextrin complex was filtered off. The remaining short-chain maltodextrin and oligosaccharide components of filtrate were hydrolyzed with amyloglucosidase. After concentration in vacuum, cyclohexene was added to precipitate alpha-cyclodextrin. After filtration, the resulting insoluble complex was re-suspended in water, and cyclohexane was removed in the final concentration step carried out in a vacuum evaporator. The final 40% dry matter-containing concentrate was crystallized in a refrigerator to get pure alpha-cyclodextrin with 24% yield. After clarification by using active carbon, the cyclohexane filtrate containing gamma-cyclodextrin was concentrated up

Fig. 4.9 Photo on the gamma-cyclodextrin from Senn Chemicals (Cat. No. 1353, Weight 1 g, γ-cyclodextrin, Lot Nr. 8702140)

to 50% and crystallized, resulting in gamma-cyclodextrin with 40% yield, calculated on the basis of total cyclodextrin content of the initial mother liquor (Seres 1980b). After satisfying an initial, approximately 10 kg beta-cyclodextrin demand of Chinoin research, a concentrated attention was focused on targeted manufacturing of other cyclodextrins.

To retrieve a remaining considerable amount of gamma-cyclodextrin from xylene complex, the filtered cake was re-suspended in water, and the xylene was eliminated from the destroyed complex by steam distillation. The yield for gamma-cyclodextrin was 2.5%, expressed on initial corn starch base. Based on 1977–1979 experiments, laboratory documentation was issued in 1980, from Chinoin Biotechnology Department (Seres 1980b).

Because of continuous development of the beta-cyclodextrin processing technology, mother liquor reprocessing turned into uneconomically slow. The average yields both for alpha-cyclodextrin and gamma-cyclodextrin reduced below 1%. The faster the demand raised from world market for cyclodextrins, the greater effort was focused on developing special manufacturing technologies for target conversion, for not only beta-cyclodextrin but alpha-cyclodextrin and gamma-cyclodextrin, too.

Laboratory conversion experiments were initiated in the late 1970s to get alpha-cyclodextrin and gamma-cyclodextrin in intentional and selective conversion models. This work started with substantial screening experiments to find a specific cyclodextrin precipitant to achieve high alpha-cyclodextrin or gamma-cyclodextrin conversion rates (Seres 1980a, b). Moreover, researchers of Chinoin Biotechnology Department screened various starch substrates, too. Laboratory-scale micro-conversions were carried out in a thermostatted block reactor, equipped with 3 mL wells. The resulting conversion mixtures were concentrated by evaporation. Residual organic precipitant content was removed by combination of chromatography and activated carbon thereafter.

Micro-reaction mixtures were analyzed either by thin layer chromatography or overpressured layer chromatography. The latter method was a revolutionary new Hungarian investment that time (Tyihák et al. 1985). By means of this equipment, hundreds of chemicals were screened as potentially selective alpha-cyclodextrin or gamma-cyclodextrin complexants.

The pilot plant production of gamma-cyclodextrin was realized in Chinoin plant CH-VIII (Seres 1980c, 1985). A 70 kg quantity of corn starch was prehydrolized with *B. subtilis* alpha amylase. This partially degraded starch was converted to a mostly gamma-cyclodextrin-containing conversion mixture using Chinoin-manufactured *B. macerans* cyclodextrin glucosyltransferase, at 40 °C, and neutral pH, in presence of 1-naphtol and methyl ethyl ketone precipitants. After filtration of the conversion mixture, the cyclodextrin-enriched filter cake was suspended in methanol, refluxed, and separated. After centrifugation the resulting naftol-containing raffinate was removed, and the residue re-suspended in methanol-water mixture and refluxed again in presence of active carbon. After centrifugation the supernatant was passed through Varion KS and Varion AD ion-exchange columns. The column effluent was concentrated by evaporation, and the product crystallized from water. Processing of raw gamma-cyclodextrin, based on ternary complexation

with 1-naphthol and methyl ethyl ketone, resulted in 11 kg of pure gamma-cyclodextrin in 1982.

The invention of Chinoin researchers was based on ternary complex formation and on the solubility-based separation of cyclodextrin complexes in different solvents, applied for patenting in 1983 and granted in 1988 (Seres et al. 1988). At first, the production of alpha-cyclodextrin was enhanced by using a proper complex-forming agent, for example, a strong ionic detergent, sodium dodecyl sulfate/methyl ethyl ketone, or a long-chain aliphatic alcohol and ketone. As the conversion was going on, the forming alpha-cyclodextrin was transformed into beta- and gamma-cyclodextrin especially in presence of ternary complex-forming agents such as toluene/methyl ethyl ketone or alpha-naphthol, respectively (Table 4.3). Both complexants were added together to the conversion mixture at the start. The synergy of the ternary system compared to the binary systems is illustrated in Fig. 4.10.

An efficient specific and selective alpha-cyclodextrin conversion technology was developed in Biotechnology Department, which refers to a patented new ternary complex precipitation scheme, applying a long carbon chain surfactant in presence of an aliphatic ketone (Seres and Barcza 1988). In this case, sodium lauryl sulfate was applied together with methyl ethyl ketone as suitable ternary complexant. Using these ternary precipitants, cyclodextrin glucosyltransferase converted gelatinized corn starch hydrolysate (degree of polymerization 16–40) to alpha-cyclodextrin. The resulted conversion liquor was saccharified by fungal amylase (Fungamyl 800 L). After filtering, the filtrate containing soluble cyclodextrin complex was passed through a strong anion exchanger (Varion-AD, in OH form). After evaporation, cyclohexane was added into the resulting concentrate to precipitate the cyclodextrin. The solid complex was filtered off, and the filter cake washed with methanol to eliminate other dextrins. The centrifuged solid matter was dissolved in water and concentrated by steam distillation to remove the deliberated cyclohexane. After active carbon clarification, filtration, and evaporation, a high output of alpha-cyclodextrin (29 g) was crystallized at refrigeration temperature from 165 g initial optimized hydrolysate. The first industrial-scale production of alpha-cyclodextrin specially was realized at Chinoin plant CH-IV (Végh's team). This procedure applied a long-chain alcohol (1-decanol) as complexant to shift the conversion to alpha-cyclodextrin. Because of violating Japanese patents, this manufacturing way was abandoned.

Table 4.3 Ratios of various cyclodextrins in conversion mixture and the yield of conversion related to starch (Seres et al. 1988)

Ternary complexant mixture	Ratio of cyclodextrins in the product (%)			Yield related to starch (%)
	Alpha	Beta	Gamma	
Methyl ethyl ketone + sodium dodecyl sulfate	14.9	0.2	< 0.1	36.6
Methyl ethyl ketone + toluene	< 0.1	19.5	0.6	52.4
Methyl ethyl ketone + alpha-naphthol	< 0.1	17.1	6.9	15

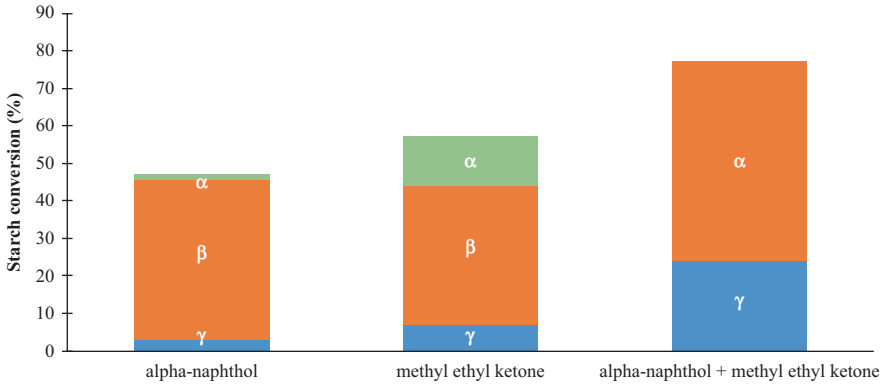

Fig. 4.10 Comparison of binary and ternary complexing systems for gamma-cyclodextrin production after 140-h conversion. (Adapted from Seres and Barcza 1988)

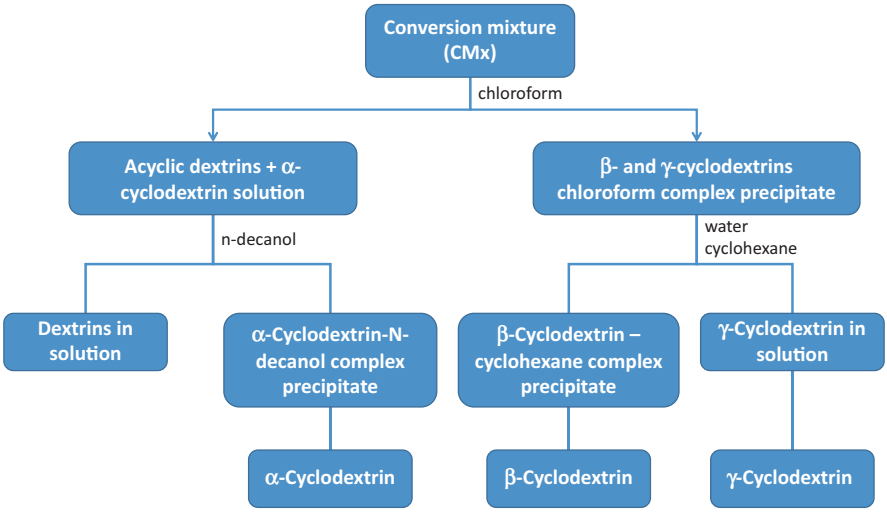

Fig. 4.11 Separation of alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin by consecutive precipitation, filtration, and crystallization. (Adapted from Seres et al. 1989)

In the scaling up of the manufacturing technology, a lot of efforts were made to establish a unified process, which is good for production of all the three cyclodextrins in the same batch. The produced alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin were separated by consecutive precipitation with various solvents as shown in Fig. 4.11 (Seres et al. 1989). Adding chloroform to the concentrated conversion mixture, beta-cyclodextrin and gamma-cyclodextrin precipitated, while alpha-cyclodextrin and the other dextrins remained in solution. This solution was concentrated after filtration, and alpha-cyclodextrin was precipitated by adding n-decanol. The precipitate was suspended in water after filtration, and the residual

solvent was removed by steam distillation. Pure alpha-cyclodextrin was obtained by crystallization upon cooling. The solid chloroform complexes of beta-cyclodextrin and gamma-cyclodextrin were suspended in water, and chloroform was removed by distillation. Cyclohexane was added in order to precipitate beta-cyclodextrin. The precipitate was re-suspended in water and cyclohexane removed by distillation. Then the pure beta-cyclodextrin was obtained by crystallization upon cooling. To obtain pure gamma-cyclodextrin, the filtrate was concentrated, and cyclohexane removed by distillation followed by crystallization. The resulting alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin products were of high purity (99.3%, 99.9%, and 99.8%, respectively). This new technology was brought into effect at the Chinoin plant CH-IV, in 1985. Overall 85.5 kg gamma-cyclodextrin was produced in four 1500 L volume conversion batches; neither alpha- nor beta-cyclodextrin was prepared by this way.

In the scaling up of alpha-cyclodextrin production based on developments of Chinoin Biotechnology Department (Seres's team), decanol was used as precipitant to convert 25 v/v % corn starch into alpha-cyclodextrin as main component. The technology transfer and optimization were finished with success at the pilot plant at Győr Distillery in the first half of 1988. During this optimization series of experiments, the achieved typical alpha-cyclodextrin content was 7–13 v/v % of conversion mixture. The average yield was 9.6 kg alpha-cyclodextrin/100 kg corn starch. Because of political and economic changeover, industrial alpha-cyclodextrin processing efforts at Győr Distillery were interrupted.

4.2.4 Determination of the Individual Cyclodextrins in the Product

At the beginning, analyses of the cyclodextrins were only semi-quantitative. Thin-layer chromatography was a sufficient mode to separate individual cyclodextrins from process samples. A unique new reverse phase thin-layer chromatography method was developed for this purpose by researchers of Chinoin Biotechnology Development. The applied mobile phase on Kieselgel layer was a dioxane/ammonium hydroxide 10/7 v/v mixture. It was a preliminary implementation of the later discovered hydrophilic interaction chromatography mode in the early 1970s and has been shown to work in this case. Later overpressured layer chromatography was also used for analysis of high number of samples.

Based on Cramer's early work on phenolphthalein cyclodextrin-induced decolorization, special quantitative analytical methods were developed by Cyclodextrin Research Laboratory team (Szejtli et al. 1978; Vikmon 1982) based on cyclodextrin complexation of various acid-base indicator dyes. The intensity of transmitted light due to the shift in absorption maxima in presence of cyclodextrin was measured spectrophotometrically. It was discussed later that appropriate dyes as methyl orange and Congo red also gave stable 1:1 complexes with cyclodextrin (Barcza and Buvari-Barcza 1989). These dyes having no any selectivity were able to detect only

overall cyclodextrin quantities. The first quantitative gas chromatographic method applied for simultaneous analysis of various cyclodextrins was based on a derivatization of cyclodextrins to their corresponding dimethyl silyl derivatives, followed by separation on a porous layer open tubular column (Armbruster and Mukhtar 1968; Armbruster 1970).

In cooperation with a group at Eötvös Loránd University Faculty of Sciences (Budapest), a liquid chromatographic method was developed for the separation of the three natural cyclodextrins (Zsadon et al. 1978). This size exclusion chromatography method applied a mixture of strongly cross-linked dextran gels, Molselect G-15 and G-25, which were Hungarian-made column packings. Detection was carried out by continuous flow polarimetry. This detector had the unique property that only chiral compounds (like cyclodextrins) gave any response. The drawback of method was the elapsed analysis duration due to the achievable low flow rates on soft gel column packing. Figure 4.12 shows the separation of the native cyclodextrins in a conversion mixture sample obtained from industrial production.

High-performance liquid chromatography was in the development phase in the second half of the 1970s. It proved to be more efficient than gel chromatography (Fig. 4.13). Although it was not postulated that time, the separation principle is a kind of hydrophilic interaction chromatography. A polar amino silica (μ-Bondapak NH2) stationary phase was applied; the mobile phase was an acetonitrile-water mixture. Due to lack of any chromophore in the cyclodextrin molecule, refractive index detection was applied. Practically, similar method was applied with Hungarian originated BST NH2 stationary phase (Seres and Greiner 1988).

To enhance sensitivity and support the common UV detection, a post-column complexation method used for sensitive detection with phenolphthalein was developed (Frijlink et al. 1987; Szathmary 1989). The principle of this method was the phenomenon that absorbance maximum of phenolphthalein dye applied to effluent

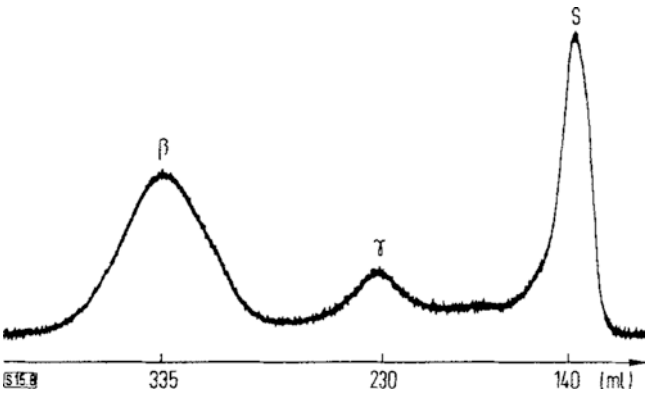

Fig. 4.12 Analysis of conversion mixture containing beta-cyclodextrin and gamma-cyclodextrin and soluble dextrins on a column of Molselect G-15 and G-25 gels (conditions, total bed volume 390 mL; flow rate 24 mL/h; eluent distilled water; Zsadon et al. 1978, CycloLab archive)

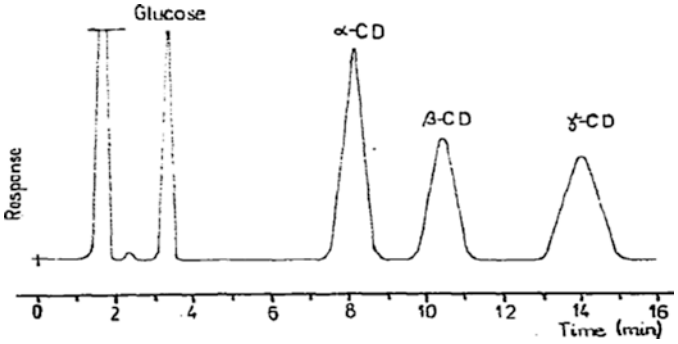

Fig. 4.13 Separation of alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin on μ-Bondapak carbohydrate column (30 m × 4 mm ID) with 2 mL/min flow rate at 25 °C using acetonitrile-water 3:1 mixture as eluent (Waters equipment with refractive index detector; Zsadon et al. 1979a; CycloLab archive)

mobile phase showed a hypsochromic shift due to cyclodextrin complexing (Vikmon 1982). With 550 nm detection wavelength setting, area of individual negative peaks existing in resulted chromatograms was directly proportional to the concentration of each cyclodextrin constituent of the sample.

4.2.5 Production of Cyclodextrin Derivatives

In the second half of the 1970s, it has been already recognized that beta-cyclodextrin having limited aqueous solubility cannot be used for parenteral applications because it forms insoluble complexes with lipids such as cholesterol resulting in renal toxicity. Therefore, a cyclodextrin derivative of high solubility was needed. 2-Hydroxypropyl-beta-cyclodextrin seemed to be the best candidate for this purpose. On the other hand, a cyclodextrin derivative not soluble at all was also required for certain applications. This was the cross-linked cyclodextrin polymer with extremely high molecular weight, swelling in a large extent in water and preserving the molecular inclusion capabilities. The experimental production of these two cyclodextrin derivatives was started in Chinoin.

2-Hydroxypropyl-Beta-Cyclodextrin

Between the 1970s and 1980s, cyclodextrin technologists were looking for the right type of cyclodextrin to fulfill the broken promise of parent beta-cyclodextrin due to its poor solubility in water, for utilizing it in pharmaceutical products. Chemical modifications were undertaken to improve aqueous solubility of parent beta-cyclodextrin, an improvement that was recognized to result in disruption of the

hydrogen bond system between secondary O-2 and O-3 hydroxyls of the adjacent glucopyranose units.

Among the early derivatives, methylated cyclodextrins were considered as promising candidates. Szejtli's team in Hungary was studying the properties of methylated beta-cyclodextrins aiming to find a pharmaceutical solubilizer complexing agent. Among methylated cyclodextrins, they found heptakis(2,6-di-O-methyl)-beta-cyclodextrin a particularly promising compound (Szejtli et al. 1980b; Szejtli 1983). They also filed a number of patents disclosing the synthesis and use of cyclodextrin-methyl-ethers, e.g., methylation (Szejtli et al. 1988a), complexes of dibenzopyran derivatives (Nógrádi et al. 1985), bile substitute (Szejtli et al. 1988b), and methyl carboxyacyl-cyclodextrins (Szabó et al. 1989). However, it was found that these beta-cyclodextrin-methyl ethers exhibited high cell membrane activity. This affinity to membrane lipids such as cholesterol resulted in cytotoxicity which prevented their utility as solubilizers in parenteral/liquid formulations.

Finally, the optimum cyclodextrin derivative was found in the early 1980s. This compound was a cyclodextrin-ether derivative, 2-hydroxypropyl-beta-cyclodextrin. In 1981, Josef Pitha, head of Macromolecular Chemistry Section at National Institute of Health Gerontology Research Center in Baltimore, prepared and studied a novel derivative with optimal properties: solubilizing power for lipophile, non-crystalline, non-crystalizing composite mixture, low parenteral toxicity, and slight membrane activity. The first synthetic route that Pitha applied to obtain this compound was a two-step method: (1) allylation of parent beta-cyclodextrin and (2) oxymercuration/demercuration of allyl beta-cyclodextrin resulting in 2-hydroxypro pyl-beta-cyclodextrin (Pitha et al. 1986).

As this synthetic method was not easy to scale up, neither was it economic, Pitha decided to move forward with the well-known propylene oxide condensation reaction. This hydroxyalkylation method was used first by industrial starch companies similarly to hydroxypropylation of starch, dextrins, and cellulose to improve their aqueous solubility. The propylene oxide condensation reaction was well applicable for cyclodextrin derivatization, too (Gramera and Caimi 1969; Parmenter et al. 1969). Pitha's team soon optimized the hydroxypropylation reaction to obtain hydroxypropyl-beta-cyclodextrin with a relatively narrow and symmetrical distribution of the degree of substitution (Pitha 1988). Besides this reaction, they developed methods for purification of hydroxypropyl-beta-cyclodextrins from the contaminating oligopropylene glycols and for reduction of propylene glycol to an acceptable level. It was also reported that these hydroxypropyl-beta-cyclodextrin preparations with lower degree of substitution than 8 could be transformed into non-hygroscopic amorphous powders. The derivatives with a degree of substitution higher than 12–14 were all semi-solids or glassy syrups of lower solubilization power (Pitha et al. 1986).

Soon after the seminal works by Pitha, Szejtli's group in Chinoin developed and optimized an upscalable industrial synthesis process for hydroxypropyl cyclodextrins. This method applied unique amounts of alkali during hydroxyalkylation step and so resulted in products where the distribution patterns of hydroxypropyl groups along the cyclodextrin ring were different from those obtained by Pitha's method (Szabó et al. 1991). The hydroxyalkylation was performed between 0 and 35 °C

under atmospheric pressure. Once the reaction was completed, the base was removed by neutralization with sulfuric acid and by cation exchange resin. The solution was concentrated by evaporation, then diluted by 2–4-carbon-atom glycols, then evaporated again, and finally diluted with alcohol and acetone to remove polypropylene glycol by-products. The precipitated salt was removed by filtration, and the final product was purified and spray-dried. The process was scaled up to hydroxypropylation of 40 kg beta-cyclodextrin in a reaction unit of 250 L according to the process on flow chart in Fig. 4.14. This optimized manufacturing process by Chinoin served the ground of a Drug Master File Type IV that was completed and used by Janssen Pharmaceutica, for regulatory filings.

Szejtli's group conducted systematic functional characterization of hydroxypropyl cyclodextrins focusing on the solubilizing and complex-forming properties of these derivatives. The study involved more than 50 different lipophilic drug substances and other natural lipophiles. It was shown for the first time that the solubilizing effect of 2-hydroxypropyl-beta-cyclodextrins strongly depends on both the properties of guest and the number of substituents (the degree of substitution) on the beta-cyclodextrin rim. In other words, not only the cavity size of the cyclodextrins matters but also the chemical environment of the cavity entrance (Szeman et al. 1988). Besides the pharmaceutical chemical characterization of hydroxypropyl cyclodextrins, Szejtli's team conducted also in-depth studies on the pharmacokinetic (absorption-distribution-metabolism-elimination, ADME) properties of hydroxypropyl-beta-cyclodextrin using ^{14}C-radiolabeled hydroxypropyl-beta-cyclodextrin upon oral and parenteral administration (Gerlóczy et al. 1990). These early studies have been further utilized and supplemented with *lege artis* pharmacokinetic studies by Janssen Pharmaceutica (Monbaliu et al. 1990; Szathmary et al. 1990).

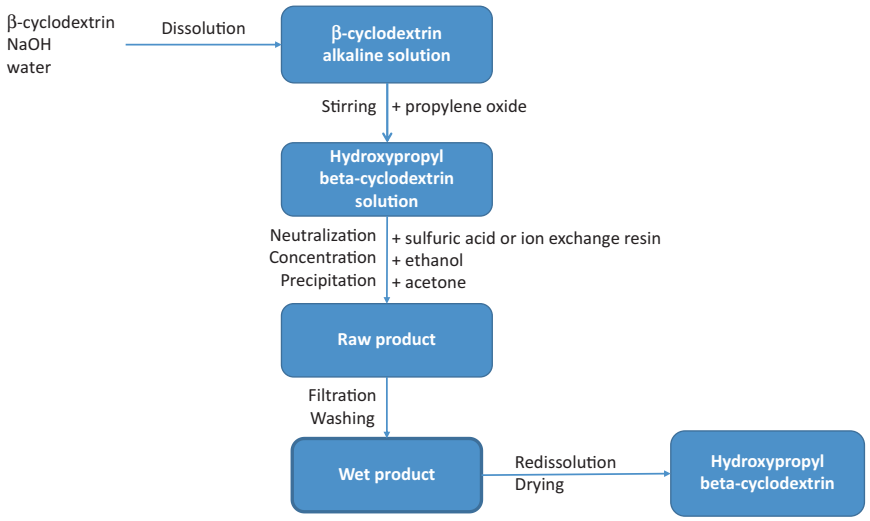

Fig. 4.14 Flow chart of hydroxypropyl-beta-cyclodextrin production

A unique intellectual property situation with hydroxypropyl-beta-cyclodextrins resulted a long interference process. At the National Institutes of Health, Josef Pitha filed a patent in early 1984 with quite broad claims on the preparation and pharmaceutical use of hydroxypropylated cyclodextrins emphasizing the unobvious amorphousness of the composite products, their enhanced water solubility, and complex-forming characteristics together with the solubilizing potency and low toxicity of these cyclodextrin derivatives (Pitha 1988).

Nearly at the same time, a patenting process started in Germany and in the USA. Company Hoechst disclosed the process of making hydroxypropyl cyclodextrins (Brandt and Felcht 1986; filed in 1983 in Germany). At the Christian-Albrecht University in Kiel was simply claimed the improvement of drug solubility and stability using cyclodextrin derivatives, in particular hydroxypropyl-beta-cyclodextrins (Müller and Brauns 1985, filed in 1983 in Germany and in 1985 in the USA, assigned to Janssen). The co-existence of US patent applications of NIH and Janssen caused a decade-long interference process, since US and European patent policies considered the patents differently: while US NIH patent by Pitha was considered the "first to invent," Müller's patent by Janssen was the "first to file" type. The long-lasting interference process was finally settled, and after 35 years of intellectual protection of hydroxypropyl cyclodextrins' use in the USA, in May 2019, (these days) the use of hydroxypropyl-beta-cyclodextrin as a drug solubility improving excipient becomes free worldwide. No such a turbulent intellectual property situation hampers any more the application of this great multifunctional excipient.

Much later, an unexpected function of hydroxypropyl-beta-cyclodextrin was discovered: it turned out to be more than just an excipient. In 2008, it was accidentally discovered that solubilizing excipient hydroxypropyl-beta-cyclodextrin showed remarkable potency in improving the lifespan of mice suffering from a rare, lysosomal storage disorder, called Niemann-Pick type C disease (Liu et al. 2008, 2009). These early observations were then further supported by other research teams searching for therapies to treat Niemann-Pick type C disease (e.g., Davidson et al. 2009).

Based on these encouraging results, the favorable safety profile, and 20-year-long pharmaceutical application as an excipient in human injectable products, regulatory orphan drug designation was given to hydroxypropyl-beta-cyclodextrin in the USA and in EU for the treatment of Niemann-Pick type C disease. This means that this cyclodextrin derivative today can be considered as safe and efficient solubilizing excipient, as well as an orphan drug for treatment of a rare, lysosomal lipid storage disease. However, the demand is very small for orphan drug applications, although extremely high quality/purity is required, but huge amounts of hydroxypropyl-beta-cyclodextrin have been used in the household toiletries: for deodorizing fabrics especially those dried in drying machines (Trinh et al. 1996).

Beta-Cyclodextrin Bead Polymer

Cyclodextrin polymers can be obtained in the form of beads when the reaction of cyclodextrin with polyfunctional compounds is carried out in aqueous phase dispersed in a non-polar solvent (Wiedenhof et al. 1971).

An independent procedure was developed for the preparation of cyclodextrin bead polymer in the second half of the 1970s in the Chinoin Biochemical Research Laboratory in cooperation with the Eötvös University Faculty of Sciences. The invention was based on applying polyvinyl alcohol, polyvinyl acetate, or polyvinyl alcohol-acetate copolymer as a protecting colloid in emulsion polymerization of cyclodextrin using a polyfunctional coupling reactant such as epichlorohydrin and/or other diepoxy compounds. The cross-linking reaction was performed in two steps: first a water-soluble pre-polymer was formed with epichlorohydrin in a homogeneous phase, and then a diepoxy compound under less alkaline conditions was used for further cross-linking in a heterogeneous phase applying toluene as water-immiscible solvent. The development started in 1976 by optimizing the reaction conditions in a laboratory scale (Fenyvesi et al. 1979). A patent was applied in 1978 and then granted in 1981 both in Hungary and in the USA (Szejtli et al. 1981). The aim was a wound healing formulation for veterinary application in the form of spherical beads of 100–300 μm diameter. The healing effect was based on the high swelling of beads which sucked up the wound exudate, thus ensuring clean wound surface and fast healing of otherwise slowly healing, oozing wounds. Utilizing cyclodextrin functioning as a drug carrier, various antiseptic agents such as iodine were added to the formulation (Fenyvesi 1988; Szejtli et al. 1988c). These antiseptic agents were released into the wound in a sustained manner.

Application of the cyclodextrin polymer beads as column packing in gel chromatography was also foreseen. In addition to the analytical applications (Zsadon et al. 1979b, 1981, 1983, 1986, 1987; Cserháti et al. 1983; Szilasi et al. 1985; Ujházi et al. 1989), the use in preparative chromatography was worked out, too. A method was developed for the selective removal of phenylalanine from protein hydrolysate aimed for nourishing patients in phenylketonuria by simply eluting the protein hydrolysate through a cyclodextrin bead polymer column (Szente et al. 1981). Another application was foreseen for the removal of bitter components such as naringin from citrus juices (Ujházi and Szejtli 1989). Based on the similarity to cross-linked dextran polymer of Pharmacia (Sweden) named Sephadex-25, this cyclodextrin polymer was named CDP-25.

The first scaling up was performed at Eötvös University Faculty of Sciences in 1981. The most important step was replacing toluene to less toxic paraffin oil. The resulting 1600 g bead polymers were of the desired size (0.09–0.31 mm), spherical shape and swelling (4.7 mL/g), and cyclodextrin content measured by iodometric titration after acidic hydrolysis (55–60%). The methods for characterization were standardized and documented (Kálóy 1980). The flow chart of preparation and the scanning electron microscopic photo are illustrated in Fig. 4.15 and Fig. 4.16, respectively.

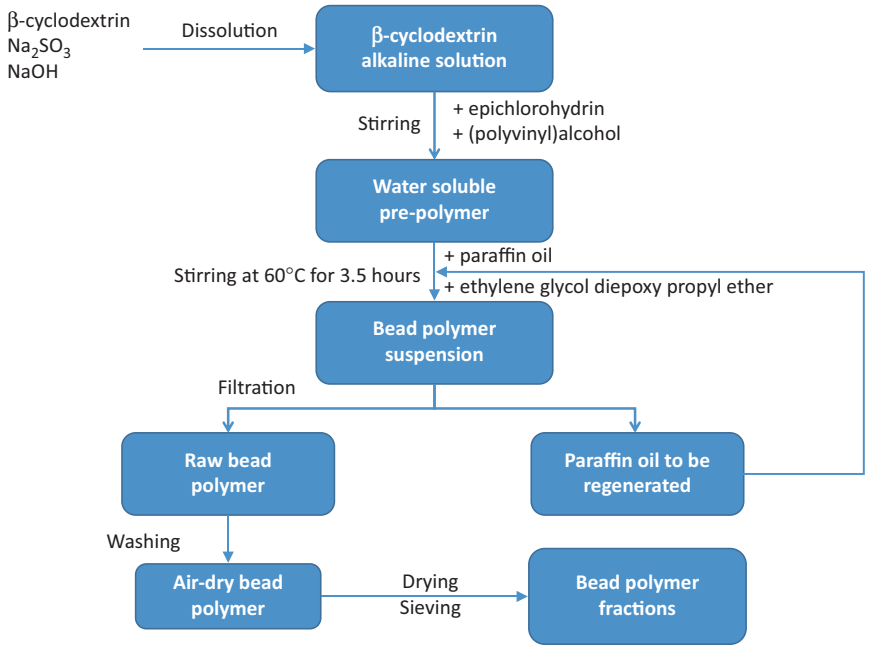

Fig. 4.15 Flow chart of cyclodextrin bead polymer preparation

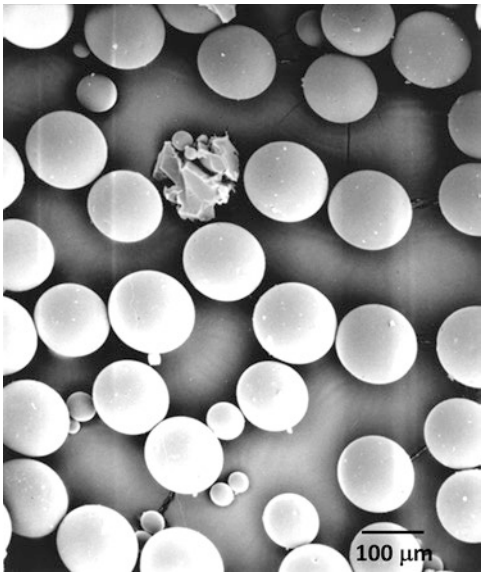

Fig. 4.16 Scanning electron microscopic photo of cyclodextrin bead polymer

After the small-scale laboratory experiments for optimizing the reaction conditions in order to get the product of proper shape, size, and swelling, the scaling up was started in Organic Chemistry Development Co. (SzVF, Budapest) in 1983. Instead of paraffin oil, dichloroethane was used as water-immiscible solvent and ethylcellulose as protecting colloid for stabilizing the emulsion. The diepoxy coupling agent in the second step of cross-linking was very expensive; therefore epichlorohydrin was used in this step, too. To improve the flowing properties of the dry beads, they were silylated. Fractionation was performed by a wet technology to replace sieving, and fluid bed dryer was used for drying. In a further development, dichloroethane was replaced by 1-butanol, thus improving the environmental footprint of the technology, and a proper surfactant was selected for stabilizing the emulsion during polymerization.

In-house acute toxicity study on mice and rats in 3000 mg/kg and 5000 mg/kg dose per os demonstrated no toxicity. Dermal toxicity study in Chinoin Toxicological Department showed no irritation when used in 5000 mg/kg dose on depilated skin of male and female rats. According to preliminary microbiological studies, the bead polymer, unlike to starch usually applied in topical powder formulations, was not a substrate for fungi causing dermatomycosis. The tissue compatibility studies by intramuscular injection of bead polymer into rats resulted in no pathological reactions.

In vivo experiments on rats proved the wound healing effect without detecting inflammatory cell reactions. In human trials, therapy-resistant ulcers were treated successfully on nine patients (Felméray et al. 1996). The overinfected, coated wounds became clear on the average in 5 days. Both the depth and the basic area of the ulcers were reduced quickly.

Approximately 130 kg bead polymers of 200–400 μm grain size, 4.7–5.6 mL/g swelling, and 48–62% cyclodextrin content were produced in 16 batches. Instructions for production were compiled, and specification set and methods for qualification worked out. The microscopic photo on the beads (Fig. 4.16) shows the regular shape and narrow size distribution of the product. Option for production and selling was granted to Wacker Chemie (Consortium für elektrochemische Industrie, Germany) by Chinoin based on an agreement in 1986, but it was not realized.

In 1987, the product with 2% iodine content was selected for development under the trade name Chinoderm as wound healing powder for veterinary application by Chinoin. A 3-year expiry date was established based on stability studies which showed no change in iodine content after 30-day storage at 40 and 50 °C, and only 12% decrease at 60 °C. In Chinoin (Nagytétény unit), 20 kg cyclodextrin bead polymer with 2% iodine content was prepared for toxicological and efficacy studies. These studies showed the beneficial effects of the iodine-releasing beads in wound healing on dogs by the University of Veterinary Medicine, Budapest.

4.2.6 The End of the Story

After the political changes in Hungary, Chinoin was sold to Sanofi Aventis in 1991. The new owner was not interested in bioprocesses. So, the fermentation plant was closed, and with this also the enzyme production was finished (Sipos et al. 1996). At that time, the site of cyclodextrin production was at Győr Distillery Co. Ltd. in western Hungary. The management has foreseen difficulties in selling cyclodextrins without the support of a big pharmaceutical company. Therefore, the cyclodextrin production was stopped soon after changing ownership in Chinoin. Although Hungary was one of the first industrial cyclodextrin producers in the world, the high potential of cyclodextrin market (today thousands of tons in a year) was not predicted. At that time, two European cyclodextrin manufacturers have already been on the market: Roquette Frères in France and Wacker Chemie in Germany.

With finishing the cyclodextrin production, the hydroxypropyl-beta-cyclodextrin manufacturing was also given up. Nowadays, both Roquette Frères and Wacker Chemie produce this derivative in extremely high volume. Experimental production of bead polymers was also stopped after the technology transfer to Wacker Chemie (Germany), and they are not produced any more.

Only the cyclodextrin research survived in Hungary by establishing a spin-off company by Professor Szejtli and his co-workers in the Biochemical Research Laboratory in 1989. CycloLab, a small private research company, not only has maintained its leading position in cyclodextrin research, but it has also developed an independent process for the production of sulfobutyl ether beta-cyclodextrin, an alternative parenteral drug carrier, and since 2008 it has been an FDA-approved GMP manufacturer of this excipient with multiple ton annual production (CycloLab 2019).

4.3 Conclusions

This chapter tells how the cyclodextrin production was started in Hungary in the 1970s and 1980s of the twentieth century, at about the same time as in Japan. The difficulties experienced in finding and isolating the proper enzyme, separating the individual cyclodextrins from the conversion mixture, analyzing the products, and scaling up to hundred kilograms scale were gradually overcome till the production of several tons beta-cyclodextrin started. The methods for producing alpha-cyclodextrin and gamma-cyclodextrin were also worked out, and some experimental lots obtained. Similarly, the productions of hydroxypropyl-beta-cyclodextrin and beta-cyclodextrin bead polymer were ready to be industrialized when the productions were abandoned owing to political changes. The laboratory headed by Professor Szejtli became a knowledge center of cyclodextrin research and development. After about two decades of break in cyclodextrin production in Hungary, this

laboratory, now CycloLab, became a company producing sulfobutylether beta-cyclodextrin using beta-cyclodextrin as starting material.

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Chapter 5
Metal Nanoparticles and Cyclodextrins for Catalytic Applications

Sébastien Noël, Anne Ponchel, Samahe Sadjadi, Eric Monflier, and Bastien Léger

Contents

Abstract The development of efficient catalysts in terms of activity and selectivity has always been a major topic for researchers since several decades. The use of colloidal metallic nanoparticles received an increasing interest due to their large surface area leading to high catalytic activities. The main problems for these nanoparticles arise from the control of their size and also their aggregation before and during the catalytic process. In this context, the use of cyclodextrins as protective agents proved to be effective and allowed the rise of a large variety of catalytic systems at the nanoscale.

In this chapter, we reviewed all the articles related to the metallic nanoparticles synthesized in the presence of cyclodextrin for catalytic applications since the 1980s

S. Noël · A. Ponchel · E. Monflier · B. Léger (✉)
Université d'Artois, CNRS, Centrale Lille, Université de Lille, UMR 8181, Unité de Catalyse et de Chimie du Solide (UCCS), Lens, France
e-mail: sebastien.noel@univ-artois.fr; anne.ponchel@univ-artois.fr; eric.monflier@univ-artois.fr; bastien.leger@univ-artois.fr

S. Sadjadi
Gas Conversion Department, Faculty of Petrochemicals, Iran Polymer and Petrochemical Institute, Tehran, Iran
e-mail: s.sadjadi@ippi.ac.ir

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_5

to early 2020. The major points are (1) the possibility of development of metal nanoparticles in solution or immobilized onto a support in the presence of cyclodextrin; (2) the multiple roles of cyclodextrin such as reducing agent, mass transfer agent, and stabilizing/dispersing agent leading to the increase of the stability of metal nanoparticles and better catalytic activities or specific selectivities; and (3) the control and the use of more complex catalytic systems where cyclodextrin is playing the main role as a supramolecular host.

Keywords History · Catalysis · Metal nanoparticles · Cyclodextrin-assisted synthesis · Cyclodextrin derivatives · Structures · Inclusion complexes · Supramolecular chemistry

Abbreviations

ACNa	1-Adamantane carboxylate sodium salt
AmCD	Poly-(6-*N*, *N*-dimethyl-propylenediamino)-(6-deoxy)-β-cyclodextrin
AO-CNTs	Acid-treated carbon nanotubes
C60	Fullerene[60]
CD	Cyclodextrin
CDNS	Cyclodextrin nanosponges
CNTs	Carbon nanotubes
FTIR	Fourier transform infrared spectroscopy
GCE	Glassy carbon electrode
Hal	Halloysite nanoclay
HEA16Cl	*N*, *N*-dimethyl, *N*-hexadecyl, *N*-(2-hydroxyethyl)ammonium chloride
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
IPTS	(3-isocyanatopropyl) triethoxysilane
RaMe-β-CD	Randomly methylated-β-cyclodextrin
rGO	Reduced graphene oxide

5.1 Introduction

Metal nanocatalysts are an interesting research field for the scientific community due to the high control of both the size and the shape of the metal nanoparticles in order to find a good compromise between stability and reactivity of the catalytic system. Metal nanoparticles can be synthesized through two approaches: the fragmentation of a bulk metal, called the top-down approach, or the chemical transformation of a metal precursor, called the bottom-up approach. The key parameter of a metal nanoparticle-based catalyst, in solvent-dispersed form or immobilized on a

support, is the choice of the stabilizing agent which ensures the good dispersion of the active phase with the desired particle size. Taking into account this, the need to develop more eco-friendly metal nanoparticle synthesis without harmful solvents, the use of water-soluble capping agents has grown since the beginning of the twenty-first century. Ammonium salts, phosphanes, dendrimers, polymers, or oligosaccharides are generally found in the literature and show interesting results in terms of catalytic activity and stability. Among these capping agents, cyclodextrins are interesting candidates in the field of nanocatalysis due to their low cost, nontoxicity, high capacity to interact with metal ions, and the possibility to form inclusion complexes with reactants in order to bring them close to the active site.

According to a bibliographic survey up to 2020 involving cyclodextrin, catalysis, and metal nanoparticles as keywords, a huge number of publications have been found. Therefore, we decided to restrict our study to the cases where cyclodextrins are present during the catalytic process using metal nanoparticles, either in solvent-dispersed form or immobilized on a support, as active phase. This means that the works dealing with cyclodextrin-assisted syntheses of supported metal nanoparticles including a calcination/carbonization step or a washing step to remove the cyclodextrin have not been considered here.

This chapter is divided into two distinct parts. In the first part, we focus on the publications concerning the solvent-dispersed nanoparticles. Several parameters such as the size of the cavity, the functionalization of the cyclodextrin rims, and the presence of co-stabilizers (surfactants, phosphanes, or polymers) or cyclodextrin-based polymers have been studied to get stable, active, and recyclable nanoheterogeneous catalysts. Cyclodextrins can be either added during the nanoparticle synthesis or after the metal nanoparticle synthesis and can consequently play the role of mass transfer agent to bring the substrate in the vicinity of the active species and improve the activity and/or the selectivity. The second part is dedicated to catalysts with nanoparticles immobilized onto and/or into a support matrix in the presence of cyclodextrins. In this case, different strategies are discussed for the synthesis of heterogeneous catalysts consisting of nanoparticles immobilized on a support, such as inorganic supports, carbonaceous materials, or polymers, in the presence of cyclodextrins either non-covalently grafted or covalently grafted on the supports. Nanoparticles can be synthesized (i) before their adsorption/incorporation onto or into the support or (ii) in the presence of the support and also of the cyclodextrins. It should be noticed that the structure of the cyclodextrin remains intact whatever the strategy. Consequently, in line with the first part, the relationships between the supramolecular structures and their activities are discussed, and the different roles of the cyclodextrin are further underlined.

5.2 Nanoparticles Stabilized by Cyclodextrins in Solution

5.2.1 Nanoparticles Stabilized by Native Cyclodextrins

The first example of the synthesis of metal nanoparticles stabilized by native cyclodextrins (α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin) was reported by Komiyama and Hirai (1983). An aqueous Rh(III) salt solution in the presence of native cyclodextrin and ethanol was refluxed in order to give Rh nanoparticles. The stability of the resulting particles was associated to the ability of the cyclodextrin to prevent aggregation via strong hydrophobic interactions between the cyclodextrin cavity and the metal surface. β-cyclodextrin gave the best colloidal dispersion with a Rh average diameter of 2.8 nm. When γ-cyclodextrin was used, no colloidal suspension was observed, and sedimentation took place. The resulting Rh particles stabilized by β-cyclodextrin were then evaluated in the catalytic hydrogenation of water-soluble α,β-conjugated carbonyls under mild experimental conditions (30 °C, 1 bar of hydrogen) with the catalytic activities ranging from 0.06 to 0.24 molH_2 g(Rh)$^{-1}$ s^{-1}. The role of β-cyclodextrin was highlighted by observing no activity for the hydrogenation of 3-buten-2-one in the presence of cyclohexanol that was a competing guest forming an inclusion complex with β-cyclodextrin.

The ability of β-cyclodextrin to stabilize solvent-dispersed metal colloids was also observed by Willner in 1987 by synthesizing TiO_2 and CdS nanoparticles with, respectively, an average diameter of 8 nm and 10 nm (Mandler and Willner 1987). The catalytic activity of the abovementioned semiconductor particles was evaluated in the photoreduction of a relay molecule (*N*, *N*′-dioctyl-4, 4′-bipyridinium) with semiconductor particles (Fig. 5.1). An increase of the local concentration of the relay in the vicinity of the semiconductor interface was explained by the association of this relay with the cavity of the β-cyclodextrin (K_{ass} = 5.6 10^3 M^{-1}). Moreover, inhibition experiments using phenol as substrate were performed where phenol was associated to β-cyclodextrin, leading to a bad electron transfer.

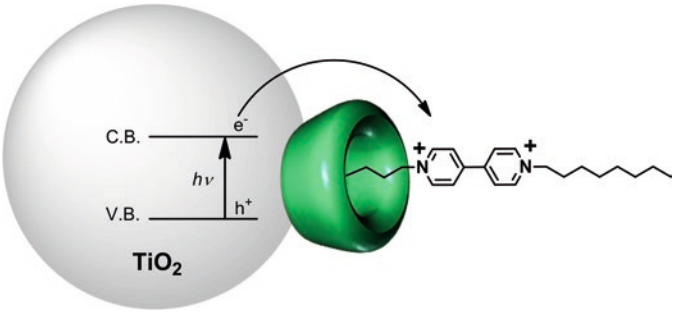


Fig. 5.1 Supposed operation of the receptor-semiconductor colloid. The interfacial electron transfer has been improved from the excited semiconductor to the relay substrate because of the increase of the local concentration of the relay substrates at the semiconductor interface due to the association of the relay with the β-cyclodextrin. (Adapted from Willner and Mandler 1987)

The same authors studied the synthesis of palladium nanoparticles stabilized by β-cyclodextrin by warming an aqueous solution of Na_2PdCl_4 containing β-cyclodextrin (1% in weight) at 60 °C via the classical polyol process (Willner and Mandler 1989). The non-reduced palladium was removed by addition of an Amberlyst® resin, and the resulting colloids were centrifuged to separate the precipitated palladium colloids. This preparation resulted in an active catalyst for the photosensitized reduction of sodium bicarbonate to sodium formate by visible light in the presence of deazariboflavin as photosensitizer, *N*, *N*′-dimethyl-4,4′-bipyridinium as the first electron donor, and sodium oxalate as the sacrificial electron donor. After kinetic studies, the authors emphasized the biomimetic character of these colloids acting as artificial enzymes. By comparing their Pd nanoparticles to other Pd nanoparticles stabilized by classical agents such as glucose or poly(*N*-vinyl-2-pyrrolidone), the authors clearly showed that the best catalytic activity was obtained with their colloids.

Despite numerous studies concerning the synthesis of gold nanoparticles in the presence of cyclodextrins, only a few of them was dedicated to catalytic applications. The first catalytic application was reported in 2009, when the group of Qi synthesized α-cyclodextrin-capped gold nanoparticles by reduction of $HAuCl_4$ in alkaline solution at 60 °C where α-cyclodextrin was playing the dual role of reducing agent of the metal precursor and stabilizing agent of Au nanoparticles (Huang et al. 2009). As in the case of palladium, Au(III) can be reduced via the polyol process in alkaline medium using the cyclodextrin hydroxyls as reductant. The concentration of α-cyclodextrin was the key parameter to get the smallest particles with a narrow size distribution; the higher the α-cyclodextrin concentration, the smaller the nanoparticles. The sodium hydroxide concentration played also an important role. For pH values lower than 10.5, α-cyclodextrin failed to reduce the gold precursor, but too high pH (pH = 12) led to the irreversible agglomeration of Au nanoparticles. These colloidal suspensions were effective hydrogen activators for the reduction of 4-nitrophenol to 4-aminophenol with a large excess of sodium borohydride. The conversion was determined by the time-dependent decay of the 4-nitrophenol absorbance at 400 nm. The kinetic reaction rate constants were inversely proportional to the particle size. These results pointed out that these α-cyclodextrin-capped Au nanoparticles showed catalytic activity and that cyclodextrin did not disturb the metal surface.

More recently, monodisperse Au nanoparticles with diameter of 15–20 nm were synthesized by the polyol process (100 °C in a phosphate buffer solution) using native cyclodextrins (α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin) as both reducing agents of metal precursor and protective agents of Au colloidal suspensions. These Au nanoparticles were used for applications in fluorescent sensing, self-assembly, and cascade catalysis (Zhao et al. 2016). The FTIR analysis clearly showed the decrease of the intensity of the hydroxyl group absorbance band. In the same time, the appearance of carboxyl groups was observed by X-ray photoelectron spectroscopy due to the oxidation of the cyclodextrins. All of these analyses respectively justified the reduction of the gold precursor in the presence of cyclodextrins and the stabilization of the resulting Au nanoparticles through the carboxylate

functions. In addition to the conventional host-guest interaction-based properties, the gold nanoparticles stabilized by these cyclodextrins showed interesting catalytic activities and exhibited mimicking properties of both glucose oxidase and horseradish peroxidase. Especially, the cascade reaction (oxidation of glucose with generation of gluconic acid and H_2O_2 followed by the oxidation of TMB (3,3′,5,5′-tetramethylbenzidine)) was well-achieved using the Au nanoparticles as the sole catalyst.

Several cucurbit[n]urils and native cyclodextrins were used as stabilizers of metastable gold nanoparticles, i.e., gold nanoparticles synthesized by chemical reduction of Au(III) with $NaBH_4$ and then the addition of the desired macromolecules (del Pozo et al. 2018). Whatever the receptor, transmission electron microscopy images showed spherical gold nanoparticles which, on the one hand, were organized into non-ordered structures with cyclodextrins and, on the other hand, were homogeneously dispersed in the case of cucurbit[n]urils with mean diameters ranging from 5.2 nm to 10.7 nm. The catalytic activity of these colloidal suspensions was evaluated in the reduction of 4-nitrophenol using $NaBH_4$ as reducing agent in the presence of these gold nanoparticles. The different stabilizers were compared by evaluating the catalytic activities with normalized rate constants depending on the gold amount (named k_c) or depending on the total gold surface (named k_s) or by determining a loss of efficiency after 2 months (Table 5.1).

The metastable gold nanoparticles, i.e., the particles with no added stabilizer, showed the highest catalytic activities which can be explained by weak interactions between the boron species and the gold nanoparticles. Nevertheless, a significant loss of performance was observed after keeping this colloidal suspension during 1 month under stirring. It clearly showed that the addition of a stabilizing agent was necessary to keep a long-term stability and also a good catalytic activity. Finally, the efficiency of the catalysts was explained by the surface coverage of nanoparticles obtaining high reaction rates with low surface coverage.

Other metal nanocatalysts were prepared using the polyol process strategy with native cyclodextrins. For example, Li et al. (2017) studied the synthesis of silver nanoparticles in alkaline medium in the presence of β-cyclodextrin at room temperature. FTIR analysis of the resulting Ag nanoparticles showed a characteristic peak at 1647 cm^{-1}, which corresponds to the oxidation of hydroxyl groups during

Table 5.1 Influence of the macrocycle on Au nanoparticles' mean diameter, rate constants, and efficiency with time

	Au nanoparticle stabilizer				
Parameter	BH_4^-	Curcubit[6] urils	Curcubit[7] urils	α-Cyclodextrin	β-Cyclodextrin
Diameter (nm)	6.6	5.4	5.2	5.8	10.7
k_c (L g^{-1} min^{-1})	1581	547.0	592.2	529.4	570.8
k_S (L m^{-2} min^{-1})	29.5	9.5	9.97	9.9	19.8
Loss of efficiency (%)	77.6	84.1	31.6	58.2	79.1

Adapted from del Pozo et al. (2018)

the polyol process. In addition, slight red shift compared with normal vibration wavelength indicated the coordination of β-cyclodextrin onto the surface of the Ag nanoparticles. Interestingly, the key parameters to get small particles with a narrow distribution (pH value, temperature, and β-cyclodextrin/Ag molar ratio) are the same as in the study of Qi concerning the gold nanoparticles. According to the authors, not only the cyclodextrin deprotonation led to the formation and the stabilization of the silver nanoparticles but also the insoluble silver oxide formation in alkaline medium which allowed a better control of the growth of the silver nanoparticles. The authors also found that the optimal synthesis temperature was 35 °C. The intensity of absorption peak increased with the temperature, but very high temperature led to Ag_2O decomposition and the loss of the control of the particle growth. For the catalytic results, the authors suggested that H bonding interactions between the cyclodextrin and the substrate are the key factor. These Ag nanoparticles that were used in the catalytic reduction of 4-nitrophenol have proven to be more active than traditional Ag nanoparticles stabilized by sodium citrate. This better catalytic activity was explained by hydrogen bonds between 4-nitrophenol and the hydroxyl groups of β-cyclodextrin which allowed a better diffusion of the substrate onto the surface of Ag nanoparticles.

Another study developed γ-cyclodextrin-capped Ag nanoparticles for the enhancement of the antibacterial efficiency of chloramphenicol (Gannimani et al. 2016). The formation of nanoparticles was confirmed by UV-Vis spectroscopy and the appearance of the surface plasmon resonance band at 412 nm. The formation of inclusion complexes was studied by ^{1}H NMR. The observed changes in the shifts could be considered as direct evidence of the existence of host-guest non-covalent interactions between γ-cyclodextrin and chloramphenicol. Moreover, an increase of the antibacterial activity of chloramphenicol was observed when it was used in combination with γ-cyclodextrin-capped Ag nanoparticles because of supramolecular interactions leading to the immobilization of chloramphenicol onto the Ag nanoparticle surface.

Using simple, economical thermal pyrolysis approach and tin(II) stearate as eco-friendly organometallic precursor, SnO_2 quantum dots with mean diameters less than 10 nm were synthesized (Haw et al. 2016) and used in both aqueous and non-aqueous media thanks to β-cyclodextrin employed for surface-ligand exchange. It was suggested that the formation of inclusion complexes between stearate-stabilized quantum dots and β-cyclodextrin could allow the phase transfer from the non-aqueous phase to the aqueous phase. Moreover, the use of the SnO_2 quantum dots for the photocatalytic hydrogen gas evolution was studied and compared with commercial SnO_2 nanoparticles. The results demonstrated higher photocatalytic activity of the former compared to the latter (~31.3% higher yield of hydrogen). The higher photocatalytic activity of SnO_2 quantum dots was attributed to their smaller size, higher surface area, and lower rates of photogenerated e^-/h^+ recombination. Noteworthy, β-cyclodextrin could enhance the surface moiety and the hydrophilicity of SnO_2 particles and consequently improve their dispersion in the aqueous solution.

An efficient combination between nanoparticles of zinc oxide and β-cyclodextrin in water for a three-component reaction has been highlighted by Sagir et al. (2016). More precisely, an *ortho*-aminothiophenol, with aromatic aldehydes and isocyanides, can give the corresponding 3-aryl-*4H*-benzo[1.4]thiazin-2-amine in the presence of a Lewis acid catalyst in aqueous medium. The authors prepared ZnO nanoparticles with a spherical shape with a diameter between 15 and 25 nm and compared their activity to classical Lewis acids. The best catalytic result was obtained using 5 mol% of ZnO nanoparticles. In order to enhance the catalytic activity, phase-transfer agents were applied (10 mol% of β-cyclodextrin, cetyltrimethylammonium bromide, or tetradecyltrimethylammonium bromide), and the best activity was obtained in the presence of β-cyclodextrin (respectively, 83% of yield after 30 min, 86% after 40 min, and 84% after 50 min). Recycling experiments showed that the catalyst could be reused during five consecutive runs without any loss of its activity. The authors compared their results to other homogeneous or nanoheterogeneous systems, and the chosen reaction conditions (water, 60 °C, 40 min of reaction) furnished a yield of 92%.

ZrO_2-β-cyclodextrin composite was synthesized by co-precipitation using $ZrOCl_2$ and β-cyclodextrin in an ammonium hydroxide solution (Girish et al. 2015). These composite nanoparticles were prepared for the solvent-free synthesis of 2, 4, 5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles. The catalyst could be recycled for three runs without any appreciable loss of activity and selectivity.

The synthesis of iron-platinum core-shell nanoparticles (Fe@Pt) for aqueous hydrogenation reactions was investigated in order to limit the use of Pt monometallic-based catalyst (Mori et al. 2009). Fe@Pt nanoparticles were synthesized by thermal decomposition of $Fe(CO)_5$ followed by chemical reduction of $Pt(acac)_2$ in the presence of oleic acid and oleylamine. After precipitation and dispersion in hexane, the particle organic-water transfer occurred after the addition of a γ-cyclodextrin aqueous solution. Transmission electron microscopy images showed a homogeneous dispersion with an average diameter of 2.5 nm. The core shell structure (iron as the core, platinum as the shell) was determined by X-ray absorption measurements. The catalytic properties of the Fe@Pt nanoparticles were evaluated in the aqueous hydrogenation of allylic alcohol under 1 atm of hydrogen. γ-cyclodextrin-capped nanoparticles were more efficient in water than those in organic solvent without cyclodextrin. This difference of activity could be explained by host-guest complexation between the substrate and the γ-cyclodextrin bringing the substrate close to the active phase. The catalyst could be recycled at least three times.

Even if water appeared as the ideal solvent (non-toxic, cheap, and readily available), its use is limited because a wide range of organic compounds are not water soluble or are unstable in this solvent. Ionic liquids had promising results, but their environmental safety is still discussed (Kunz and Häckl 2016). Recently, low melting mixtures (solvents prepared by mixing high melting point starting materials, which form a liquid by hydrogen bond interactions) (Francisco et al. 2013) were developed for the catalytic applications with homogeneous metal catalyst (Ferreira et al. 2015). These low melting mixtures are generally cheap and easy to prepare

from readily available materials. Zhao et al. (2014) investigated the palladium-catalyzed Suzuki coupling of phenyl boronic acid with aryl bromides in different carbohydrate-urea-inorganic salt mixtures. A β-cyclodextrin/*N*-methylurea mixture was used as solvent for the stabilization of Pd nanoparticles. 80 °C is generally required to get active Pd nanoparticles for C-C coupling reactions, and *N*-methylurea was necessary to achieve this temperature. Cyclodextrin reduced the palladium ions to get palladium nanoparticles. The model reaction was the coupling between bromobenzene and phenylboronic acid with 0.05 mol% Pd, using K_2CO_3 as base giving 90% of biphenyl after 2 h. A catalytic amount of water improved the yield up to 95%. Other aryl halides were tested, and the catalytic system showed a great tolerance toward a broad range of functional groups such as $–NO_2$, $–NH_2$, and –CN functionalities. The recyclability was studied, and the catalytic system preserved its activity and stability after four runs.

A second type of non-conventional media has been developed and consisted into performing the reaction without any solvent. In this case, where the catalyst and the substrate are in the solid state, mechanochemistry appeared as an interesting alternative strategy. Gold nanoparticles were mechano-synthesized and were used as nanocatalysts in the reduction of substituted nitrobenzene derivatives by ball milling (Menuel et al. 2016). Several cyclodextrins and saccharide additives were tested to afford well-dispersed Au nanoparticles. The smallest Au average particle size was obtained with β-cyclodextrin. X-ray photoelectron spectroscopy data confirmed the presence of zerovalent Au nanoparticles. Several parameters were studied to see their influence on the activity of the gold nanoparticles during the nitroarene reduction. First, the nature of the saccharide was evaluated. Except in the case of methylated saccharides, all additives improved the catalytic activity of Au nanoparticles, especially in the case of cyclodextrins. The best enhancement was obtained with β-cyclodextrin. Water played a crucial role during the catalytic process. Recycling experiments were performed, and the best results were obtained for β-cyclodextrin where no loss of the activity was noticed after three successive runs. Several nitrobenzene compounds were tested, and, whatever the substrate, the *para*-substituted derivatives showed lower activities than the *ortho*- or *meta*-ones. The authors explained these differences by favored/unfavored routes due to, respectively, unstable/stable complexes between the cyclodextrin and the substrate (Fig. 5.2). The *para*-substituted compounds can form stable complexes, which limit the approach of the substrate close to Au nanoparticle surface.

5.2.2 Nanoparticles Stabilized by Functionalized Cyclodextrins

In order to improve the stability of the solvent-dispersed metal nanoparticles, the use of molecular functionalized cyclodextrins was investigated. According to our literature survey, these functionalized cyclodextrins could be divided in two families: (1) the thiolated cyclodextrins and (2) the alkylated cyclodextrins.

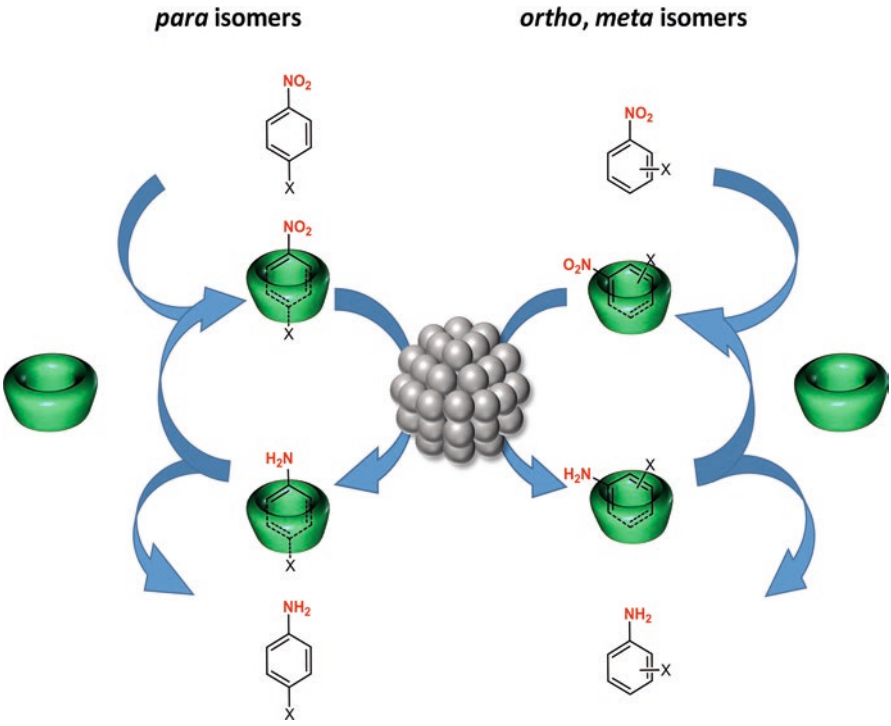


Fig. 5.2 Schematic representation of dynamics of exchange between cyclodextrins and halogenonitrobenzene derivatives. The catalytic activity depends upon the strength of the inclusion complex between the substrate and the cyclodextrin or between the product and the cyclodextrin. The conversion is decreasing when the inclusion complex between the substrate (or the product) and cyclodextrin is stronger. (Adapted from Menuel et al. 2016)

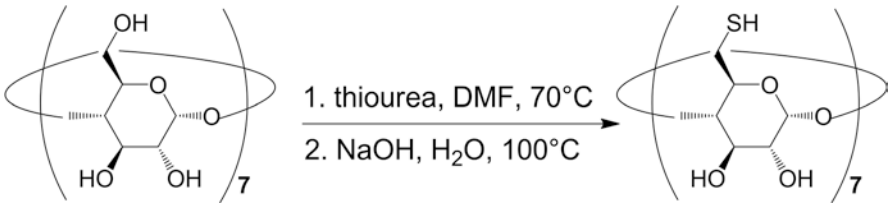
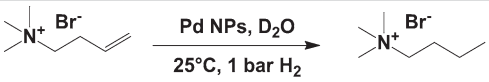


Fig. 5.3 Synthesis of *per*-6-thio-β-cyclodextrin. *per*-6-thio-β-cyclodextrin has been synthesized into two steps with a final yield of 85%. (Adapted from Alvarez et al. 2000)

Nanoparticles Stabilized by Thiolated Cyclodextrins

Alvarez et al. (2000) reported the use of thiolated cyclodextrins for the stabilization of platinum and palladium nanoparticles in water for the catalytic hydrogenation of allylamine. More precisely, solutions of MCl_4^{2-} (M = Pt or Pd) sodium salts in a

Table 5.2 Hydrogenation of trimethylbutenyl ammonium bromide in the presence of *per*-6-thio-β-cyclodextrin[a]



Entry	Additive	Concentration (mM)	Turnover frequency (h^{-1})
1	None		320
2		0.5	131
3		3	112
4	Me_4N^+ Br^-	3	311
5	Et_4N^+ Br^-	3	290
6	Adamantanol	0.5	192
7		0.5	230

Adapted from Liu et al. (2001)

[a]Reaction conditions: trimethylbutenyl ammonium bromide (3 mM), Pd nanoparticles (8 μg mL^{-1}), D_2O, 1 bar H_2, 25 °C

DMSO:H_2O mixture were reduced with sodium borohydride in the presence of *per*-6-thio-β-cyclodextrin (Fig. 5.3) leading to a dark precipitate.

The interaction of the thiolated cyclodextrin with the metal nanoparticles was justified by the disappearance of the S–H stretching peak at 2560 cm^{-1} in the FTIR spectra of the resulting materials. Transmission electron microscopy measurements showed spherical metal nanoparticles with an average diameter of 14.1 ± 2.2 and 15.6 ± 1.3 nm, respectively, for Pt and Pd particles. The catalytic activity of these nanoparticles was evaluated in the hydrogenation of allylamine under 1 atmosphere of hydrogen, at room temperature in D_2O solution in order to follow the reaction by ^1H NMR. Full conversions were obtained for both catalytic systems after 6 h of reaction with a selectivity of 100% toward propylamine. The same authors also optimized the synthesis of the palladium nanoparticles with an average particle size decrease (from 15.6 nm to 3.5 nm) by increasing the thiolated cyclodextrin amount, which is generally observed in the synthesis of solvent-dispersed nanoparticles. These new aqueous dispersed nanoparticles were tested in hydrogenation (Liu et al. 2001) and Suzuki coupling reactions (Strimbu et al. 2003) (Fig. 5.5). For the hydrogenation study, the authors tried to tune the catalytic activity of *per*-6-thio-β-cyclodextrin-stabilized Pd nanoparticles by ordering host-guest interactions between the receptors and chosen guests in the solution (Table 5.2).

The addition of molecules such as adamantanol or ferrocenyl ammonium derivatives, which strongly interact with cyclodextrins via host-guest inclusion complexes, led to a decrease of the catalytic activity of the palladium nanoparticles. The highest inhibitive effect was observed with a ferrocenyl ammonium derivative (Fig. 5.4).

For the Suzuki reaction (Fig. 5.5), the catalytic activities are similar whatever the functional group on the aromatic group. Higher activities were obtained in the case

of iodo derivatives in comparison to bromo derivatives (respectively, turnover frequency from 41 to 48 h^{-1} and from 7.8 to 13 h^{-1}) which is generally observed in C-C coupling reactions. Interestingly, the authors compared their values to poly(*N*-vinyl-2-pyrrolidone)-stabilized Pd nanoparticles (Li et al. 2002). These lower values can be explained by too strong interactions between the thiolated cyclodextrin with the palladium nanoparticles. In the case of iodoferrocene, substrate which can form an inclusion complex with the thiolated cyclodextrin, the catalytic activity of the corresponding palladium nanoparticles was improved in the presence of the cyclodextrin. It is important to note that the authors awarded the opposing solubility requirements which constitute the use of cyclodextrin-capped metal nanoparticles.

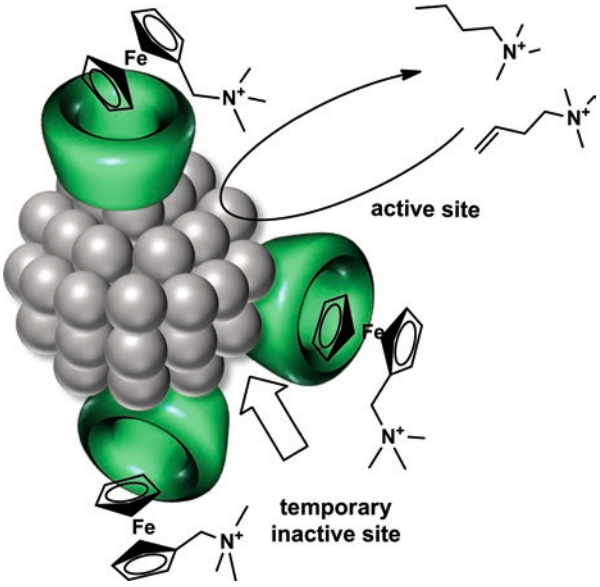


Fig. 5.4 Deactivation of active catalytic sites by binding ferrocenyl-based molecules to the cyclodextrin hosts. The addition of a cationic ferrocene derivative is leading to a decrease of the catalytic activity due to the creation of a Coulomb barrier when the positively charged substrate is approaching the surface of the Pd nanoparticle. (Adapted from Liu et al. 2001)

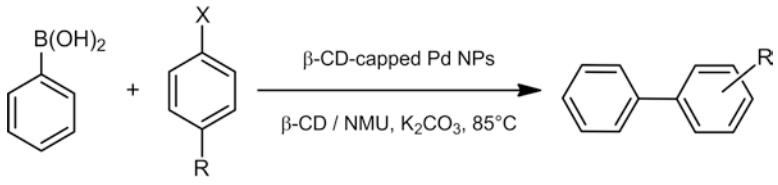
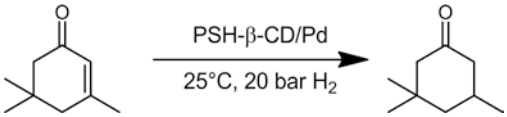


Fig. 5.5 Suzuki cross-coupling reaction using *per*-6-thio-β-cyclodextrin-capped Pd nanoparticles. Isolated yields ranging from 77% to 98% were obtained depending on the nature of the substituents R and X. (Adapted from Strimbu et al. 2003)

Table 5.3 Catalytic C=C double bond hydrogenation of isophorone in the presence of Pd nanoparticles[a] (Mhadgut et al. 2005)



Entry	Catalyst	Solvent	Yield (%)
1	*per*-thiolated-β-cyclodextrin/Pd	Ethanol	25
2	Pd black	Ethanol	100
3	*per*-thiolated-β-cyclodextrin/Pd	Water	100
4	Pd black	Water	2
5[b]	*per*-thiolated-β-cyclodextrin/Pd	Water	45

[a]Reaction conditions: 1 mmol isophorone, 10 mg catalyst, 5 mL of solvent, 20 bar H_2, 25 °C, 2 h
[b]Reaction conditions: standard reaction conditions with 1 mmol adamantane

Mhadgut et al. (2005) studied the hydrogenation of isophorone in the presence of *per*-thiolated-β-cyclodextrin (PSH-β-cyclodextrin)-stabilized palladium nanoparticles dispersed in water (Table 5.3).

A synergistic effect between *per*-thiolated-β-cyclodextrin (phase-transfer catalyst) and Pd nanoparticles on the overall catalytic process was observed using adamantane as a competitive substrate in the hydrogenation of isophorone (entry 3 vs. entry 5). In 2007, they extended the use of these nanocatalysts in the Sonogashira reaction without phosphine and copper (Xue et al. 2007). The synthesized nanoparticles showed high catalytic activity in aqueous medium with isolated yields ranging from 52% to 93% depending of the nature of the substrates. These good activities were explained by the good dispersion of Pd nanoparticles as well as the mass transfer ability of the cyclodextrins confirmed by the catalytic test realized in the presence of adamantane.

The development of combined catalysts based on thiolated cyclodextrin-modified gold nanoparticles with homogeneous complexes is rare. Li et al. (2008) synthesized gold nanoparticles stabilized by *per*-6-thiol-β-cyclodextrin and used them as a support for triethylenetetramine-adamantane-based copper complexes via supramolecular assembly (Fig. 5.6). These dual catalysts showed a typical Michaelis-Menten kinetics for the cleavage of 4, 4′-dinitrophenylcarbonate. The kinetic analyses indicated the synergistic action of bimetallic catalytic centers and three-dimensional structure of gold nanoparticles for the rate improvement of carbonate hydrolysis.

Contreras Carballada et al. (2012) developed a similar approach with platinum nanoparticles stabilized by *per*-thiolated cyclodextrin combined with a ruthenium or iridium complexes (Fig. 5.7). These catalytic systems were used for the reduction of proton for the production of hydrogen, and the authors have clearly shown that the combination of homogeneous complex with Pt nanoparticles had a beneficial effect on the catalytic activity. This high hydrogen production is also due to the good stabilization of the platinum colloids by the *per*-thiolated cyclodextrin.

More recently, aqueous Cu nanoparticles with an average size of 2 nm were synthesized using *mono*-6-thio-β-cyclodextrin as stabilizer and hydrazine as reducing agent (Zhong et al. 2016) (Fig. 5.8). The FTIR spectrum of the synthesized nanoparticles compared with that of *mono*-6-thio-β-cyclodextrin showed several shifts,

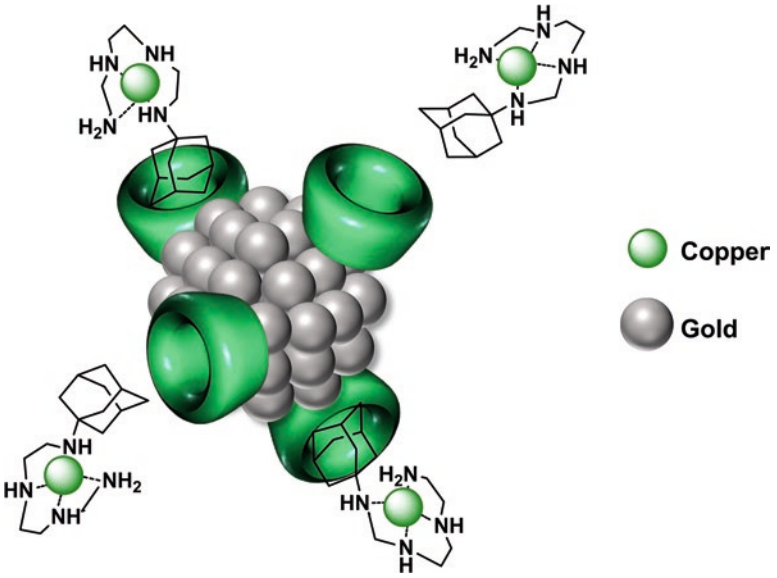


Fig. 5.6 Copper complexes adsorbed onto gold nanoparticle through adamantyl inclusion into cyclodextrin cavity. This cyclodextrin-modified gold nanozyme proved to be catalytically active in the carbonate hydrolysis. The kinetic analyses clearly showed that a synergistic effect was observed between the multi-metal catalytic centers and the Au nanoparticles leading to an increase of the activity. (Adapted from Li et al. 2008)

indicating the interactions between the thiolated cyclodextrin and the surface of the nanoparticles (3356 and 1415 cm^{-1} vs. 3375 and 1371 cm^{-1} for the hydroxyl bands). These copper nanoparticles were tested as enzyme mimic, and the cyclodextrin had a strong effect on the reaction rate. The peroxidase-like catalysis of Cu nanoclusters showed the Michaelis-Menten kinetics, which was similar to that of horseradish peroxidase. On the basis of its unique and attractive catalytic activity, a simple and selective colorimetric assay for H_2O_2 and glucose has been developed. Compared with the natural enzymes, Cu nanoclusters as a mimic peroxidase showed several advantages such as the ease of preparation, the low cost, as well as the high stability and activity under harsh conditions, which made it a promising candidate as enzyme mimics in biotechnology and clinical diagnosis applications.

Nanoparticles Stabilized by Alkylated Cyclodextrins

Alkylated cyclodextrins such as randomly methylated β-cyclodextrin (RaMe-β-cyclodextrin) and hydroxypropylated β-cyclodextrin (HP-β-cyclodextrin) (Fig. 5.9) have also been used for the stabilization of metal nanoparticles.

The synthesis of ruthenium nanoparticles in water using randomly methylated cyclodextrins as protective agents was reported for the first time by Monflier and Roucoux (Nowicki et al. 2006; Denicourt-Nowicki et al. 2007). These cyclodextrins had some advantages such as high solubility in water, low cost, non-toxicity, and

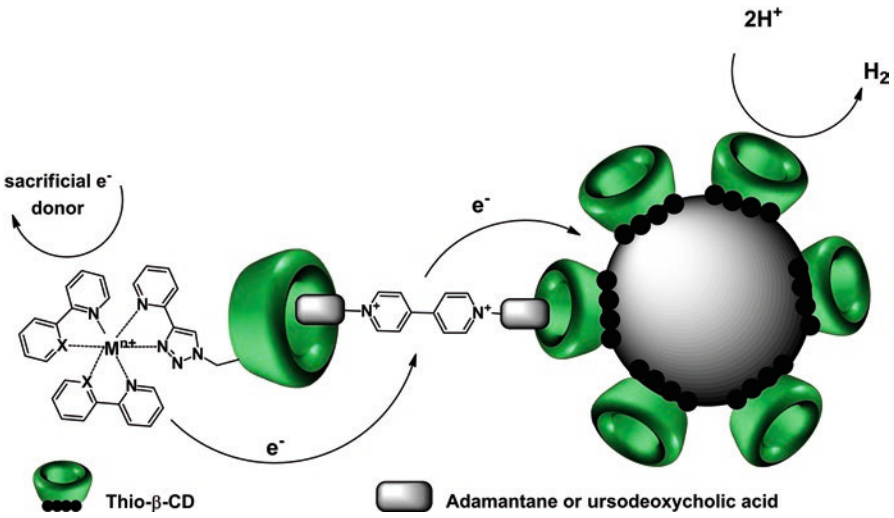


Fig. 5.7 Self-assembled three-component catalytic system for the photo-induced electron transfer. This catalytic system is including an iridium complex as the photosensitizer, methyl viologen as electron relay, and thiolated-β-cyclodextrin-coated platinum nanoparticles as the catalyst. During the production of hydrogen, the photosensitizer is consumed and has to be regenerated using EDTA as sacrificial donor. (Adapted from Contreras Carballada et al. 2012)

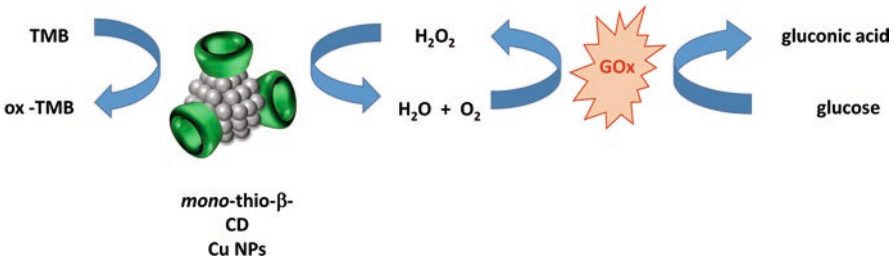
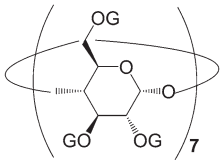


Fig. 5.8 Schematic illustration of β-cyclodextrin-protected Cu nanoclusters as peroxidase mimics for colorimetric detection of H_2O_2 and glucose. In this catalytic system, *mono*-6-thio-β-cyclodextrin is used as stabilizing agent of Cu nanoparticles but also modulator in order to increase the peroxidase-like catalytic rate. (Adapted from Zhong et al. 2016)

availability and had already proven to be efficient phase-transfer catalysts (Leclercq et al. 2007) (Table 5.4).

Ru nanoparticles were synthesized by chemical reduction of ruthenium trichloride with an excess of sodium borohydride in aqueous solution of randomly methylated cyclodextrins with different sizes (α, β, γ) and substitution degrees. The best compromise between the stability and activity was obtained with a cyclodextrin/Ru molar ratio of 10, which had been considered as the standard ratio.

According to the transmission electron microscopy, ruthenium nanoparticles were dispersed into non-ordered superstructures with an average particle size of



RaMe-β-CD **G = -CH_3 (60%) or -H (40%)**

HP-β-CD **G = -$CH_2CHOHCH_3$ (20%) or -H (80%)**

Fig. 5.9 Chemical structures of randomly methylated β-cyclodextrin (RaMe-β-CD) and hydroxypropylated β-cyclodextrin (HP-β-CD)

Table 5.4 Description of randomly methylated cyclodextrins

Abbreviation	*n*	Average number of OH groups substituted per glucopyranose unit
RaMe-α-cyclodextrin	6	1.8
RaMe-β-cyclodextrin (1.8)	7	1.8
RaMe-β-cyclodextrin (0.7)	7	0.7
RaMe-γ-cyclodextrin	8	1.8

Table 5.5 Hydrogenation of long-chain alkenes in presence of RaMe-cyclodextrin-stabilized Ru nanoparticles[a]

Entry	Substrate	Cyclodextrin (SD[b])	Turnover frequency (h^{-1})[c]
1	Decene	RaMe-α-cyclodextrin	17
2	Decene	RaMe-β-cyclodextrin (0.7)	18
3	Decene	RaMe-β-cyclodextrin (1.8)	17
4	Decene	RaMe-γ-cyclodextrin	22
5	Dodecene	RaMe-β-cyclodextrin (1.8)	15
6	Tetradecene	RaMe-β-cyclodextrin (1.8)	12

Adapted from Denicourt-Nowicki et al. (2007)

[a]Reaction conditions: catalyst (1.4×10^{-5} mol), cyclodextrin (1.4×10^{-4} mol), substrate (1.4×10^{-3} mol), hydrogen pressure (1 bar), temperature (20 °C), stirring rate (1500 rpm), 10 mL water

[b]*SD* substitution degree

[c]Turnover frequency defined as number of mol of substrate per mol of ruthenium per hour

2.5 nm. The catalytic activity of these ruthenium nanoparticles was evaluated in the hydrogenation of various unsaturated substrates such as long-chain alkenes under 1 bar of hydrogen at room temperature (Table 5.5).

These alkenes were totally hydrogenated to their saturated analogues with turnover frequencies (TOFs) ranging from 12 to 22 h^{-1}. These TOFs are modest in comparison to other aqueous nanocatalytic systems, but the experimental conditions are less harsh. It is worth noting that the catalytic activity decreased with increasing the chain length ($C_{10} > C_{12} > C_{14}$). This phenomenon could be attributed to a lower solubility of the resulting inclusion complex in water. These colloids were also evaluated in the hydrogenation of various arene derivatives (Table 5.6).

Table 5.6 Hydrogenation of *mono*-substituted aromatic compounds in presence of RaMe-cyclodextrin-stabilized Ru nanoparticles[a]

Entry	Substrate	Cyclodextrin (SD[b])	Product	Turnover frequency (h^{-1})
1	Benzene	RaMe-α-cyclodextrin	Benzene	–
2	Benzene	RaMe-β-cyclodextrin (0.7)	Cyclohexane	25
3	Benzene	RaMe-β-cyclodextrin (1.8)	Cyclohexane	25
4	Benzene	RaMe-γ-cyclodextrin	Cyclohexane	10
5	Styrene	RaMe-α-cyclodextrin	Ethylbenzene	10
6	Styrene	RaMe-β-cyclodextrin (0.7)	Ethylcyclohexane	9
7	Styrene	RaMe-β-cyclodextrin (1.8)	Ethylbenzene	9
8	Styrene	RaMe-γ-cyclodextrin	Ethylcyclohexane	4
9	Ethylbenzene	RaMe-α-cyclodextrin	Ethylbenzene	–
10	Ethylbenzene	RaMe-β-cyclodextrin (0.7)	Ethylcyclohexane	9
11	Ethylbenzene	RaMe-β-cyclodextrin (1.8)	Ethylbenzene	–
12	Ethylbenzene	RaMe-γ-cyclodextrin	Ethylcyclohexane	4
13	Toluene	RaMe-β-cyclodextrin (0.7)	Methylcyclohexane	17
14	Toluene	RaMe-β-cyclodextrin (1.8)	Methylcyclohexane	17
15	Allylbenzene	RaMe-β-cyclodextrin (0.7)	Propylcyclohexane	8
16	Allylbenzene	RaMe-β-cyclodextrin (1.8)	Propylbenzene	34
17	Propylbenzene	RaMe-β-cyclodextrin (0.7)	Propylcyclohexane	9
18	Propylbenzene	RaMe-β-cyclodextrin (1.8)	Propylbenzene	–

Adapted from Denicourt-Nowicki et al. (2007)

[a]Reaction conditions: Ru (1.5×10^{-5} mol), cyclodextrin (1.5×10^{-4} mol), substrate (1.5×10^{-3} mol), hydrogen pressure (1 bar), temperature (20 °C), stirring rate (1500 rpm), 10 mL water, 24 h

[b]*SD* substitution degree

Very interestingly, the hydrogenation of aromatic rings depended both on the type of methylated cyclodextrin (α, β, γ) and on the substitution degree. Indeed, when RaMe-α-cyclodextrin was used as the stabilizer, the aromatic rings were not hydrogenated. In contrast, their total hydrogenation was observed with RaMe-γ-cyclodextrin-stabilized Ru nanoparticles. These results can be explained by the cavity size of the different cyclodextrins which leads to more or less important interactions with the substrates. In the case of the RaMe-β-cyclodextrin, the selectivities were related to the substitution degree. These catalytic results can be correlated to the deeper hydrophobic host cavity of the RaMe-β-cyclodextrin with the highest degree of substitution which can wrap more efficiently the aromatic rings of the substrate avoiding their hydrogenation. The turnover frequency values are modest compared to other catalytic systems, but the reactions were carried out at room temperature under atmospheric hydrogen pressure.

More recently, the synthesis of Ru nanoparticles stabilized in the aqueous phase by RaMe-β-cyclodextrin was performed following two new optimized strategies (Guerrero et al. 2013) (Fig. 5.10).

The comparison had been made on the size and the dispersion of the resulting particles on the one hand and also on the stability, the catalytic activity, and the selectivity in the hydrogenation of various hydrophobic substrates on the other hand. The one-pot approach consisted in the reduction of ruthenium trichloride salt by hydrogen in the presence of RaMe-β-cyclodextrin in water. In contrast, the cascade method was carried out in two successive steps. A Ru hydrosol was obtained by controlled $NaBH_4$ reduction with dropwise addition, to avoid particle agglomeration. Then, RaMe-β-cyclodextrin was added in the abovementioned hydrosol. Whatever the strategy, stable colloidal suspensions were obtained, confirming that RaMe-β-cyclodextrin was an efficient stabilizer for Ru nanoparticles. As evidenced by transmission electron microscopy measurements, both approaches led to well-dispersed nanoparticles. The one-pot strategy allowed stabilizing particles with an average diameter of 1.0 ± 0.2 nm, while the cascade method led to a mean particle

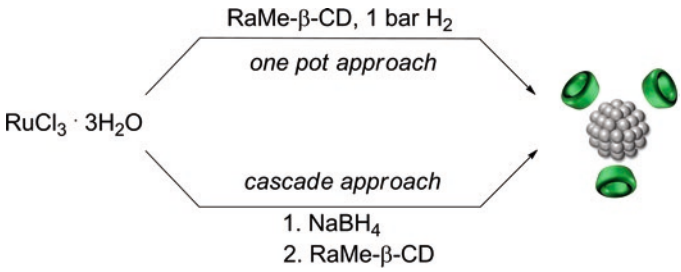


Fig. 5.10 Two methodologies for Ru nanoparticles stabilized by RaMe-β-cyclodextrin in water. The one-pot approach consists into the reduction of Ru metal precursor reduced under atmospheric hydrogen pressure in the presence of RaMe-β-cyclodextrin. The cascade approach consists into the chemical reduction of the Ru metal precursor by sodium borohydride in a first step followed by the addition of an aqueous solution of RaMe-β-cyclodextrin in a second step. (Adapted from Guerrero et al. 2013)

size of 1.4 ± 0.2 nm. To have a deeper insight into the interactions between the randomly methylated cyclodextrins and metal surface in both methods, diffusion ordered spectroscopy experiments had been carried out in D_2O solution. Whatever the synthesis strategy, similar values of diffusion coefficients and hydrodynamic radius were obtained. Contrary to what is usually observed with strongly interacting ligands, such as phosphines, the ^1H NMR experiments exhibited no significant difference in the chemical shifts of the cyclodextrins, indicating weak interactions between RaMe-β-cyclodextrin and the surface of the metal nanoparticles. Consequently, the authors gave a dispersive agent behavior to the cyclodextrin instead of a stabilizing effect of a classical ligand. The catalytic activity of the Ru nanoparticles prepared by each strategy was evaluated in the hydrogenation of several model substrates, including 3-methylanisole, methyl-2-acetamidoacrylate, and ethyl pyruvate, under 20 bar of hydrogen. For ethyl pyruvate and methyl-2-acetamidoacrylate, the catalytic activities related to the nanoparticles prepared by the cascade method were slightly higher. The possibility of recycling these catalytic systems was investigated on the hydrogenation of ethyl pyruvate, and whatever the strategy, it showed that four successive runs were achieved without any significant loss of stability and activity.

More recently, these methodologies (one-pot and cascade approaches) were extended to prepare ruthenium nanoparticles stabilized by randomly methylated β-cyclodextrins grafted with chiral amino acid moieties, such as L-leucine and L-alanine (Chau et al. 2013) (Fig. 5.11).

The influence of the ligand and synthesis methodology on the size, dispersion, and surface properties was studied. These Ru nanoparticles stabilized by amino acid-grafted RaMe-β-cyclodextrin were evaluated in the hydrogenation of prochiral model substrates such as acetophenone, ethyl pyruvate, methyl-2-acetamidoacrylate, and 3-methylanisole under 20 bar of H_2 at room temperature. The stability of the

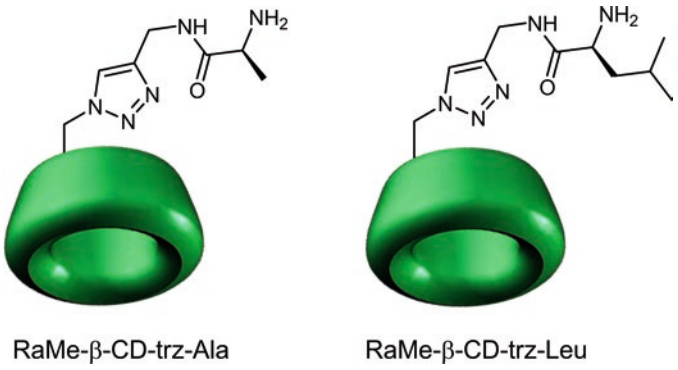


Fig. 5.11 Structure of grafted RaMe-β-cyclodextrin with chiral amino acid moieties as stabilizers and mass transfer agents for catalytically active ruthenium nanoparticles dispersed in water for asymmetric hydrogenation of acetophenone, ethyl pyruvate, methyl-2-acetamidoacrylate, and 3-methylanisole under 20 bar of H_2 at room temperature in aqueous phase. (Adapted from Chau et al. 2013)

aqueous colloidal suspensions under reaction conditions was established, indicating that RaMe-β-cyclodextrin bearing optically active moieties acted as an efficient protective agent around the nanoparticle surface. In addition, the catalytic data showed that, whatever the strategy, Ru nanoparticles stabilized by RaMe-β-cyclodextrin-trz-Leu were more active than those capped by RaMe-β-cyclodextrin-trz-Ala (respectively, 100% vs. 54% of ethyl-2-hydroxypropanoate). However, no significant enantiomeric excess was measured probably due to the weak or deficient interaction between the chirally modified cyclodextrin and the nanoparticle surface.

The first work of Malta on the synthesis of palladium nanoparticles stabilized by hydroxypropyl-α-cyclodextrin for catalytic applications was reported in 2009 (Senra et al. 2009). Interestingly, the authors reported that hydroxypropyl-α-cyclodextrin could play several roles such as capping agent like the randomly methylated cyclodextrins or thiolated cyclodextrins but also as reducing agent. A black precipitate was obtained after the addition of hydroxypropyl-α-cyclodextrin in an aqueous $PdCl_2$ solution. The nanoparticles were characterized by several physicochemical techniques that revealed the formation of spherical particles in the size range of 2–7 nm. Further analyses by FTIR spectroscopy and ^{1}H NMR did not show covalent bonds between cyclodextrins and palladium nanoparticles, suggesting that hydroxypropyl-α-cyclodextrin was only physically adsorbed on the metal surface. These observations were presumably due to hydrophobic interactions enabling the limitation of the mutual coalescence of nanoclusters. The catalytic activity of these colloids was evaluated in several Pd-catalyzed C-C coupling reactions, such as Suzuki, Heck, and Sonogashira reactions, in water with good yields, and Pd nanoparticles stabilized by hydroxypropyl-α-cyclodextrin were reused during four consecutive runs without any significant loss of activity. More recently, the influence of the size of the hydroxypropyl cyclodextrin (α, β, γ) and the Pd-to-cyclodextrin ratio was studied to observe eventual changes in the particle size of the resulting particles and to exploit the surface/cavity effects in the Suzuki-Miyaura reaction (Senra et al. 2016). The differences in catalytic activities between the Pd nanoparticles stabilized by different cyclodextrins were explained by the formation of inclusion complex, and the best activities were obtained with hydroxypropyl-β-cyclodextrin which had the strongest complexation capacity.

The use of hydroxypropyl cyclodextrin as capping agent for the synthesis of silver nanoparticles was reported for the first time in 2013 (Devi and Mandal 2013). A series of hydroxypropyl-cyclodextrin-capped Ag nanoparticles was synthesized by the reduction of silver nitrate in alkaline aqueous medium at 60 °C. The resulting nanoparticles were tested in the reduction of *p*-nitrophenol using sodium borohydride. The catalytic activity of hydroxypropyl-cyclodextrin-stabilized Ag nanoparticles was much higher than other cyclodextrin-capped nanoparticles. These catalytic results were correlated with the size and morphology of the particles. Whereas native α-cyclodextrin and β-cyclodextrin seemed to form aggregated nanostructures, hydroxypropyl cyclodextrin (α and β) formed a chain-like assembly.

A novel hybrid nanocomposite prepared from hydroxypropyl-β-cyclodextrin and alginate was used as stabilizer to synthesize Ag nanoparticles (Nguyen et al. 2018). Aqueous extract of *J. subtriplinerve* leaves was used as reducing agent in order to

avoid too toxic compounds such as $NaBH_4$ or hydrazine. The silver nanoparticles were tested in the catalytic degradation of methyl orange, rhodamine, and 4-nitrophenol. 4-nitrophenol was completely converted into 4-aminophenol within 25 min when rhodamine and methyl orange were completely converted within 22 min.

Bhoi et al. (2016) prepared spherical monodispersed silver and gold nanoparticles dispersed in alkaline medium by chemical reduction of the corresponding metallic precursor using cyclodextrins such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, and hydroxypropyl-β-cyclodextrin as both stabilizing and reducing agent (Fig. 5.12).

The corresponding core-shell (Ag@Au and Au@Ag) were also synthesized via the polyol process, and the particle size of the corresponding core-shell nanoparticles was determined by static light scattering measurements (Table 5.7). All these colloidal suspensions showed radical scavenging behavior from the quenching of 2, 2′-diphenyl-1-picrylhydrazyl light adsorption. A kinetic study had been particularly done in the case of Ag nanoparticles, and in this case, a pseudo first-order rate constant of 1.79×10^{-2} min^{-1} was obtained, but a deviation of the linearity was observed after 80 min of reaction time which could be explained by the decrease of Ag nanoparticle concentration.

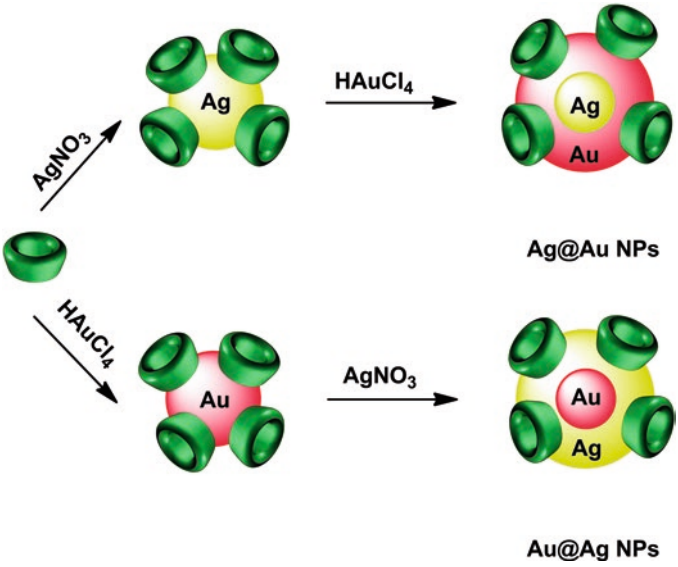


Fig. 5.12 Schematic representation for the formation of mono- and bimetallic nanoparticles by chemical reduction in alkaline medium of the corresponding metal precursors ($AgNO_3$ and $HAuCl_4$) by cyclodextrins. The chosen cyclodextrins (α, β, γ, and hydroxypropyl-β) played a dual role of stabilizer and reducing agent, and the resulting metal nanoparticles showed high catalytic activity for the radical scavenging reaction of the stable free radical 2, 2′-diphenyl-1-picrylhydrazyl. (Adapted from Bhoi et al. 2016)

Table 5.7 Particle size of nanoparticles (in nm) with different cyclodextrin measured by static light scattering

Cyclodextrin	Ag NPs[a]	Au NPs[a]	Ag@Au NPs[a]	Au@Ag NPs[a]
α-Cyclodextrin	13 ± 1	12 ± 2	14 ± 3	15 ± 1
β-Cyclodextrin	12 ± 0.5	11 ± 2	15 ± 2	16 ± 2
γ-Cyclodextrin	10 ± 1	11 ± 1	14 ± 1	16 ± 2
Hydroxypropyl-β-cyclodextrin	9 ± 1	10 ± 2	14 ± 2	15 ± 1

Adapted from Bhoi et al. (2016)
[a]*NPs* nanoparticles

5.2.3 Nanoparticles Stabilized by Polymers in the Presence of Cyclodextrin

Nanoparticles Stabilized by a Physical Mixture of Polymer and Cyclodextrin

Another way to stabilize aqueous dispersed metal nanoparticles is the possibility of using water-soluble polymer in the presence of cyclodextrins. The use of cyclodextrins as additives in the synthesis of poly(*N*-vinyl-2-pyrrolidone)-stabilized metal nanoparticles was studied (Herbois et al. 2012). For this purpose, Ru nanoparticles were synthesized in the presence of poly(*N*-vinyl-2-pyrrolidone)/cyclodextrin mixture with a controlled ratio, and the transmission electron microscopy images of the corresponding particles were carefully compared. For the standard Ru nanoparticles, i.e., Ru nanoparticles stabilized by poly(*N*-vinyl-2-pyrrolidone) alone, the particles were entrapped in string-like assemblies by the effect of poly(*N*-vinyl-2-pyrrolidone) chains. The morphology did not seem to be altered by the presence of cyclodextrin. However, a slight decrease in the mean particle size was noticed when cyclodextrins were added to the poly(*N*-vinyl-2-pyrrolidone) (2.5 and 2.3 nm, respectively, for β-cyclodextrin and RaMe-β-cyclodextrin against 3.0 nm without cyclodextrin). The well-known aggregation of cyclodextrins in aqueous solutions, which can give rise to large agglomerates in the 200–300 nm range, was deeply disturbed by the presence of poly(*N*-vinyl-2-pyrrolidone). According to the dynamic light scattering experiments, it was observed that these cyclodextrin aggregates had the tendency to significantly disappear in the presence of poly(*N*-vinyl-2-pyrrolidone) in favor of small-sized assemblies of only two or three cyclodextrin units as evidenced by the presence of a population centered on a mean diameter about 2–3 nm. The disaggregated cyclodextrins were assumed to interact easier with the soluble Ru(III) precursor than poly(*N*-vinyl-2-pyrrolidone), thus increasing the efficiency in controlling the growth of the Ru nanoparticles after the reduction step (Fig. 5.13).

To confirm this hypothesis, an additional experiment was realized, in which cyclodextrins were added to a preformed poly(*N*-vinyl-2-pyrrolidone)-stabilized Ru colloidal suspension and kept under stirring during 24 supplementary hours. Notably, the size range of the particles was the same to that of the control

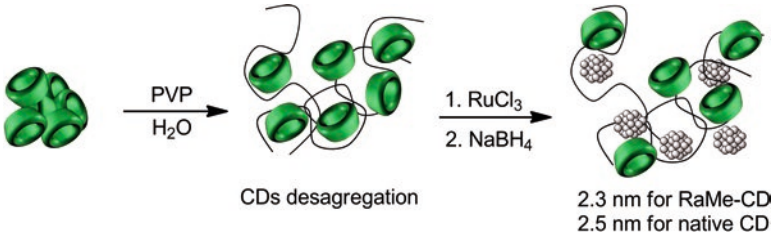


Fig. 5.13 Schematic representation of a proposal for the Ru nanoparticle synthesis in the presence of a mixture of poly(*N*-vinyl-2-pyrrolidone) and cyclodextrin. Each part of the mixture has a specific role: the cyclodextrin can be seen as a metal particle size controller, whereas poly(*N*-vinyl-2-pyrrolidone) ensures the long-term stability of the Ru particles but also allows breaking cyclodextrin aggregates to get monomeric species to improve ruthenium ion and cyclodextrin interactions before the reduction step. The size of the synthesized metal nanoparticles depends of the nature of the cyclodextrins (2.3 nm for randomly methylated cyclodextrins against 2.5 nm for the native ones). (Adapted from Herbois et al. 2012)

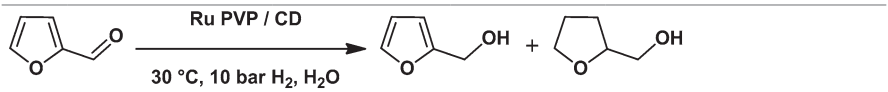
preparation without cyclodextrins. It is important to mention that the presence of poly(*N*-vinyl-2-pyrrolidone) was crucial in order to ensure long-term stability of the Ru nanoparticles, knowing that a ratio of poly(*N*-vinyl-2-pyrrolidone) to Ru higher than 8 was absolutely required.

The influence of the quantity of cyclodextrin on the catalytic activity of the resulting Ru nanoparticles was studied, performing for the hydrogenation of furfural, a biosourced substrate, under mild experimental conditions (30 °C, 10 bar of H_2) (Table 5.8). Whatever the poly(*N*-vinyl-2-pyrrolidone)/cyclodextrin ratio, the Ru nanoparticles were visually stable, and no sedimentation was observed at the end of the catalytic test. According to the results gathered in Table 5.8, only a small amount of cyclodextrin was required to get an activity improvement. The obtained results were rationalized in terms of size and morphology control of the Ru nanoparticles. In line with what is generally observed in nanocatalysis, the decrease in the particle size resulted in the increase of the number of available surface active sites and, consequently, increased the catalytic efficiency.

In another study, Kuklin et al. (2016) investigated the role of free and supported cyclodextrin on the selective hydrogenation of phenol to cyclohexanone in aqueous media and a *n*-hexyltriethylammonium bromide ionic liquid ($N_{6222}Br$) using Rh nanoparticles stabilized by polyacrylic acid. Noteworthy, the catalytic activity and selectivity of the Rh nanoparticles depended on the presence of cyclodextrin. It was attributed to the fact that both substrate and the cyclohexenol, which was formed as an intermediate, could form inclusion complexes with cyclodextrin (Fig. 5.14).

Upon formation of inclusion complex with the intermediate, it would be desorbed from Rh nanoparticles. High stability of this complex made the repeated adsorption of cyclohexenol unlikely (Fig. 5.14). The presence of ionic liquid was also crucial as it could form inclusion complexes with cyclodextrin and fix it in the surface layer and facilitate the desorption of cyclohexenol from the surface of Rh nanoparticles. Other factors which affect the reaction were the nature of the cyclodextrin and the

Table 5.8 Hydrogenation of furfural with Ru nanoparticles[a] (Herbois et al. 2012)



Entry	Cyclodextrin	PVP[b]/ cyclodextrin	Conversion (%)	Furfuryl alcohol selectivity (%)
	–	8: 0	30	94
1	α-Cyclodextrin	8: 2	30	95
2	γ-Cyclodextrin	8: 2	38	94
3	RaMe-α-cyclodextrin	8: 2	34	97
4	RaMe-γ-cyclodextrin	8: 2	61	90
5	RaMe-β-cyclodextrin	8: 2	53	90
6	RaMe-β-cyclodextrin	8: 0.5	37	97
7	RaMe-β-cyclodextrin	8: 1	52	93
8	RaMe-β-cyclodextrin	8: 4	52	90

[a]Reaction conditions: Ru (3.8×10^{-5} mol), poly(*N*-vinyl-2-pyrrolidone)-K30 (3.0×10^{-4} mol), substrate/Ru (mol/mol) = 50, H_2O (12 mL), H_2 (10 bar), stirring rate (750 rpm), 30 °C, 1.5 h
[b]*PVP* poly(*N*-vinyl-2-pyrrolidone)

reaction media. Using optimum reaction condition, 80 °C, P(H_2) = 10–40 bars, the product was obtained with the yield of 100% in 1 h.

The influence of cyclodextrin derivatives X-cyclodextrins (X = OH, NH_2 or SH) on the aerobic oxidative kinetic resolution of racemic secondary alcohols using poly(*N*-vinyl-2-pyrrolidone)-stabilized Au nanoparticles was studied (Hirano et al. 2019). 1.8 ± 0.6 nm gold nanoparticles stabilized by poly(*N*-vinyl-2-pyrrolidone) were obtained after the chemical reduction of $HAuCl_4$ by $NaBH_4$. The effect of the coordinating ability of different cyclodextrins on the catalytic performance of the Au nanoparticles was determined by the comparison of the s factor in the case of the oxidation of a racemic mixture of 1-(2-naphtyl)ethanol. Native β-cyclodextrin (X = OH) brought no modification on the selectivity of the reaction. The thiolated-β-cyclodextrin improved the selectivity but with a dramatic activity decrease. Amino-β-cyclodextrin (X = NH_2) gave the best results both in activity and selectivity. The authors suggested, by comparing the size of the NH_2-cyclodextrin and by using a competitive guest, that the enantioselective oxidation could be explained by an eventual inclusion of the alcohol into the chiral cavity of the cyclodextrin.

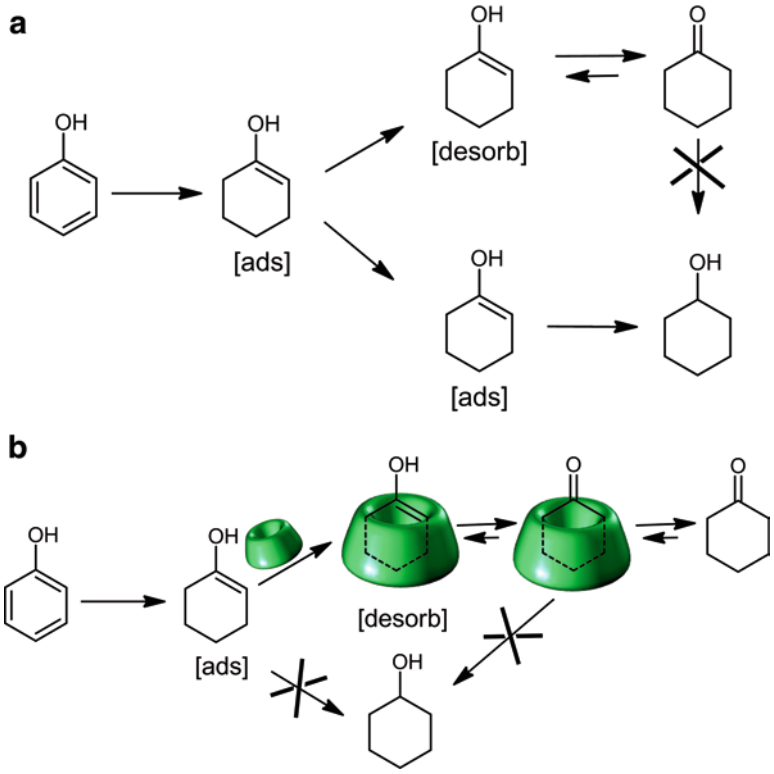


Fig. 5.14 Proposed mechanism for the phenol hydrogenation without cyclodextrin (**a**) and with the assistance of cyclodextrin (**b**). Phenol was firstly reduced to cyclohexenol and then to cyclohexanol. Just a small amount of cyclohexenol could desorb from the catalyst and could equilibrate itself to cyclohexanone which did not adsorb on catalyst and could not be reduced to cyclohexanol (path a). In the presence of cyclodextrin (path b), all the cyclohexenol amount was desorbed from the catalyst by making an inclusion complex and avoided the hydrogenation of this molecule toward cyclohexanol. (Adapted from Kuklin et al. 2016)

Nanoparticles Stabilized by Cyclodextrin-Grafted Polymer

The first example of metal nanoparticles stabilized by a cyclodextrin-based polymer was referenced by Shiraishi's group (Shiraishi et al. 2007; Taylor et al. 2010). Palladium nanoparticles were prepared by refluxing an alcohol/water solution of palladium acetate in the presence of the cross-linked cyclodextrin-based polymer. The catalytic activity was evaluated in the hydrogenation of unsaturated carboxylic acids. The cavity of the cyclodextrin played a crucial role by forming inclusion complex with the substrate. Pt nanoparticles were synthesized by the photoreduction of hexachloroplatinic acid by a UV irradiation in the presence of a cyclodextrin-based polymer. According to transmission electron micrographs, Pt colloids with average particle size of 1–6 nm range were observed with an increase of the average particle size with the cyclodextrin size. The Pt colloids were tested in the superoxide

anion quenching reaction and showed higher activity than polyacrylic acid-stabilized Pt nanoparticles. These results could be explained by too strong interactions between the metal nanoparticles and the polyacrylic acid.

Meo et al. (2012) developed a novel heterogeneous catalysts based on stabilization of Ag nanoparticles as a core with poly-(6-*N*,*N*-dimethyl-propylenediamino)-(6-deoxy)-β-cyclodextrin (AmCD) as a capping agent which surrounded the nanoparticles like a shell. The synthetic procedure involved reaction of $[Ag(NH_3)_2]^+$ complex in the presence of a proper amount of AmCD with an excess of formaldehyde at 40 °C for 90 min. It was believed that the shell could act as a steric and electrostatic barrier to avoid the aggregation. The obtained nanoparticles were then used as catalysts for the reduction of nitroarenes in the presence of $NaBH_4$. The authors studied the kinetics of the reaction and the effect of the *para*-substituent on the substrate and the trends of the induction period observed at the beginning of the reaction. It was established that the presence of electron-donating groups on the nitroarene could influence the reaction course, implying that the nanoparticle surface acted as an electrophile toward the nitro group. Nevertheless, the presence of negatively charged or bulky groups on the nitroarene had a slightly detrimental effect, which could emerge from the difficulty for the substrate to approach the nanoparticle surface. The AmCD-covered catalyst surface seemed less active, because of the intrinsic stability of the substrate-AmCD inclusion complex.

In line with the stabilization of Ru nanoparticles by functionalized cyclodextrins, Noël et al. (2012) studied the synthesis of metal nanoparticles in the presence of cyclodextrin-based polymer leading to greater complexity of the protective agent structure. Rhodium trichloride was reduced by sodium borohydride in the presence of poly(mono(β-cyclodextrin-2-yl)-maleate-*alt*-maleate-*alt*-methylvinylether) (Fig. 5.15). It could be noticed that a control experiment was performed using the same polymer backbone but without any presence of grafted cyclodextrin. The two colloidal suspensions were characterized by transmission

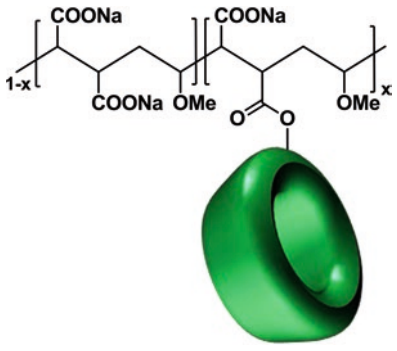


Fig. 5.15 Structure of the two polymers used: poly(mono-(β-cyclodextrin- 2-yl)-maleate-alt-maleate-*alt*-methylvinylether) (x = 0.04) and poly(maleate-*alt*-methylvinylether) (x = 0) for the synthesis of aqueous rhodium nanoparticles. The cyclodextrin-functionalized polymer afforded to get well-dispersed metal nanoparticles and better catalytic activities due to this good dispersion but also to the intrinsic mass transfer property of the cyclodextrin. (Adapted from Noël et al. 2012)

electron microscopy, and the corresponding images clearly showed two different types of nanoparticle organization.

Thus, for the Rh nanoparticles stabilized by the polymer containing cyclodextrins, a mono and well-dispersed size distribution was clearly obtained, whereas those prepared from the cyclodextrin-free polycarboxylate (control polymer) was organized into non-ordered superstructures, in which the nanoparticles were entrapped in string-like assemblies with a bigger average particle size. The catalytic properties were evaluated in the hydrogenation of various alkene and arene derivatives. For instance, in the case of 1-tetradecene, the turnover frequency was equal to 2000 h^{-1} and 420 h^{-1} for the hydrogenation reaction catalyzed by Rh nanoparticles stabilized by polyCOONa-β-cyclodextrin and polyCOONa, respectively. These results were correlated with both the average particle size and the dispersion of the rhodium nanoparticles stabilized by the above stabilizers. In order to have a better insight into the beneficial effect of the structure of the polymer, an additional experiment has been performed using a physical mixture, i.e., adding the same amount of β-cyclodextrin in the polycarboxylate solution. The turnover frequency was very close to the value of the polycarboxylate alone, but the colloidal suspension after the catalytic test was unstable. All these experiments undoubtedly supported the view that the β-cyclodextrin covalently linked to the polymer chain induced a significant effect in terms of activity and reusability. The recyclability was studied by reusing the aqueous catalytic layer during five successive hydrogenation runs of 1-tetradecene with no loss of stability and activity. The rhodium leaching in the organic phase of each catalytic test was very low (<0.2 ppm), while the transmission electron microscopy experiments confirmed the robustness of the colloidal suspensions, with no change in terms of particle size and morphology.

A deeper study on the stability and the catalytic activity of the rhodium nanoparticles was performed by modifying the pH value of the solution before the reduction step and by using different ratios of grafted cyclodextrin (Noël et al. 2014). According to transmission electron microscopy experiments, homogeneous dispersions of the metal nanoparticles were observed for the lowest initial pH value (5.1), and, on the contrary, unstable colloids were observed for highest pH value (7.7). It seemed that there was no link between the mean particle size and the amount of grafted cyclodextrin onto the polymer backbone. The catalytic activities were evaluated in the hydrogenation of methyl linoleate under 10 bar of hydrogen at 30 °C. Several Rh nanoparticles called controls were also synthesized (Rh nanoparticles stabilized by a β-cyclodextrin and polycarboxylate mixture with a ratio corresponding to the grafted polycarboxylates). According to the catalytic results, the grafted polycarboxylates gave higher activities, and, in terms of recovery, the colloids with the physical mixture showed stable emulsions which led to non-recoverable catalytic systems.

Herbois et al. (2015) reported another work which consisted into the encapsulation of fine water-dispersible Ru nanoparticles (with size of ~1.8 nm) into 3D β-cyclodextrin-based polymer (poly(CTR-β-cyclodextrin) derived from controlled polycondensation of β-cyclodextrin with citric acid). The synthetic procedure included reduction of Ru precursor, ruthenium nitrosyl nitrate, by $NaBH_4$ in the

presence of as-prepared poly(CTR-β-cyclodextrin). It was confirmed that carboxylate moieties in the backbone of the polymer could render the surface of the globules negatively charged and consequently stabilize them due to electrostatic repulsion. Moreover, these functionalities played an important role in the interaction with Ru^{3+}, affecting the nucleation of metal clusters in the initial stages of reduction. Finally, the catalytic utility of the hybrid system as an efficient catalyst for aqueous phase hydrogenation of biomass-derived 2-furaldehyde and 3-(2-furyl)acrolein at 1 MPa pressure and 303 K was confirmed. Notably, the catalyst was reusable for five reaction runs, and the transmission electron microscopy analyses demonstrated that the reuse of the catalyst did not induce any significant change in the morphology of the catalyst. It was suggested that the high catalytic activity and stability came from the ability of poly(CTR-β-cyclodextrin) to provide a good balance of stabilizing properties with the metal surface, both in terms of steric and electrostatic interactions without hindering the catalytic activity. Additionally, each globule could be considered as a confined space, microreactor, for promoting the hydrogenation process.

Another cyclodextrin-based polymer was used to stabilize ruthenium nanoparticles in aqueous medium. This polymer was synthesized by reacting β-cyclodextrin with epichlorohydrin and glycidyltrimethylammonium chloride in alkaline medium (Noël et al. 2017). The resulting Ru nanoparticles were tested in the hydrogenation of different petro and biosourced substrates and showed a catalytic activity close to the Ru/poly(CTR-β-cyclodextrin) nanoparticles. Interestingly, these nanoparticles could be used in acidic medium (pH 3) for the hydrogenation of unsaturated carboxylic acids, especially linoleic and oleic acid. The catalytic system showed a strong robustness because no loss of activity and stability had been observed by transmission electron microscopy experiments after ten consecutive runs in the tetradecene hydrogenation.

In an interesting study, Au/Ag bimetallic core-shell nanoparticles with different core diameters were synthesized by Haldar et al. (2014) through a β-cyclodextrin-assisted synthetic procedure. The authors investigated the effect of core size (10–100 nm) on the catalytic properties of the nanoparticles for the reduction of 4-nitrophenol in the presence of sodium borohydride. It was found that the catalytic activity was influenced by the size of the core and differed from 41.8% to 96.5%. Noteworthy, the core-shell system with core size of 100 nm was 12 times more efficient than Au nanoparticles of the same size, indicating the effect of the core-shell structure on the catalytic activity.

Vasconcelos et al. (2016) reported the synthesis of polyurethane nanosponges through reaction of hexamethylenediisocyanate and β-cyclodextrin and used the prepared nanosponges as a template for the synthesis of Au_n quantum clusters, by the core etching of glutathione-capped Au nanoparticles. The authors investigated the effect of the Au: nanosponge ratio on the nanocluster formation step. It was established that the longer reaction time, the smaller clusters were formed. Initially, the clusters formed in the cavities of cyclodextrin (Au_7 and Au_{15}), while for longer reaction time, the cluster concentration in cavities increased. Further increase in the reaction time led to the formation of larger clusters that could not be hosted in the

cavities of cyclodextrin but may interact with other functional groups such as carbonyls and nitrogenated groups. The catalytic activity of Au_n clusters for reduction of 4-nitrophenol in the presence of $NaBH_4$ was also studied. It was found that Langmuir-Hinshelwood kinetic model fitted the reaction and the reaction proceeded with no induction time.

Subnanometer size noble metal colloids were synthesized using a cyclodextrin polymer-based network (from azido-β-cyclodextrin and diethynylbenzene using click chemistry) as stabilizing agent. Transmission electron microscopy images showed ultra-small Pd nanoparticles which were well-dispersed in the polymeric matrix. The catalytic activity of these colloids was evaluated in the reduction of 4-nitrophenol and in a C–C coupling reaction. In the case of the 4-nitrophenol reduction, the authors emphasize the role of the cavity of the cyclodextrin. The cyclodextrin, whose secondary face is free, formed inclusion complex and allowed the guest molecule to be close to the metal surface.

5.2.4 Nanoparticles Stabilized by Cyclodextrin-Based Inclusion Complex

The combination of cyclodextrins with other stabilizing agents, i.e., alkyl ammonium salts, phosphanes, and dendrimers, was also reported for the synthesis of metallic nanoparticles dispersed into the aqueous phase. Another strategy consisted into the combination of cyclodextrins with polymers likely to form supramolecular complexes leading to the development of a new reaction medium named hydrogel. Whatever the strategy, the catalytic activity of these colloidal suspensions was also evaluated for different kinds of reactions.

Nanoparticles Stabilized by Quaternary Ammonium-Based Salts/ Cyclodextrin Inclusion Complexes

Ionic surfactants such as alkyl ammonium salts are known to be good candidates to stabilize active metallic nanoparticles. Moreover, this family of surfactants is well known to strongly interact with β-cyclodextrin derivatives. Randomly methylated cyclodextrins combined with ammonium salts bearing a lipophilic chain was used for the synthesis of aqueous Ru nanoparticles (Hubert et al. 2009) (Fig. 5.16).

NMR spectroscopic studies were performed to prove the formation of an inclusion complex between RaMe-β-cyclodextrin and the chloride salt of *N, N*-dimethyl, *N*-hexadecyl, *N*-(2-hydroxyethyl)ammonium (HEA16Cl) in water. The continuous variation technique, named Job's method, and transverse rotating-frame Overhauser effect spectroscopy experiments emphasized the existence of such a complex. The resulting nanoparticles were characterized by transmission electron microscopy and showed a homogeneous distribution with an average size of about 4 nm. The

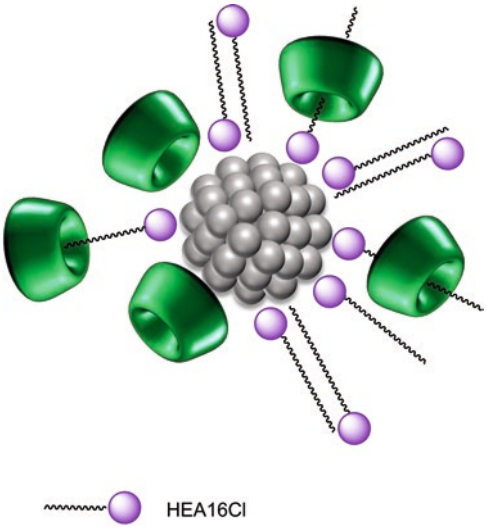


Fig. 5.16 Aqueous ruthenium nanoparticle synthesis in the presence of RaMe-β-cyclodextrin/HEA16Cl. The ruthenium nanoparticles were stabilized by a mixture of free cyclodextrins, alkyl ammoniums, and inclusion complexes. It was suggested that RaMe-β-cyclodextrin affected the adsorption of the surfactant on the metal surface and prevented the double layer formation which is observed for Ru nanoparticles stabilized by HEA16Cl alone. The cyclodextrin could act as a spacer between the alkyl chains and reduced the intermolecular interactions, thus allowing a better mobility and diffusion of the substrate at the vicinity of the metal surface. (Adapted from Hubert et al. 2009)

particles were organized into superstructures similarly to those previously observed with the Ru nanoparticles stabilized by free RaMe-β-cyclodextrin. The catalytic activity of the Ru colloidal suspension stabilized by RaMe-β-cyclodextrin:HEA16Cl mixture with a ratio of 1:1 was evaluated in the hydrogenation of several functionalized aromatic compounds (i.e., anisole, toluene, and styrene), and their performances were compared to the Ru nanoparticles prepared using only the ammonium salt surfactant (Table 5.9).

Whatever the substrate, the RaMe-β-cyclodextrin/HEA16Cl-stabilized Ru nanoparticle was the most active catalytic system, indicating a beneficial effect of the inclusion complex as stabilizer. In the case of anisole, the catalytic activity of the above nanoparticles was three times higher than the nanoparticles stabilized by the ammonium surfactant. The same tendency was observed for toluene and styrene hydrogenation. The difference of the activity was related to a different organization of the stabilizer around the metal surface. Indeed, whereas the Ru nanoparticles stabilized by HEA16Cl were protected by a surfactant double layer, as already described by other groups, it was suggested that RaMe-β-cyclodextrin affected the adsorption of the surfactant on the metal surface and prevented the double layer formation. The cyclodextrin could act as a spacer between the alkyl chains and

Table 5.9 Hydrogenation of aromatic compounds with RaMe-β-cyclodextrin/HEA16Cl-stabilized Ru nanoparticles[a]

Entry	Substrate	Stabilizer	Turnover frequency (h^{-1})
1	Anisole	HEA16Cl	3.4
2	Anisole	RaMe-β-cyclodextrin/HEA16Cl	10.2
3	Toluene	HEA16Cl	2.2
4	Toluene	RaMe-β-cyclodextrin/HEA16Cl	10.1
5	Styrene	HEA16Cl	14.3
6	Styrene	RaMe-β-cyclodextrin/HEA16Cl	26.7

Adapted from Hubert et al. (2009)

[a]Reaction conditions: Ru (3.8×10^{-5} mol), HEA16Cl (7.6×10^{-5} mol) or HEA16Cl (3.8×10^{-5} mol) + RaMe-β-cyclodextrin (3.8×10^{-5} mol), substrate (3.8×10^{-3} mol), hydrogen pressure (1 bar), temperature (20 °C), stirring (1500 min^{-1}), 10 mL water

reduced the intermolecular interactions, thus allowing a better mobility and diffusion of the substrate at the vicinity of the metal surface.

More recently, Thanh Chau et al. (2016) developed a novel protective agent for the formation of very fine Rh nanoparticles. To prepare the inclusion complexes, the authors used randomly methylated β-cyclodextrin or its leucine-grafted analogue (RaMeCDLeu) and an optically active ammonium salt (QCD16Br = (1S,2R,4S,5R)-(+)-*N*-hexadecyl-5-vinyl-2-quinuclidinium-methanol bromide) or *N, N*-dimethyl-*N*-hexadecyl-*N*-(2-hydroxyethyl)-ammonium chloride (HEA16Cl) as surfactants. Typically, catalysts were synthesized by reduction of Rh salts by $NaBH_4$ in the presence of cyclodextrin and surfactant. Notably, to reach stable nanoparticles, the cyclodextrin/surfactant ratio must be optimized. By transmission electron microscopy analyses, it was found that the dispersion of the spherical Rh nanoparticles was very good and their size varied from 1.2 nm to 1.5 nm depending on the type of cyclodextrin and surfactant. It was also proven that these systems could act as efficient and stable catalysts for promoting biphasic hydrogenation of various substrates including ketones and olefins such as methyl-2-acetamidoacrylate, ethyl pyruvate, or acetophenone with high catalytic activities and interesting specific activity under mild experimental conditions.

In another study, gold nanoparticles were synthesized using α-cyclodextrin as stabilizing agent in aqueous medium (Peng et al. 2014). The addition of a *trans*-azobenzene-based surfactant led to the phase transfer of the gold nanoparticles. By UV irradiation, the azo-benzene compound isomerized itself giving the *cis*-azo-benzene and consequently leading to the inverse phase transfer in water (Fig. 5.17). These gold nanoparticles were tested in the 4-nitrophenol reduction using $NaBH_4$. The recovery and recycling can be achieved by a visible irradiation which gave again *trans* form which bring the nanoparticles in organic phase.

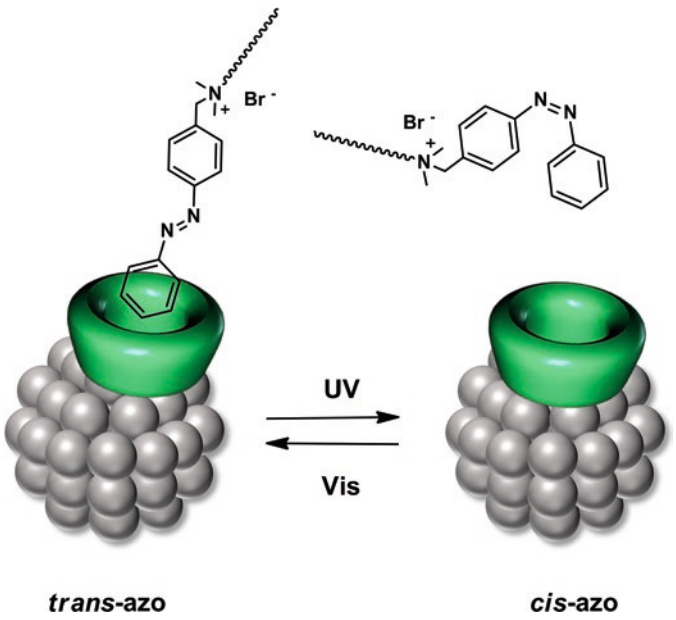


Fig. 5.17 Photoreversible inclusion of azo-ligand onto α-cyclodextrin-coated Au nanoparticles. The gold nanoparticles are dispersed in organic phase. The photo isomerization of *trans*-azo-benzene to *cis*-azo-benzene by UV light irradiation prevents the inclusion of this latter into the cyclodextrin cavity, and a phase transfer of the gold nanoparticles is observed from organic to aqueous phase. The catalytic nitrophenol reduction can also be performed in aqueous phase. The catalyst recovery can be effective by the reverse isomerization reaction. (Adapted from Peng et al. 2014)

Nanoparticles Stabilized by Phosphanes/Cyclodextrin Inclusion Complexes

Cyclodextrins have been used as mass transfer promoters in biphasic aqueous phase catalysis processes using water-soluble organometallic complexes with sulfonated phosphines as ligands since a long time. Spectroscopic studies demonstrated that, depending on the nature and the position of the substituents on the aromatic ring, sulfonated phosphines could interact with RaMe-β-cyclodextrin by forming inclusion complexes and tune the catalytic performances of the metal centers. The idea was to combine the advantages of a sulfonated diphosphine as water-soluble stabilizer of nanoparticles with a cyclodextrin for its shuttle and supramolecular control effects in biphasic aqueous phase catalysis (Monflier et al. 1999). Thus, ruthenium nanoparticles were synthesized by hydrogen reduction of the organometallic ruthenium complex [Ru(cod)(cot)] and stabilized either with 1,4-bis[(di-m-sulfonatophenyl)phosphine]butane (dppbs) or its combination with RaMe-β-cyclodextrin in tetrahydrofuran (Guerrero et al. 2013, 2014) (Fig. 5.18). The so-obtained Ru nanoparticles were isolated by precipitation and finally easily re-dispersed in water.

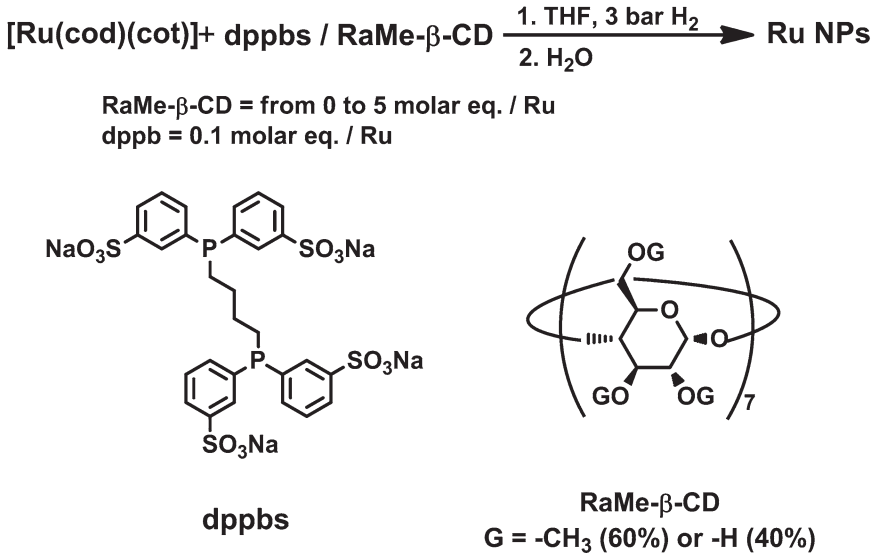


Fig. 5.18 Synthesis of dppbs: RaMe-β-cyclodextrin Ru nanoparticle system. (Adapted from Guerrero et al. 2013)

The synthesized nanoparticles (diphosphine alone and phosphine-cyclodextrin mixture) were fully characterized by several techniques (transmission electron microscopy, high-resolution transmission electron microscopy, wide-angle X-ray scattering, dynamic light scattering, liquid and solid NMR spectroscopy). Whatever the stabilizer (without or with cyclodextrin as co-additive), transmission electron microscopy images showed small and well-dispersed particles with an average diameter between 1.2 nm and 1.5 nm. The nanoparticle environment in solution was studied by dynamic light scattering. The results showed that the hydrodynamic radius depended on the amount of cyclodextrin present during the nanoparticle synthesis which was a strong indication that the cyclodextrins surround the metal nanoparticle surface. Resonance shifts in ^{1}H and ^{31}P NMR in D_2O confirmed the presence of a weak interaction between the dppbs and RaMe-β-cyclodextrin (aromatic protons and protons which are in the cyclodextrin cavity). However, the addition of RaMe-β-cyclodextrin on a preformed dppbs-stabilized Ru nanoparticle solution did not change the NMR spectra, thus evidencing that the dppbs/cyclodextrin complex was formed only if the diphosphine and cyclodextrin were both present at the beginning of the synthesis.

In order to investigate the influence of the cyclodextrin on the catalytic performances of the diphosphine-stabilized nanoparticles, the hydrogenation of model compounds such as styrene, acetophenone, and *m*-methylanisole was carried out. Based on turnover frequency values, whatever the substrate, an activity improvement was observed with increasing the initial amount of cyclodextrin. More interestingly, in the case of *m*-methylanisole, it was observed that the quantity of cyclodextrin dramatically influenced the stereoselectivity toward the preferential

formation of the *cis* isomer (51% vs. 100% for dppbs and dppbs/5.0 cyclodextrin, respectively).

Nanoparticles Stabilized by Dendrimers

Astruc et al. (2012) exploited mono-, bis-, and tris(4-ferrocenyl-1,2,3-triazolylmethyl)arene-β-cyclodextrin adducts, i.e., 4-methoxy-1-(4-ferrocenyl-1,2,3-triazolylmethyl) benzene-β-cyclodextrin, *p*-bis(4-ferrocenyl-1,2,3-triazolylmethyl)-benzene-β-cyclodextrin, and 1,3,5-tris(4-ferrocenyl-1,2,3-triazolylmethyl) benzene-β-cyclodextrin, for stabilizing Pd nanoparticles (Fig. 5.19). The reasons behind this design were the facts that ferrocene could form an inclusion complex with cyclodextrin and led to water solubilization of the catalytic system and the role of triazolyl group as ligand for stabilization of the Pd nanoparticles. The transmission electron microscopy analyses showed that fine Pd nanoparticles (5–6 nm) as well as large aggregates could be formed. The authors studied the catalytic activities of the catalysts for C–C coupling reactions including Miyaura-Suzuki and Heck reactions that were, respectively, performed at ambient temperature and 80 °C. The comparison of the catalytic performances of three catalysts established that the bolaamphiphile-like bis- and tris-cyclodextrin systems led to much better pre-catalysts, indicating the efficiency of encapsulation of a hydrophobic catalytic system with two or three peripheral water-solubilizing cyclodextrin caps. The authors studied the effect of mol ratio of Pd/cyclodextrin. Interestingly, in the case of Miyaura-Suzuki reaction, the yield improved by increasing this value from 1 to 2. In the Heck reaction, however, the effect of this value was more pronounced. The authors attributed the different effect of Pd/cyclodextrin ratio for Heck and Miyaura-Suzuki reaction to the different reaction temperatures (higher temperature could render the ferrocenyl encapsulation reversible and allowed free cyclodextrins to inhibit the reaction through hosting Pd nanoparticles) and mechanism.

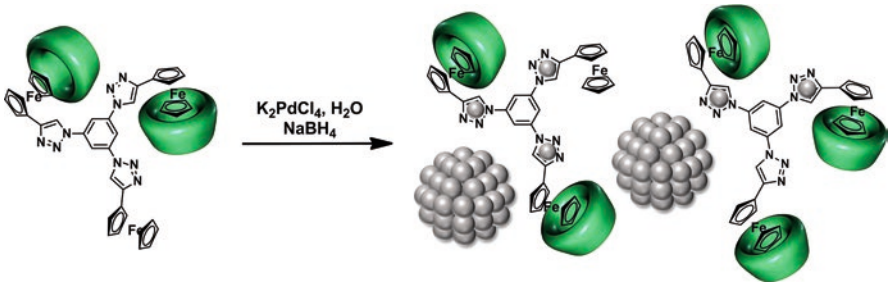


Fig. 5.19 Preparation of Pd nanoparticle materials. Here, the tris(4-ferrocenyl-1,2,3-triazolylmethyl) benzene in combination with β-cyclodextrin was used as stabilizer of Pd nanoparticles in aqueous medium. The Pd(II) reduction using $NaBH_4$ gave Pd nanoparticles but also mono Pd(0) atoms which are stabilized by the triazol groups. (Adapted from Liang et al. 2012)

Taking advantage of CuI-catalyzed azide-alkyne cycloaddition, also known as click reaction, Wang et al. (2016a) developed a series of ligands containing bifunctional 1,2,3-triazole for stabilization of water-solubilized gold nanoparticles of 3.0–11.2 nm. In one designed ligand, β-cyclodextrin and biocompatible polyethylene glycol were substituted on the triazole ring. The authors believed that the synthesized gold nanoparticles could have potential applications for encapsulation, catalysis, and sensing and confirmed the catalytic activity of the gold nanoparticles for reduction of 4-nitrophenol in the presence of $NaBH_4$. Noteworthy the catalytic activity of the Au nanoparticles stabilized by triazoles was superior ($k = 7.0 \times 10^{-3}\ s^{-1}$, when 0.5% Au nanoparticles is used) to that of the thiolate Au nanoparticles. This observation was attributed to the easier removal of the triazole ligands by the substrate from the fine gold nanoparticles.

Nanoparticles Stabilized by Cyclodextrin-Based Supramolecular Hydrogels

Moreover, more and more sophisticated catalytic systems were developed in order to furnish active and selective catalysts playing on the confinement of the metal nanoparticles with the substrate. Among the reported systems, hydrogel applications have become popular in a wide range of applications such as medicine, materials, and catalysis. The embedment of metal nanoparticles into the supramolecular-structured hydrogels based on host-guest interactions in the presence of cyclodextrins was investigated.

The first example had been developed by the group of Zhang in 2009. Silver nanoparticles were embedded in a supramolecular hydrogel made from Pluronic® F-68, an amphiphilic block copolymer of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) and α-cyclodextrin (Ma et al. 2009). These colloidal suspensions were finally used for the catalytic reduction of methylene blue in the presence of sodium borohydride. The colloidal suspension was synthesized within two successive steps. The first step consisted into the reduction of a silver nitrate in an aqueous solution of Pluronic® F-68 which played the role of reducing agent leading to the formation of Ag nanoparticles. The second step evolved the addition of an α-cyclodextrin solution to the pre-synthesized colloidal suspension conducting to the formation of a gel due to the supramolecular self-assembly between α-cyclodextrin and the block copolymer. These colloidal suspensions in the gel state were fully characterized by viscosimetry measurements, wide-angle X-ray diffraction, and scanning electron microscopy. The authors clearly showed that gelation time decreased with the increase of block copolymer concentration and that the supramolecular hybrid hydrogels demonstrated to have predominantly a solid-like behavior. The beneficial effect of α-cyclodextrin was evidenced in the catalytic reduction of methylene blue. Indeed, when Ag nanoparticles were used in an aqueous solution of Pluronic® F-68, the relative absorbance of methylene blue decreased very slowly, and when Ag nanoparticles were used in a hybrid hydrogel, the

catalytic activity widely increased demonstrated by a sharp decrease of the relative absorbance of methylene blue.

A similar strategy had been reported by Wang et al. (2010) where colloidal silver hydrosols were synthesized using Pluronic® F-68 and then incorporated in situ into an α-cyclodextrin-assisted supramolecular hydrogel. An absorption peak around 430 nm was observed for the synthesized silver nanoparticles that were attributed to the characteristic surface plasmon resonance effect, showing the reduction and stabilization performances of the Pluronic®F-68. According to transmission electron microscopy images, the silver nanoparticles were deposited on the surface of Pluronic® aggregates. Pluronic® F-68 can also interact with α-cyclodextrin, and it was shown that the higher the Pluronic® concentration, the better the gelation process. The effects of the silver nanoparticles on the gelation process and the hydrogel strength were investigated through several physicochemical analyses. The catalytic activity of the resulting hydrogel-embedded silver nanoparticles was evaluated for the reduction of methylene blue using sodium borohydride. In the presence of the hybrid hydrogel, methylene blue was consumed (80% converted in 10 min) which was not the case in the absence of it. Léger et al. (2012) developed a thermoresponsive hydrogel for the synthesis of Ru nanoparticles and their activation for hydrogenation reactions. The hydrogel template properties have been taken to access size-controlled Ru nanoparticles. More precisely, once metal nanoparticles have been embedded into the supramolecular matrix, the system was heated above the sol-gel transition temperature to give a sol phase where the catalytic reaction took place. First, the polypseudorotaxane template was prepared from the mixture of the *N*-alkylpyridinium amphiphilic [py-*N*-$(CH_2)_{12}OC_6H_3$-3, 5-$(OMe)_2$]$^+$ (Br^-) and α-cyclodextrin. The self-assembly of these molecules yielded a thermoresponsive hydrogel with a sol-gel transition temperature of 42 °C. The synthesis of Ru nanoparticles was realized by classical chemical reduction of ruthenium metallic salt solubilized in hydrogel at the sol state (50 °C) by an excess of sodium borohydride. Transmission electron microscopy analysis clearly showed homogeneous dispersion of spherical Ru nanoparticles with an average diameter of 1.6 nm within the hydrogel network, which is smaller than that observed using surfactants or ionic liquids as Ru nanoparticle stabilizers. This result emphasized the effective control exerted by the hydrogel internal network structure over the Ru nanoparticle growth. The catalytic hydrogenation of various substrates, ranging from hydrophobic long-chain to hydrophilic olefins such as 2-methyl-3-buten-2-ol, was evaluated. Under H_2 pressure ranging from 10 to 40 bar at 50 °C, turnover frequency comprised between 4 and 350 h^{-1} was obtained. At the end of the catalytic test, after cooling to ambient temperature, the hydrogel spontaneously returned to the gel state, and consequently the products could be easily recovered (Fig. 5.20). The recycling of the nanoparticles entrapped in the hydrogel had been successfully performed using 1-decene.

The same group had also reported a similar strategy involving the synthesis of gold nanoparticles embedded into a thermoresponsive hydrogel made from the combination of Tetronic® 90R4 and α-cyclodextrin and their use in the catalytic hydrogenation of alkenes, alkynes, and aldehydes (Chevry et al. 2019). In this case, the first step consisted into the reduction of $AuCl_3$ metal precursor in a Tetronic®

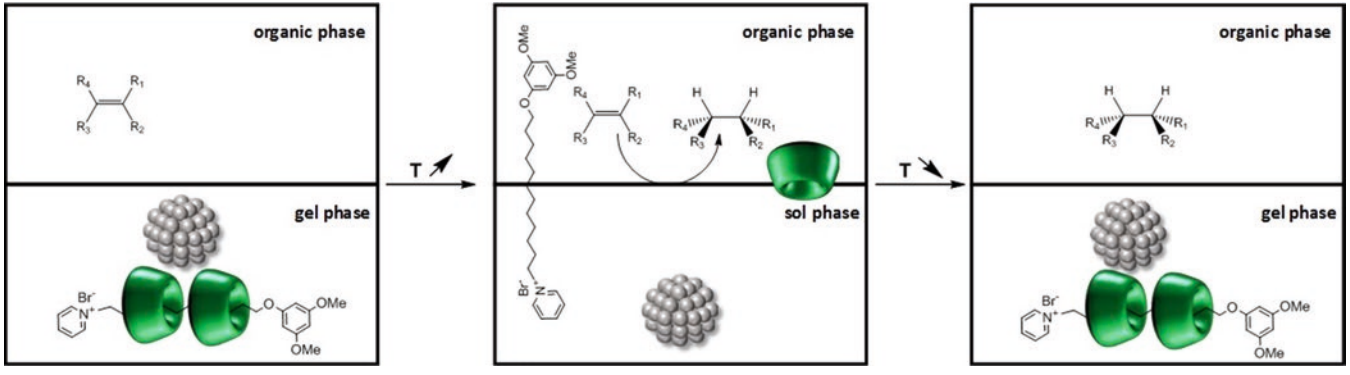


Fig. 5.20 Thermoregulated Ru nanoparticle-catalyzed hydrogenation of alkenes. The ruthenium nanoparticles were embedded in the rotaxane-based gel phase. When temperature has increased, the gel-sol transition occurred, and cyclodextrins could play the role of mass transfer and "bring" alkenes into the Ru nanoparticle aqueous phase for their conversion into the corresponding alkanes. The catalytic system was recovered by the return of the temperature beyond the transition phase temperature. (Adapted from Léger et al. 2012)

90R4 solution at 40 °C leading to the formation of Au nanoparticles where poloxamine played the role of the reducing agent. After heating of this solution, α-cyclodextrin was added to the colloidal suspension, and after cooling down to room temperature, Au nanoparticles were incorporated into α-cyclodextrin/Tetronic® 90R4 hydrogel. The addition of α-cyclodextrin was very important because it allowed the formation of the supramolecular hydrogel coming from the sliding of α-cyclodextrin along the copolymer chain. Moreover, by repeating heating/cooling cycles, the authors clearly showed that the presence of α-cyclodextrin improved the long-term stability of the Au nanoparticles by additional steric stabilization effects. Colloidal suspensions were synthesized considering Au concentration ranging from 0.1 mM to 2 mM. No significant influence of the Au concentration was noticed on the final mean diameters of Au nanoparticles always centered around 7 nm. The catalytic activity of the colloidal suspension prepared with Au concentration of 0.5 mM was particularly studied in the hydrogenation of terminal and internal alkenes and also alkynes under mild experimental conditions. Conversions were ranging from 5% to 54% depending on the nature of the substrate. The recyclability study was also realized in the styrene hydrogenation, and Au nanoparticles could be reused during five successive runs without any loss of activity, showing as well the robustness of this kind of catalytic system.

Ag nanoparticles were synthesized into thermosensitive poly(NIPAAm-co-AMPS) hydrogels by chemical reduction of silver nitrate with sodium borohydride (Wang et al. 2016c). Small-sized Ag nanoparticles were homogeneously dispersed into this hydrogel with a mean diameter centered on 3.5 nm. In this study, the silver colloidal suspensions were used in the catalytic reduction of 4-nitrophenol, and α-cyclodextrin was added before the catalytic test. The catalytic activity of Ag nanoparticles was better in the presence of α-cyclodextrin, and it was explained by the formation of an inclusion complex between the cyclodextrin and the substrate and a decrease of the activation energy.

Jia et al. (2015) reported a simple method for the immobilization of catalytically active gold nanoparticles in acrylate α-cyclodextrin-modified poly(*N*-vinylcaprolactam) microgels. According to transmission electron microscopy images, monodispersed gold nanoparticles with an average diameter of 5–6 nm were obtained without addition of any reducing agent. The reduction of the gold ions can be explained by the presence of the hydroxyl groups of poly(*N*-vinylcaprolactam) microgels. The homogeneous distribution of the particles could be attributed to the acrylate α-cyclodextrin through the capping efficiency on the surface of the gold particles due to the carboxylate-gold interactions. The immobilization of the gold particles did not influence the swelling-deswelling properties of the microgels. The poly(*N*-vinylcaprolactam)-α-cyclodextrin gold composite particles showed efficient catalytic activity for the reduction of aromatic nitro compounds. The host-guest capacity of cyclodextrin was proven through the reduction of *p*-nitrophenol, and the catalytic activity was much higher than in the case of dimethyl-*p*-nitrophenol.

In the same way, a thermosensitive catalytic system based on silver nanoparticles immobilized into a network of poly(NIPAAm-*co*-AMPS) hydrogels was studied

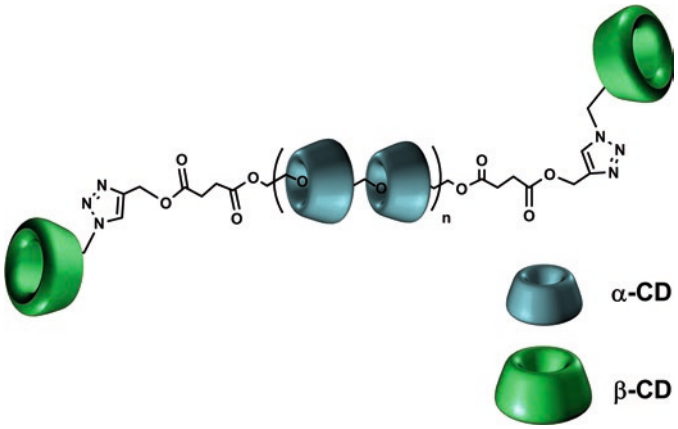


Fig. 5.21 Polyrotaxane synthesized by Gao and co-workers for the deposition of platinum nanoparticles in order to get nanowires. The catalytic activity is evaluated in the 4-nitrophenol reduction using sodium borohydride. (Adapted from Wu et al. 2010)

(Wang et al. 2016c). The catalytic performances could be adjusted by choosing the adequate reaction temperature. The post-addition of α-cyclodextrin improved the catalytic activity by forming a complex with the 4-nitrophenol.

The complexation of guest molecules in the cyclodextrin cavity had also been studied with polymers. For example, Li et al. (1994) had put forward the formation of inclusion complexes called poly*pseudo*rotaxanes between poly(ethyleneglycol) and α-cyclodextrin in the 1990s. In order to immobilize cyclodextrin along the polymer chain, a large number of polymers with stoppers, called polyrotaxanes, had been reported. Thus, Wu et al. (2010) succeeded in stabilizing platinum nanoparticles in a water/ethylene glycol mixture, in the presence of a polyrotaxane in which α-cyclodextrin was threated onto poly(ethyleneglycol) chains capped with triazole-β-cyclodextrins (Fig. 5.21). The Pt nanoparticles were tested in the reduction of 4-nitrophenol by sodium borohydride. The authors assume that the high catalytic activity came from the high density and high surface area of the nanoparticles that had been adsorbed on the surface of the template.

5.3 Nanoparticles Immobilized on a Support in the Presence of Cyclodextrin

Another strategy consists into the immobilization of metal nanoparticles on a support in order to improve the stability of these nanoheterogeneous catalysts. Moreover, the interaction between the support and nanoparticles could also influence the catalytic activity and the selectivity of the reaction. Considering the state of the art for nanoparticles immobilized on a support in the presence of cyclodextrin, two main strategies have been reported; whatever the nature of the support, it

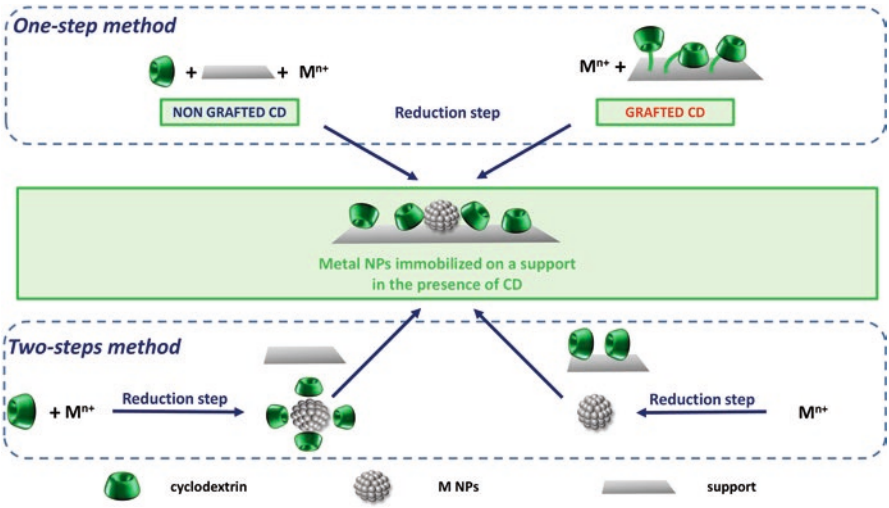


Fig. 5.22 General scheme involving the different ways of synthesis of nanoparticles immobilized on a support in the presence of cyclodextrin. The one-step method involves multi-task properties of the cyclodextrin: stabilizing agent, active phase dispersing agent, mass transfer agent, reducing agent in some cases. The two-step method involves the immobilization of preformed metal particles where cyclodextrins have different roles: stabilizing agent for the synthesis of the metal particles or preformed metal nanoparticle dispersing agent immobilized onto/into the support

means inorganic supports or organic supports. It could be done regarding two different ways of preparation: (1) the one-pot method where the synthesis of nanoparticles is realized in the presence of the support and (2) the two-step method where the synthesis of nanoparticles is realized before the addition of the support. Whatever the strategy which will be considered, the multiple roles of the cyclodextrin described in the first part of this chapter related to the synthesis of the nanocatalysts and also to the catalytic processes will be further discussed in this part. All of the strategies mentioned before will be detailed above in this second part (Fig. 5.22).

5.3.1 Nanoparticles Immobilized on a Support Considering One-Step Method

Nanoparticles Immobilized on a Support in the Presence of Non-grafted Cyclodextrin

A cooperation of cyclodextrin with heterogeneous metal nanocatalyst was reported by Tang et al. (2015). They synthesized silver nanoparticles supported on cellulose nanocrystals and studied the reduction of 4-nitrophenol using $NaBH_4$ as reducing agent. The initial rate was improved in the presence of native β-cyclodextrin, which

can be explained by host-guest interactions between 4-nitrophenol and β-cyclodextrin.

In an attractive research, Li et al. (2014) benefited from the hybrid of β-cyclodextrin and graphene nanosheets as a support for the synthesis of Pt nanoparticles. This hybrid material was prepared through a simple wet chemical method which included the formation of graphene nanosheets-cyclodextrin material via reduction of graphene in the presence of cyclodextrin and hydrazine followed by the addition of $PtCl_6^{2-}$ and its subsequent reduction by sodium borohydride or formic acid leading to a heterogeneous catalyst with a hydrangea-like morphology. The authors believed that combination of cyclodextrin and graphene nanosheets could furnish a support with high surface area, conductivity, and recognition property. Noteworthy, the content of cyclodextrin was estimated to be 32 wt% which made the hybrid system water soluble. The hybrid system was successfully used as an electrocatalyst for the oxidation of MeOH with the catalytic activity and CO tolerance superior to those of conventional catalysts such as Pt/graphene nanosheets and Pt/Vulcan X72R. The higher catalytic activity, which made this electrocatalyst very promising for the use in direct methanol fuel cell, was attributed to the well dispersion of Pt nanoparticles and their specific morphologies.

Patil et al. (2018) prepared ruthenium nanoparticles supported on cyclodextrin-modified graphene oxide for the selective aerobic oxidation of alcohols in aqueous medium but also in stilbene derivatives' hydrogenation. $NaBH_4$ reduced both ruthenium precursor and graphene oxide in the presence of RaMe-β-cyclodextrin in a one-pot strategy. RaMe-β-cyclodextrin not only acted as a capping agent for Ru nanoparticles but also intercalated between the layers of graphene oxide and functionalized the surface of reduced graphene oxide by H bonding. The amount of RaMe-β-cyclodextrin in rGO@Ru-RaMe-β-cyclodextrin was found to be 42.33 wt% by thermogravimetric analysis when the amount of Ru, determined by ICP-AES analysis, was about 2.5%. The best catalytic results related to the piperonyl alcohol oxidation were obtained with rGO@Ru-RaMe-β-cyclodextrin in the presence of K_2CO_3. After this optimization step, the catalyst was tested for a wide range of benzylic alcohols with various substituents such as Cl, NO_2, NH_2, or OMe. Yields ranging from 88% to 94% were obtained with selectivities higher than 99%. This heterogeneous catalyst was also active in the reduction of several alkenes such as stilbene and its derivatives. The recyclability of rGO@Ru-RaMe-β-cyclodextrin was studied, and a slight decrease of the catalytic activity was observed after five runs which could came from the leaching of Ru, confirmed by ICP-AES, and also the leaching of RaMe-β-cyclodextrin, confirmed by thermogravimetric analysis.

The group of Montazer studied the influence of the amount of native β-cyclodextrin in the synthesis of a nanocomposite. Ag/TiO_2 was prepared by addition of a solution containing cyclodextrin and silver to a TiO_2 dispersion under irradiation (Attarchi et al. 2013). They studied the influence of the amount of β-cyclodextrin, and according to dynamic light scattering experiments, the average hydrodynamic diameter in water increased with the amount of cyclodextrin which was still present in the composite. The methylene blue photodegradation was studied with these composite nanomaterials, and the reactivity was faster with Ag/TiO_2/β-cyclodextrin (65% of

degraded methylene) than pure TiO_2 (39%) or Ag/TiO_2 (52%). These results can be explained by the strong affinity of cyclodextrin toward TiO_2 surface via the outer hydroxyl groups of the cyclodextrin making a bridge between the titanium oxide and methylene blue. Moreover, cyclodextrin could act as a host molecule. However, the use of excess cyclodextrin had a detrimental role in the degradation rate.

Another study reported the synthesis of Ag-β-cyclodextrin/TiO_2 loaded onto activated carbon by using microwave-assisted procedure and its use for the photocatalytic degradation of naphthalene (Chen et al. 2018). In comparison to some control catalysts, the best catalytic activities were obtained with Ag-β-cyclodextrin/TiO_2/AC catalyst due to host-guest interactions between β-cyclodextrin and naphthalene leading to an increase of the interactions between the substrate and TiO_2 surface.

A nanocomposite based on iron oxide nanoparticles and β-cyclodextrin (Fe_3O_4@β-cyclodextrin) was prepared via a one-pot strategy by mixing iron salts and β-cyclodextrin in sulfuric acid aqueous solution (Wang et al. 2016b). According to transmission electron microscopy images, Fe_3O_4 and Fe_3O_4@β-cyclodextrin particles were spherical with an average diameter between 10 nm and 20 nm. X-ray diffraction patterns indicated a spinel structure with no crystal structure modification in the presence of β-cyclodextrin, but the intensity of the peaks decreased. This composite was tested in the 4-chorophenol degradation using hydrogen peroxide. According to the kinetic following, the composite was 2.3 times more active than the iron oxide alone. This catalytic activity enhancement can be explained by host-guest interactions between β-cyclodextrin and the 4-chorophenol.

Hydroxypropyl-β-cyclodextrin was used both as fullerene [60] dispersing agent in water and stabilizing agent for the synthesis of supported Pd nanoparticles for electrocatalytic applications (Zhang et al. 2015). Two controls, i.e., Pd nanoparticles synthesized without hydroxypropyl-β-cyclodextrin and one without fullerene, were considered to show the beneficial effect of the C_{60}-hydroxypropyl-β-cyclodextrin combination. According to transmission electron microscopy experiments, a uniform size distribution and a good adsorption of the Pd nanoparticles on fullerene were observed on the composite material. Aggregates were obtained without cyclodextrin, and a less uniform distribution was obtained without fullerene. According to X-ray diffraction patterns, neither hydroxypropyl-β-cyclodextrin nor C_{60} had influence on the nanoparticle crystallinity, but the adsorption of hydroxypropyl-β-cyclodextrin on the fullerene surface was observed by elemental mapping measurement. According to thermogravimetric analysis, the cyclodextrin content was around 5%. The catalytic activity of Pd nanoparticles supported on the composite material was evaluated in the ethanol electrooxidation. Pd supported on hydroxypropyl-β-cyclodextrin/C_{60} showed better electrocatalytic activity which was explained by a smaller size and a better distribution of the nanoparticles onto the support.

The synthesis of carbon-based cobalt oxide (Co_3O_4/C) and gold nanoparticles immobilized on Co_3O_4/C using several ways (impregnation, microwave irradiation, impregnation, and microwave irradiation) in aqueous medium in the presence of β-cyclodextrin was recently reported (Kepenienė et al. 2020). These materials were evaluated in the catalytic oxygen reduction reaction, and the Au supported on Co_3O_4/C gave the highest activities.

Nanoparticles Immobilized on a Cyclodextrin-Grafted Support

Another strategy consisted in the use of cyclodextrin-decorated magnetic nanoparticles. In this context, γ-Fe_2O_3@SiO_2-cyclodextrin core-shell hollow sphere can be mentioned (Sadjadi et al. 2017). The hybrid system was developed by initial synthesis of γ-Fe_2O_3@SiO_2 core-shell system followed by amine functionalization by using 3-*N*-(2-(trimethoxysilyl)ethyl)methanediamine and subsequent reaction with tosylated cyclodextrin. The system was then applied for the immobilization of silver nanoparticles which were reduced and capped by Hollyhock flower extract. Notably, upon introduction of non-magnetic component, the maximum saturation magnetization (Ms) value of the hybrid system did not decreased remarkably compared to bare Fe_2O_3. Finally, the catalytic activity of the ternary hybrid was studied for ultrasonic-assisted A^3 and KA^2 coupling reactions of phenyl acetylene, amines, aldehydes, or ketones. The results established the excellent performance of the magnetic hybrid system, which was superior to some of previous reports. Hot filtration test confirmed that the silver leaching was considerably controlled and the catalyst could be reused up to four reaction runs.

In another example, Azaroon and Kiasat (2018) developed an organometallic magnetic catalyst for selective reduction of nitro functionality to corresponding amine compounds. To prepare the catalyst, magnetic hydroxyapatite (HAp) γ-Fe_2O_3@HAp was first synthesized, and its surface was amine functionalized. The final catalyst was obtained through reaction with 1,1-carbonyldiimidazole-β-cyclodextrin followed by incorporation of silver nanoparticles. The authors believed that the cavity of cyclodextrin could stabilize silver nanoparticles and avoid them from aggregation. Notably, the catalyst, γ-Fe_2O_3@HAp-cyclodextrin.Ag, could be recovered magnetically and recycled for five reaction runs with negligible loss of the catalytic activity.

Chalasani and Vasudevan (2013) developed cyclodextrin-functionalized Fe_3O_4@TiO_2 core-shell nanoparticle via a two-step process. Initially, spherical Fe_3O_4 nanocrystals were prepared via thermal decomposition of FeOOH in a high boiling octadecene solution and covered by a titania shell through the hydrolysis of tetrabutyl titanate. The resultant compound was then capped with carboxymethyl-β-cyclodextrin in the presence of carbodiimide (Fig. 5.23). The transmission electron

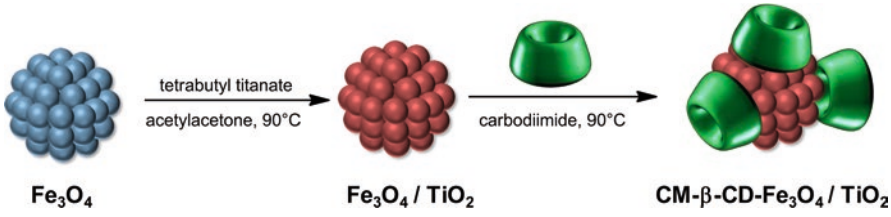


Fig. 5.23 Preparation of carboxymethyl-β-cyclodextrin-Fe_3O_4@TiO_2. Firstly, magnetic nanocrystals as cores were prepared through thermal decomposition of FeOOH and then coated with titania shell. Then, the nanoparticles were capped with carboxymethyl-β-cyclodextrin. (Adapted from Chalasani and Vasudevan 2013)

microscopy analysis revealed that the nanocrystals had the mean diameter of 12 nm and core of about 9 nm. The hybrid system was used as a photocatalyst for the degradation of bisphenol A and dibutyl phthalate, in aqueous media. Notably, the catalytic performance of cyclodextrin-functionalized Fe_3O_4@TiO_2 core-shell nanoparticle was higher than that of Fe_3O_4@TiO_2 core-shell nanoparticles. This could be attributed to the role of carboxymethyl-β-cyclodextrin coming from its ability to disperse the nanoparticles in the aqueous phase and to form an inclusion complex with pollutants. The authors believed that this cost-effective catalyst could be simply recovered and reused.

Sadjadi (2018) reported β-cyclodextrin-decorated halloysite nanoclay (Hal) as a potential support for the immobilization of Pd nanoparticles. The hybrid catalyst, Pd@Hal-T-cyclodextrin, was simply prepared through Cl-functionalization of halloysite nanoclay and its subsequent reaction with thiourea and tosylated cyclodextrin (Fig. 5.24). Pd@Hal-T-cyclodextrin was successfully used for catalyzing copper and ligand-free Sonogashira coupling reaction under mild reaction conditions. Noteworthy, the catalyst was recyclable and could be successfully recovered and recycled up to five reaction runs.

Khalafi-Nezhad and Panahi (2014) introduced an organic-inorganic hybrid catalyst, PdNP-silica cyclodextrin, by the synthesis of 1–10 nm Pd nanoparticles in the presence of cyclodextrin grafted onto silica. The catalytic activity of the hybrid catalyst was studied for Heck coupling reaction. Notably, the catalyst exhibited high reusability and could be reused up to six reaction runs with only negligible loss of the catalytic activity.

In another attempt, Martina et al. (2016) developed an efficient, green, and rapid microwave-assisted protocol for ligand-free Suzuki and Heck C–C coupling reaction as well as semi-hydrogenation of phenyl acetylene by using a novel catalyst, Pd/Si-cyclodextrin. The catalyst was prepared though reaction of

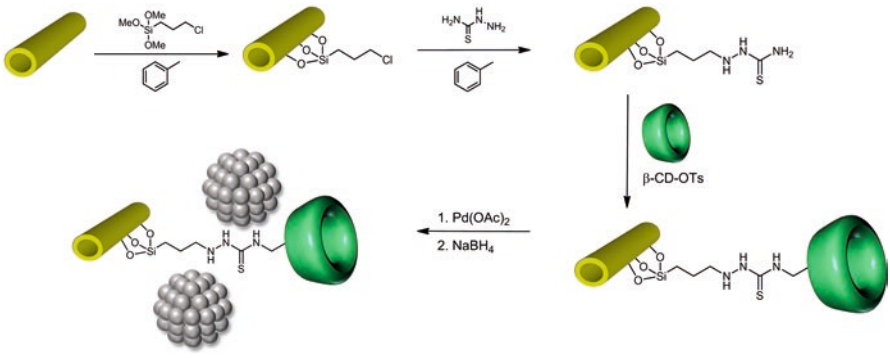


Fig. 5.24 The schematic process for the fabrication of Pd@Hal-T-cyclodextrin. Halloysite nanoclay was first Cl-functionalized and then reacted with thiourea and tosylated cyclodextrin. The prepared support was applied for Pd stabilization. It is presumed that the presence of cyclodextrin in the structure of the catalyst could act both as a capping agent for Pd nanoparticles and a phase-transfer agent for the hydrophobic substrate in coupling reaction. (Adapted from Sadjadi 2018)

(3-glycidoxypropyl)methyltriethoxysilane and silica SIPERNAT. The modified silica, Si-GPMS, reacted with 10-undecynil-1-amine under microwave irradiation to afford Si-G-Und. The latter reacted with 6-monoazido-β-cyclodextrin in the presence of ascorbic acid and $CuSO_4{\cdot}4H_2O$ to furnish Si-cyclodextrin which subsequently tolerated reaction with $Pd(OAc)_2$. Pd nanoparticle immobilization on Si-cyclodextrin was achieved through reduction of Pd salt in EtOH or H_2O. This step could be carried out under ultrasonic irradiation. It was found that the presence of cyclodextrin could increase the Pd content in the final catalyst. Moreover, this value was affected by the solvent and the reaction condition used in the final step. The highest loading, 6 wt%, was observed upon using EtOH under reflux conditions. Noteworthy, cyclodextrin also affected the size distribution of Pd nanoparticles. Studying the reusability of the catalyst for four reuses established only slight loss of the catalytic activity. High yields, low reaction times, and low amount of the catalyst were other benefits of this protocol.

Considering the potential of cyclodextrin as both reducing agent and dispersant, Li et al. (2015) designed and synthesized a β-cyclodextrin and multiwalled carbon nanotube hybrid material for deposition of PtRh nanoparticles through a one-pot hydrothermal approach (Fig. 5.25). Briefly, a solution of β-CD in water was added

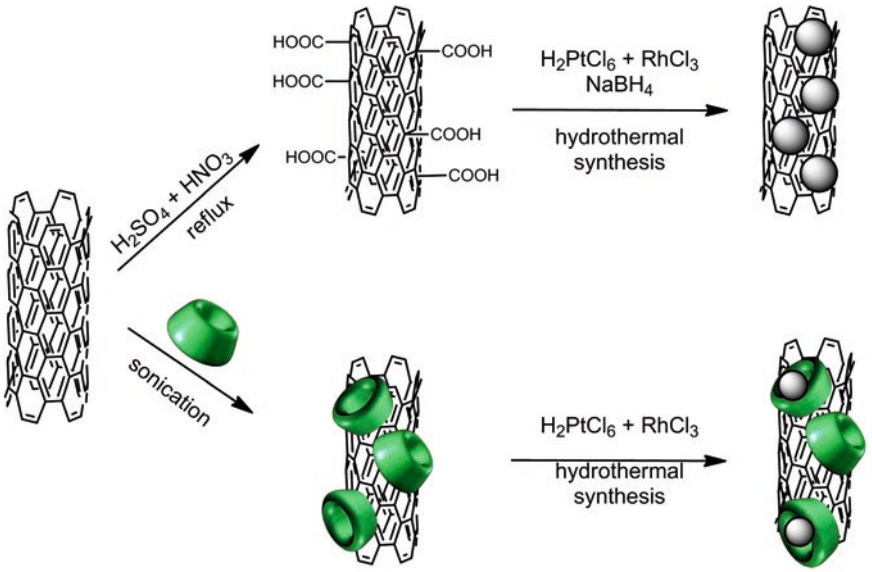


Fig. 5.25 Schematic illustration of the fabrication of PtRh/acid-treated carbon nanotubes (upper) and PtRh/β-cyclodextrin-carbon nanotubes (below). As depicted, for the preparation of PtRh/β--cyclodextrin-carbon nanotubes, an aqueous solution of cyclodextrin and multiwalled carbon nanotube suspension was sonicated, and then the metal precursors were added, and the mixture was hydrothermally treated. In the case of PtRh/AO-carbon nanotubes, however, multiwalled carbon nanotube was acid treated, and the metallic particles were obtained via reduction by $NaBH_4$. Notably, in the case of PtRh/β-cyclodextrin-carbon nanotubes, the nanoparticles with smaller sizes and better dispersion were obtained. (Adapted from Li et al. 2015)

to the suspension of multiwalled carbon nanotubes and then sonicated. The solutions of metal precursors were introduced, and the obtained mixture was subjected to the hydrothermal treatment. FTIR analysis of this composite material was done, and it clearly showed that β-cyclodextrin was attached to the surface of the pristine carbon nanotubes. Moreover, the amount of β-cyclodextrin attached to the multiwalled carbon nanotubes was determined by thermogravimetric analysis experiment and was about 9.3% in the PtRh/β-cyclodextrin-CNT material. The obtained hybrid system, PtRh/β-cyclodextrin-CNTs, was used as an electrocatalyst for promoting methanol oxidation. The authors also compared the efficiency of the cyclodextrin-containing hybrid with the PtRh nanoparticles supported on multiwalled acid-treated carbon nanotubes (AO-CNTs) which was obtained through reduction by $NaBH_4$. The results established the smallest size and highest dispersion of the metallic components in PtRh/β-cyclodextrin-CNTs and consequently excellent electrocatalytic activity compared to PtRh/AO-CNTs. Notably, the authors studied the effect of Pt/Rh atomic ratio and found the atomic ratio of 1:1 as the best choice.

In another report, Sadjadi et al. (2018b) covalently conjugated carbon nanotubes (CNT) with cyclodextrin nanosponges (CDNS) and applied the hybrid system as a heterogeneous support for the immobilization of Pd nanoparticles. The hybrid system Pd@CDNS-CNT that benefited from the chemistry of both carbon nanotubes and cyclodextrin nanosponges chemistry was then used as an efficient catalyst for catalyzing the ligand and copper-free Sonogashira and Heck coupling reactions in aqueous media. The comparison of the catalytic activity of Pd@CDNS-CNT with that of control catalysts, Pd@CNT, Pd@CDNS, and Pd@CNT + CDNS, established that the hybrid catalyst exhibited superior catalytic activity, indicating that hybridization of carbon nanotubes and cyclodextrin nanosponges was more effective than the use of each one separately or as individual. The recyclability of the catalyst up to six reaction runs was also confirmed.

Taking advantage of β-cyclodextrin-decorated reduced graphene oxide (rGO) as support, β-cyclodextrin-rGO, Ran et al. (2017) developed a mild and efficient procedure for the synthesis of very small (size of 2 nm) and well-dispersed Pd-Pt bimetallic nanoclusters, Pd-Pt@β-cyclodextrin-rGO (Fig. 5.26). The synthetic process took place in an aqueous solution at ambient temperature and considering a very

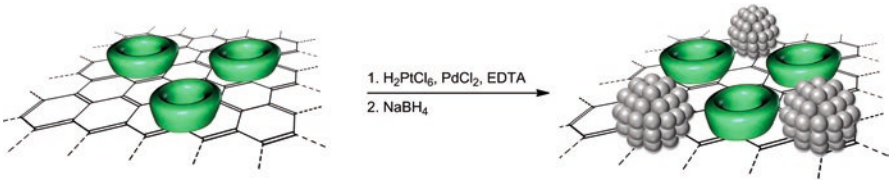


Fig. 5.26 Schematic presentation for the preparation of the Pd-Pt@β-cyclodextrin-reduced graphene oxide nanohybrid using the in situ reduction method. The presence of cyclodextrin in the structure of the support prevented the bimetallic clusters from aggregation and led to the formation of small particles with high dispersion. (Adapted from Ran et al. 2017)

short reaction time of 30 min in the absence of organic solvents. FTIR experiment was done, and it clearly showed that β-cyclodextrin was attached to reduced graphene oxide. By thermogravimetric analysis, the amount of β-cyclodextrin was determined and was about 28 wt%. This grafting of β-cyclodextrin could prevent the aggregation of the bimetallic clusters. The hybrid system was used as an electrocatalyst for promoting methanol and ethanol oxidation. The comparison of the catalytic activity of this hybrid system with conventional Pd/C and Pd@β-CD-rGO, Pt@β-CDrGO, and Pd-Pt@rGO confirmed its superior catalytic activity, poison tolerance, and durability which could emerge from very tiny size, high monodispersity, and uniformity of bimetallic catalyst, using a hybrid support with high surface area and synergistic effects due to the coexistence of Pd and Pt atoms on the surface.

Putta et al. (2015) disclosed a novel hybrid system, Pd@cyclodextrin-graphene nanosheets, containing Pd nanoparticles, β-cyclodextrin, and graphene nanosheets with the utility as a catalyst for promoting phosphine-free Suzuki-Miyaura, Heck-Mizoroki, and C-C coupling reactions in aqueous media. To prepare cyclodextrin-graphene nanosheets, the suspension of graphene oxide in deionized water was well dispersed by using ultrasonic irradiation and mixed with the solution of β-cyclodextrin and ammonia. Then, hydrazine solution was added, and the resulting mixture reacted under stirring to afford cyclodextrin-graphene nanosheets. To incorporate Pd nanoparticles, cyclodextrin-graphene nanosheets in ethanol were dispersed and reacted with $PdCl_2$. Ethanol played the role of green solvent and in situ reducing agent. The Pd loading in the final catalyst was calculated to be 6.2 wt%. The authors believed that the presence of cyclodextrin on graphene nanosheets could stabilize the Pd nanoparticles, improve their dispersion, and avoid agglomeration. Moreover, the cyclodextrin cavity could serve as an inclusion site for the reagents. These factors as well as "Breslow effect" and formation of ternary cyclodextrin/substrate/additive complexes on the Pd-graphene nanosheet surface led to high catalytic activity of the hybrid system. Notably, the catalyst was reusable and could promote four successive reaction runs with loss of the catalytic activity to some extent (about 20% for the fourth reaction run compared to the first run). The hot filtration test as well as ICP-AES analysis proved 0.31 wt% Pd leaching in the reused catalyst after three reaction runs compared to fresh catalyst. Low amount of the catalyst, high yields, green and simple procedure, and wide substrate scope were the merits of this strategy.

To improve the water disposability of fullerene, C_{60}, it was modified with hydroxypropyl-β-cyclodextrin. The hybrid system was then applied for supporting Pd nanoclusters with mean particle size of 2.5 nm (Zhang et al. 2015). Hydroxypropyl-β-cyclodextrin acted as a coordination agent and surfactant and improved the disparity and compositional uniformity of nanoparticles. The hybrid system with an electrochemical surface area of 41.6 $m^2\ g^{-1}$ exhibited outstanding electrocatalytic activity for the oxidation of formic acid. Moreover, the much more negative onset potentials and better stability compared to electrodes modified by other electrocatalysts were observed, implying the promising utility of this system for use in a direct formic acid fuel cell.

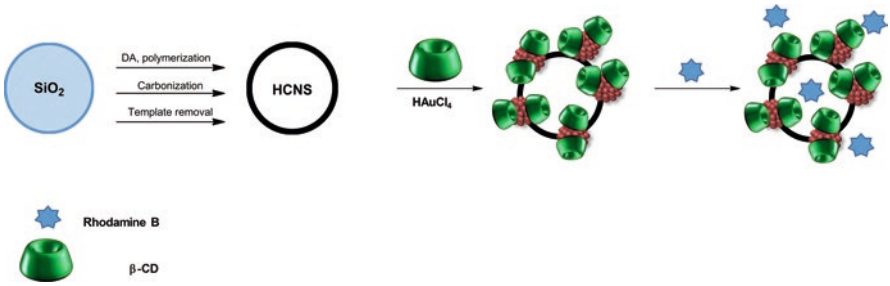


Fig. 5.27 Representation of electrochemically sensing of RhB (the blue star) based on β-cyclodextrin-Au-nanoparticles/hollow carbon nanosphere nanohybrids. As shown, for the synthesis of the catalyst, SiO_2 particles were reacted with dopamine (DA) to form silica@polydopamine. The latter was then carbonized and silica template was removed by treating with HF. Subsequently, the resulting hollow carbon nanospheres were used for Au immobilization. Finally, Au-nanoparticles/hollow carbon nanospheres were mixed with cyclodextrin and sonicated. (Adapted from Yi et al. 2015)

Considering the high electrocatalytic activity of Au nanoparticles, the recognition ability and hydrophilicity of cyclodextrin, and high surface area and electrochemical features of hollow carbon nanospheres (HCNS), Yi et al. (2015) developed an Au-based hybrid system, β-cyclodextrin-AuNPs/HCNS, based on the initial synthesis of silica@polydopamine followed by carbonization to afford hollow carbon nanospheres and subsequent introduction of gold nanoparticles and β-cyclodextrin (Fig. 5.27). The resulting nanocomposite was used as an electrode material to detect RhB by electrochemical method. The comparison of the performance of β-cyclodextrin-Au nanoparticles/HCNS/GCE (GCE stands for glassy carbon electrode) with HCNS/GCE and Au nanoparticles/HCNS/GCE established the superior performance of the former, the detection limit of 0.96 μg L^{-1}, indicating the synergistic effects between the three components, cyclodextrin, hollow carbon nanospheres, and gold nanoparticles.

Among the different organic supports which could be considered in order to support metal nanoparticles, the use of polymer network has also been reported. Huang et al. (2019) had reported in 2019 the use of cyclodextrin polymer networks decorated by different metal nanoparticles. In this case, ultra-small noble metal nanoparticles based on Pd, Ag, Pt, Au, and Rh were prepared by a simple chemical reduction of the metal precursor by sodium borohydride. Ultra-small nanoparticles were obtained with mean diameters ranging from 0.5 nm to 0.9 nm, respectively, for Ag nanoparticles and Pd nanoparticles. The Pd nanoparticles deposited onto cyclodextrin polymer networks were fully characterized by powder X-ray diffraction, HAADF-STEM, X-ray photoelectron spectroscopy, and ICP. The authors clearly showed the importance of 1,2,3-triazolyl groups in order to obtain very small nanoparticles dispersed homogeneously onto the cyclodextrin polymer network. Finally, the catalytic activity of these Pd nanoparticles was evaluated in the reduction of 4-nitrophenol. The beneficial effect of the cyclodextrin was evidenced by a reaction conducted in the presence of 1-adamantane carboxylate sodium salt

(ACNa) which is known to strongly interact with β-cyclodextrin. A decrease of the conversion was observed in the presence of ACNa in comparison with the catalytic test made without ACNa. Indeed, the adsorption of 4-nitrophenol onto Pd nanoparticle surface could be enhanced by the complexation of 4-nitrophenol with β-cyclodextrin. The recyclability of this catalytic system was also studied, and it was reused during seven successive catalytic runs without any loss of activity and increase of the mean diameter of the Pd nanoparticles. Moreover, these Pd nanoparticles revealed to be active in the hydrogenation of a wide variety of nitroarenes and also in the Suzuki-Miyaura coupling reaction.

Palladium nanoparticles were immobilized on cyclodextrin-modified poly(amidoamine)s (PAAs) by a chemical reduction of $Pd(OAc)_2$ in dimethylsulfoxide (Zhang et al. 2019). FTIR data confirmed the presence of the polymer and the cyclodextrin structures in the material. Scanning electron microscopy image showed that the Pd nanoparticles were uniformly dispersed onto the PAAs-cyclodextrin with a globular radius of 10 nm. The catalytic activity of these supported Pd nanoparticles was evaluated in the Suzuki reaction in aqueous medium. The temperature and the nature of the base were studied for the optimization of the reaction between the phenylboronic acid and 4-bromoethoxybenzene. The catalyst showed good activities which is probably due to the cyclodextrin moiety which ensured a good dispersion of the heterogeneous catalyst in water. The beneficial effect of the cyclodextrin through inhibitive experiments using adamantane was confirmed by an activity decrease. The study was then extended to a variety of aryl halides, and the cross-coupling products were obtained from moderate to excellent yields. The catalytic system could finally be recycled by maintaining activity after six successive runs.

The development of nanofibers has received an increasing interest since several years. This kind of material could be considered for the development of heterogeneous catalysts by the deposition or the incorporation of metal nanoparticles onto and into the nanofibers. The group of Uyar is a precursor in this field. Indeed, in 2019, they reported the incorporation of Ag nanoparticles into nanofibers made from the electrospinning of hydroxypropyl-β-cyclodextrin solution containing Ag nanoparticles (Celebioglu et al. 2019b). In this case, Ag nanoparticles were synthesized before the electrospinning step using hydroxypropyl-β-cyclodextrin as reducing agent of silver metal precursor in an alkaline solution. Hydroxypropyl-β-cyclodextrin was also used for the production of the nanofiber mats. The catalytic nanofibers were prepared starting from a dimethylformamide solution or an aqueous solution. Ag nanoparticles were homogeneously dispersed onto the nanofiber mats, and the mean diameter of Ag nanoparticles increased when the nanofibers were prepared in dimethylformamide instead of aqueous solutions and when the amount of silver increased in the nanofiber mats from 1 wt. % to 2 wt. %. Indeed, the mean size of Ag nanoparticles in the fiber matrix produced from dimethylformamide increased from 3.5 nm to 4.8 nm for, respectively, 1 wt. % and 2 wt. % of Ag loading. And the mean size of Ag nanoparticles in the fiber matrix produced from aqueous solutions increased from 1.9 nm to 2.3 nm for, respectively, 1 wt. % and 2 wt. %. The same tendency was observed for the mean diameter of the electrospun nanofibers. The

antibacterial properties of the nanofiber mats against gram-negative (*E. coli*) and gram-positive (*S. aureus*) were finally evaluated. These hydroxypropyl-β-cyclodextrin/Ag nanoparticles composite nanofibers showed antibacterial activities, and it was directly due to the presence of Ag nanoparticles in the nanofiber mats.

The same strategy was considered by the same team for the incorporation of Pd nanoparticles into cyclodextrin nanofibers which were used for the catalytic reduction of nitroarene (Celebioglu et al. 2019a). These nanocomposite nanofibers were prepared by electrospinning a hydroxypropyl-β-cyclodextrin solution containing $Pd(OAc)_2$ as palladium precursor. Hydroxypropyl-β-cyclodextrin played the role of reducing agent of the palladium source and was very important in order to manufacture the electrospun nanofibers. Different parameters such as the Pd loading and the nature of the solvent were studied. These composite nanofibers were fully characterized by FTIR, transmission electron microscopy, scanning electron microscopy, and X-ray photoelectron spectroscopy. Pd nanoparticles were homogeneously dispersed into and onto the nanofibers with mean diameter ranging from 3.7 and 4.9 nm depending on the nature of the solvent or the Pd loading. These nanofibers containing Pd nanoparticles were catalytically active in the reduction of 4-nitrophenol into 4-aminophenol with turnover frequency ranging from 10.17 h^{-1} to 12.25 h^{-1}. The authors clearly showed the multiple role of hydroxypropyl-β-cyclodextrin for the preparation of these catalytic nanofibers; it means the role of reducing agent of palladium metal precursor, the role of stabilizing agent of Pd nanoparticles, and also the role of handy nanofibrous carrier matrix.

Another strategy has been developed by the same team and consisted into the production of cyclodextrin nanofibers by the electrospinning of an aqueous solution of hydroxypropyl-β-cyclodextrin containing a multifunctional cross-linker (1,2,3,4-butanetetracarboxylic acid, BTCA) in order to improve the robustness of the nanofibers. After manufacturing of these poly-cyclodextrin nanowebs, Pd nanoparticles were supported onto this material by atomic layer deposition (Celebioglu et al. 2017). Transmission electron microscopy measurements clearly showed that Pd nanoparticles were homogeneously dispersed onto the nanofiber mats with a mean diameter centered on 4.34 nm. These nanofibers were used for the catalytic reduction of 4-nitrophenol which was completely converted into 4-aminophenol within 35 min. The reusability of these catalytic nanofibers was also studied, and it was possible to reuse the Pd nanoparticles deposited onto electrospun nanofibers during five successive runs without any loss of activity which clearly showed that the Pd nanoparticles were strongly anchored onto the poly-cyclodextrin nanowebs.

Yi et al. (2013) employed β-cyclodextrin for modification of multiwalled carbon nanotubes (MWCNT) immobilized on Ti plates to prepare a novel electrode on which binary Pd-Ni nanoparticles were electrodeposited. It was confirmed that incorporation of β-cyclodextrin could improve the dispersion of nanoparticles and led to nanoparticles with smaller sizes compared with the material without β-cyclodextrin. The authors studied the electrocatalytic performance of the electrode for alcohol electrooxidation and compared it with those of PdNi/MWCNT/Ti and PdNi/Ti. The results established the superior electrocatalytic activity of the former.

Shen et al. (2013) synthesized a composite material based on reduced graphene oxide rGO/β-cyclodextrin/TiO_2 in a one-pot hydrothermal strategy. FTIR analysis clearly showed that β-cyclodextrin molecules were still attached to the surface of rGO. Moreover, by transmission electron microscopy, the author explained that the sheets tend to form small aggregates due to the cross-linked rGO sheets with β-cyclodextrin molecules. In this composite material, β-cyclodextrin acted as a linker between rGO and TiO_2 nanoparticles. The photocatalytic and adsorption efficiencies are higher than rGO/TiO_2 or rGO/β-cyclodextrin materials which can be explained by the interactions between the three components.

Sadjadi et al. (2018a) disclosed the utility of a hybrid system composed of halloysite nanotube and cyclodextrin nanosponges (CDNS), prepared from reaction of cyclodextrins monomers and diphenyl carbonate, for the immobilization of Pd nanoparticles. To suppress the leaching of Pd nanoparticles, graphitic carbon nitride, *g*-C_3N_4, was also introduced to the hybrid system via hydrothermal treatment (Fig. 5.28). The final catalytic system, Pd@Hal-CDNS-*g*-C_3N_4, was successfully used for promoting ligand and copper-free Sonogashira and Heck coupling reactions under mild and environmentally benign conditions. The authors believed that cyclodextrin nanosponges could contribute to the catalysis through formation of inclusion complex with the substrates and closing them to the catalytic sites. Notably, the catalyst showed high recyclability, up to ten consecutive reaction runs with slight loss of the catalytic activity and Pd leaching. Using control catalysts, the authors also confirmed the contribution of each hybrid components to the catalysis as well as the synergism between them.

5.3.2 *Nanoparticles Immobilized on a Support Considering Two-Step Method*

Among the different methods reported for obtaining well-dispersed supported metallic nanoparticles, the deposition of metallic nanoparticles onto a porous support from stabilized colloidal suspensions has received attention since 2005. For

Fig. 5.28 The procedure for the preparation of Pd@Hal-CDNS-*g*-C_3N_4. As shown, cyclodextrin nanosponges (CDNS) was first prepared and amine functionalized and then reacted with Cl-functionalized halloysite nanoclay. In the next step, the as-prepared hybrid was palladated and hydrothermally reacted with *g*-C_3N_4. It is believed that cyclodextrin nanosponges served as a phase-transfer agent, while *g*-C_3N_4 could suppress Pd leaching. (Adapted from Sadjadi et al. 2018b)

example, Ponchel and co-workers have studied the preparation of carbon-supported ruthenium catalysts for gas-phase hydrogenation reactions (Denicourt-Nowicki et al. 2008; Wyrwalski et al. 2011). The idea was to take advantage of an efficient anchoring of the metallic nanoparticles onto the carbon support via hydrophobic interactions coming from the presence of the cyclodextrin. To validate the strategy, a series of carbon-supported ruthenium nanocatalysts were prepared by the adsorption on a porous activated carbon of Ru nanoparticles preformed in aqueous solution by chemical reduction of $RuCl_3$ in the presence of RaMe-cyclodextrin (α, β, and γ). Nitrogen adsorption measurements showed that the immobilization of the RaMe-cyclodextrin-stabilized Ru nanoparticles deeply affected the textural properties of the porous carbon material. Moreover, thermogravimetric measurements proved that the prepared catalysts were thermally stable up to 235 °C under both inert and reducing atmospheres. Finally, the study of the dispersion and morphology of the supported particles was carried out by transmission electron microscopy analysis. For instance, the transmission electron microscopy characterization of the Ru-3-β-cyclodextrin/C sample showed that nanoparticles had a spherical shape with an average diameter of 2.4 nm. The catalytic activity of the Ru nanoparticles was evaluated in the hydrogenation of xylene isomers in gas phase at 85 °C. The catalytic results had clearly shown that the cyclodextrin-based Ru catalysts were more efficient than the control Ru/C. Moreover, the catalytic activity depended on the cyclodextrin size and initial cyclodextrin/Ru ratio. In terms of stereoselectivity, the *trans* to *cis* ratio was improved in the presence of cyclodextrin-based catalysts and thus whatever the substrate. These results can be explained by several factors such as the dispersion of the active species through a promoting effect of the cyclodextrin and the host-guest interactions occurring between the substrate and cyclodextrin, which is adsorbed onto the nanoparticles.

The generation of materials from the incorporation of metal particles into polymer matrix received a growing interest due to applications in electrocatalysis such as methanol oxidation (Chen et al. 2014) or dioxygen electroreduction (Gopalan et al. 2006; Chen et al. 2015). For example, gold nanoparticles were stabilized by an inclusion complex of cyclodextrin with 4-aminothiophenol. These nanoparticles were then electrochemically deposited on glass electrode forming Au(0) nanoparticles and poly(aminothiophenol). A repairable catalytic system was considered on the basis of pre-synthesized gold nanoparticles stabilized by thiolated-β-cyclodextrin and porous nickel (PNi) containing azobenzene compounds to adsorb these metal nanoparticles by the formation of an inclusion complex (Zhou et al. 2017). The high specific surface area and connected porous structure of porous nickel provided a good opportunity to achieve the multivalent interactions between β-cyclodextrin-Au nanoparticles and PNi@IPTS-Azo. Additionally, the reactant solution could be catalyzed by flowing through the pores of the PNi@IPTS-Azo@β-CD-AuNPs. This catalytic model showed a high efficiency close to 95%. Because of the reversible multivalent host-guest interactions between thiolated β-cyclodextrin and azobenzene, the catalytic system could be regenerated by removing the deactivated Au nanoparticles with UV light irradiation and recombining new ones through in situ multivalent interactions. Because of the large specific surface area and connected

porous structure of nickel, a large number of Au nanoparticles could be anchored on the surface through multivalent host-guest interactions, and the reactant solution could be catalyzed by flowing through the pores. Because of the photoisomerization property of azobenzene, the multivalent host-guest interactions between β-cyclodextrin and azobenzene could be removed by UV irradiation. Thus, the gold nanoparticles could be anchored on or removed from the surface of the porous nickel. Different electrocatalysts were prepared by increasing the gold amount. These electrocatalysts had been evaluated in the oxygen electroreduction and compared to the unmodified electrode. The authors observed an activity enhancement for the poly(aminothiophenol)-Au_{nano} which can be explained by small crystallite sizes and good distribution of gold nanoparticles on the surface of the polymer. Platinum nanoworms self-assemble with a β-cyclodextrin polymer/reduced graphene oxide via the use of 4-aminothiophenol as nanoparticle capping agent incorporated in the cyclodextrin cavities (Gopalan et al. 2006). The cyclodextrin-based polymer was synthesized by cross-linking β-cyclodextrin with epichlorohydrin and the graphene oxide from natural graphite. The polymer of cyclodextrin was modified on graphene oxide, and the resulting composite was dispersed in ethanol and mixed with polyaminothiophenol. The modified graphene oxide was reduced by hydrazine and filtered before the addition of Pt nanoworms. The interactions of the 4-aminothiophenol and the polymer of cyclodextrin were evaluated by UV-Vis spectroscopy and by FTIR spectroscopy. One interaction gave a red shift corresponding to the thiol/amino group from 251 nm to 256 nm. Moreover, all the characteristic peaks of 4-aminothiophenol were not observed because 4-aminothiophenol molecules were embedded inside the cyclodextrin cavity, lowering the vibrations of absorption bands. Energy-dispersive X-ray spectroscopy experiments were performed to determine the content of the platinum nanoworms anchoring on the composite. The main elements which were found were Pt, C, N, O, and S, confirming that both inclusion complex-based polymer and platinum were anchored on reduced graphene oxide. Thermogravimetric analysis confirmed the above results. This heterogeneous catalyst had proved to be electrocatalytic active for oxygen reduction reaction and was stable because no significant decrease of the current response was observed after 1 week.

In 2015, pre-synthesized gold nanoparticles were adsorbed on the same composite (cyclodextrin-based polymer with reduced graphene oxide) (Chen et al. 2015). Moreover, the surface properties were characterized by static contact angles where the more polymer is adsorbed on reduced graphene oxide, the stronger the hydrophilicity of the composite is. The interactions of the 4-aminothiophenol and the polymer of cyclodextrin was evaluated by UV-Vis and ^{1}H NMR spectroscopy. The presence of the gold nanoparticles on the composite material was confirmed by UV-Vis spectroscopy by the observation of one red shift of the surface plasmon resonance of gold nanoparticles, from 522 nm to 568 nm, due to the interaction of the 4-aminothiophenol with the particles. This interaction gave another red shift corresponding to the thiol/amino group from 251 nm to 253 nm. Structural analyses were also performed (X-ray diffraction and energy-dispersive X-ray spectroscopy). The catalytic activity of these materials was evaluated in the oxygen

electroreduction in a 0.1 M H_2SO_4 solution under several atmospheres. According to the voltammetric data, the Au nanoparticles supported on 4-ATP_β-CDP/rGO showed a good activity toward oxygen reduction. The catalytic activity increased with the Au nanoparticle loading.

Immobilized gold nanoparticles (Fe_3O_4@Au) were synthesized through a self-assembly route between thiolated-β-cyclodextrin gold nanoparticles and ferrocenyl-functionalized iron oxide Fe_3O_4 nanoparticles (Qu et al. 2018). This catalyst showed a high catalytic activity in the reduction of 4-nitrophenol in comparison of control experiments. The Fe_3O_4@Au ensured good recyclability by an easy recovery due to the magnetic properties of the support and by keeping the catalytic activity even after ten runs. The catalyst could be disassembled via redox properties by using hydrogen peroxide. This latter oxidizes the ferrocenyl moiety, and the corresponding oxidized product could not interact with the cyclodextrin cavity, leading to the disassembly process.

Combining the advantages of click chemistry and supramolecular assembly, Li et al. (2016) developed a novel hybrid nanocatalyst containing a movable platinum nanocluster encapsulated in temperature- and pH-responsive polymer brushes decorated through a template-assisted protocol. The authors studied the catalytic activity of the inorganic-polymer nanocomposite for the reduction of 4-nitrophenol in the presence of $NaBH_4$. The results established the high catalytic activity and reusability of the catalyst. It is suggested that the hairy hybrid nanorattles which contained the hydrophilic poly(*N*-vinylcaprolactam) brushes on their surface could improve the dispersion in the aqueous media. Notably, diverse catalysts of this type could be prepared by altering the thickness of P[MAA-co-(PMA-click-β-cyclodextrin)] shell and the length of poly(*N*-vinylcaprolactam) brushes and changing the size of SiO_2 intertemplate layer during the sol-gel process into a cross-linked β-cyclodextrin polymer network.

5.4 Conclusion

This chapter has highlighted several historical roles of the cyclodextrin in catalysis using metal nanoparticles as active phase; whatever the nature of the catalyst, it means solvent-dispersed nanoparticles or nanoparticles immobilized on a support. Indeed, cyclodextrin as stabilizing agent of metal nanocatalyst has been widely studied since the first study of Komiyama and Hirai in 1983. The stability, the catalytic activity, and the recyclability of the resulting nanoparticles have been improved by using more complex cyclodextrin-based protective agents. From the first studies using native cyclodextrins to cyclodextrin-based polymers or rotaxanes, native and functionalized cyclodextrins have proven their ability to protect metal nanoparticles against agglomeration via different stabilizing properties (electrostatic, steric, and electrosteric). Most of the examples reported in this chapter clearly showed that cyclodextrin-based systems have improved both the average size decrease and the dispersion of the metal nanoparticles in comparison to their free cyclodextrin

controls leading to the enhancement of their catalytic activity. According to several studies, cyclodextrins could be also used as reducing agents of metal precursor by their sugar-like reducing properties.

Due to a dynamic organization at the surface of metal nanoparticles, the classical mass transfer property of cyclodextrins has also been exploited with solvent-dispersed nanoparticles or nanoparticles immobilized on a support. The catalytic activity is generally improved thanks to the inclusion complex formed between the substrate and the cyclodextrin via hydrophobic interactions. This inclusion complex could also, in some cases, improve the selectivity of the reaction by inhibiting some side reactions. Cyclodextrins could also serve as agent to get confining catalytic systems by forming supramolecular hydrogels where the metal nanoparticles can be embedded. This confinement could improve the selectivity of the reaction, the catalytic activity by enhancing the proximity between the substrate and the metal particles, and also the stability leading to longer lifetime which is very important from an economical point of view.

The combination of cyclodextrin and polymer in a physical mixture and as cyclodextrin-based polymer where the cyclodextrin is directly incorporated into the polymer structure has recently proven to be very promising both in the use of nanoparticles dispersed into a solvent or immobilized on cyclodextrin polymer where it could play the role of stabilizing agent and also the role of support.

In the near future, the perspectives and the challenges are numerous concerning the development of nanoheterogeneous catalysis in the presence of cyclodextrin. Indeed, in terms of nanocatalyst design, in order to draw a parallel with the supramolecular chemistry defined by Jean-Marie Lehn, it would be very interesting, in the case of cyclodextrin-based nanoheterogeneous catalytic systems, to develop more complex and more controlled structures in order to work at a higher-dimensional scale. The preparation of supramolecular materials could lead to some synergistic effects with the aims to improve the catalytic activity or selectivity, for example. The design of cyclodextrin-based metal-organic frameworks containing metal nanoparticles could answer to some of these issues. From a catalytic point of view, always keeping in mind the multi-task agent properties of cyclodextrin for the development of nanoheterogeneous catalysis, it would be innovative to consider multimetallic nanocatalysts applied for cascade reactions for the valorization of bio-sourced compounds.

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Chapter 6
Cyclodextrin-Based Polymers for Food and Pharmaceutical Applications: A Historical Review

Max Petitjean, Iñigo X. García-Zubiri, and José Ramón Isasi

Contents

Abstract The encapsulation capabilities of cyclodextrins and the controlled release of guest molecules can be modulated with the aid of the additional functionality of a polymeric macrostructure. In addition, the covalent attachment of cyclodextrin moieties to a pre-existing material is intended to immobilize them, as in the case of medical devices or packaging applications. The first references dealing with the potential use of cyclodextrin polymers as macromolecular carriers date back to the 1980s. Since then, they have been incorporated into many constructions, such as hydrogels, nanosponges, dendrimers, interpenetrating networks, molecular imprinted polymers, and other smart biomaterials.

The present chapter discusses, from a historical perspective, the evolution of the synthesis procedures to prepare covalently linked cyclodextrins, either by grafting or cross-linking mechanisms. Then, their applications in the food and pharmaceutical sectors are presented. Debittering of juices and retention of flavors were the first

M. Petitjean · J. R. Isasi (✉)
Departamento de Química, Facultad de Ciencias, Universidad de Navarra, Pamplona, Spain
e-mail: mpetitjean@alumni.unav.es; jrisasi@unav.es

I. X. García-Zubiri
Magnesitas Navarras, Zubiri, Navarra, Spain
e-mail: inigo.garcia@magnesitasnavarras.es

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_6

proposed uses in food science, and, more recently, smart packaging using cyclodextrin polymers is being developed. In the case of the pharmaceutical and biomedical applications, numerous studies on cyclodextrin polymers are being published in the last years, mainly in drug release, but also as polymeric vectors for gene delivery as well as in the field of regenerative medicine.

Keywords History · Cyclodextrin polymers · Covalent networks · Food · Pharmacy · Drug delivery · Inclusion complexes

6.1 Introduction

In addition to their remarkable capability to establish supramolecular (host-guest) interactions by themselves because of their toroidal shape and nonpolar inside, cyclodextrins can also be covalently attached in different ways to originate more complex structures. Materials containing more than two covalently linked cyclodextrin units are known as cyclodextrin polymers. The three procedures to produce these materials are the attachment of cyclodextrins (or their derivatives) to a pre-existing polymer by grafting reactions, the cross-linking of cyclodextrins by polycondensation using multifunctional reagents, and the polymerization of cyclodextrin derivative monomers. The examples of the latter procedure are scarce in comparison with the cross-linking and grafting cases.

This chapter will cover, from a historical point of view, the synthesis and characterization of such cyclodextrin derivatives. After these new materials have been introduced, the following section will be devoted to their applications both in food chemistry and pharmaceutics and biomedicine. It needs to be mentioned that, in contrast to the enormous amount of studies on the uses of cyclodextrins in these two sectors (see Fig. 6.1), cyclodextrin polymer references are not as abundant. As a matter of fact, we will show that most of the examples found in the literature correspond to the last 10–15 years.

There are several reasons to produce cyclodextrin polymers in order to achieve new potential applications in these areas. For instance, in the case of drug delivery, which is by far the most frequently investigated subject among the biomedical applications, the complexation capabilities of cyclodextrins and the controlled release rate of the guest drugs can be modulated with the aid of the additional functionality of a polymeric macrostructure. In other cases, the covalent attachment of cyclodextrin moieties to a pre-existing structure is intended to immobilize them, as in the case of medical devices or packaging applications.

According to the previous definition of cyclodextrin polymers, this chapter will deal with those materials in which at least three cyclodextrin units are covalently attached either with each other or to a pre-existing polymer. Thus, we will not cover the functionalization of non-polymeric supports such as silica beads or inorganic nanoparticles (i.e., cyclodextrin nanocomposites). Amphiphilic cyclodextrins and star polymers with a cyclodextrin core are also very interesting macromolecular derivatives, produced by making use of the multiple hydroxyl groups that can be

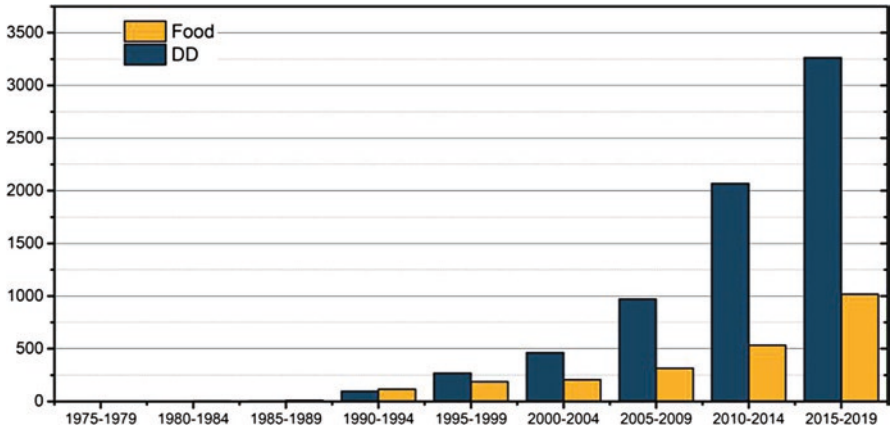

Fig. 6.1 Evolution of literature references regarding the use of cyclodextrins for food and "drug delivery" (DD) pharmaceutical applications. Although the first applications in the food sector appeared earlier, they were outnumbered by drug delivery investigations in the late 1990s. The exponential growth is still evident for both sectors

decorated with chains of different nature and lengths. In this case, we have unimeric cyclodextrins, and the host-guest interactions are not as relevant. Other remarkable materials involving cyclodextrins and polymers are polyrotaxanes. For such architectures, the threading of the cyclodextrin rings onto the polymer chains and the subsequent association among these structures yield interesting biomedical applications involving new biomaterials, such as hydrogels and scaffolds in tissue engineering. Although the functionalization of inorganic supports with cyclodextrins has been known for years and many successful results have been achieved in separation technologies, the studies on the potential applications of polyrotaxanes and amphiphilic cyclodextrins are more recent.

The first references dealing with the potential use of cyclodextrin-containing covalent structures as macromolecular carriers date back to the 1980s. Since then, they have been incorporated into many constructions, such as hydrogels, nanosponges, dendrimers, interpenetrating networks, molecular imprinted polymers, or electrospinned fibers. In addition, some of these systems have proved to be responsive to stimuli, leading to the design of smart multifunctional biomaterials which can be triggered by different factors.

6.2 Cyclodextrin Polymers

6.2.1 Historical Perspective of Cyclodextrin Polymers

Following the timeline of the three main classes of cyclodextrin polymers, i.e., cross-linked networks, polymerization of cyclodextrin monomers, and grafting, the starting point belongs to those with covalent cross-linked cyclodextrin units. The

pioneering work of Solms and Egli in 1965 can be considered as the first landmark in the field of cyclodextrin polymers (Solms and Egli 1965). In that patent, the authors used epichlorohydrin as the cross-linker in an alkaline bulk reaction, and, since then, that one has been the most abundant in the literature of cyclodextrin polymers. Also in those early years, Wiedenhof et al. (1969) improved the properties of the irregular cross-linked cyclodextrin particles that were obtained in the first procedure and produced bead microparticles that, for instance, were suitable to be used in chromatographic columns.

Polyurethane-type cyclodextrin networks were prepared using diisocyanates by Buckler et al. (1969). Acid dihalides and many other potentially useful space arms, such as dihalogenated alkenes and glutaraldehyde, were also considered in the same patent. Various possible applications of those "anchored" cyclodextrins were in fact explored in that patent filing: cigarette filters, extraction of juice aromas, separation of chemicals, etc.

A few years after that, in the mid-1970s, the first cyclodextrin monomers were produced and polymerized by Furue et al. (1975). The acrylic monomers of α- and β-cyclodextrin were obtained by reacting the respective nitrophenyl esters with the natural cyclodextrins to yield water-soluble poly(acryloyl-β-cyclodextrin), with a medium molecular weight (10^4–10^5 Da). This acrylic polymer exhibited a greater catalytic effect in the hydrolysis of *p*-nitrophenyl esters due to the "cooperative effect" between two neighboring cyclodextrin moieties on a polymeric chain (Harada et al. 1977). Other polymerizable cyclodextrin monomers were obtained in the following years, but this second method to produce cyclodextrin polymers was always the least frequent (Fig. 6.2).

The third type of cyclodextrin polymers in our classification corresponds to the attachment of cyclodextrin moieties to previously existing macromolecular materials. In this case, Szetjli et al. (1979) attached cyclodextrin units to poly(vinyl

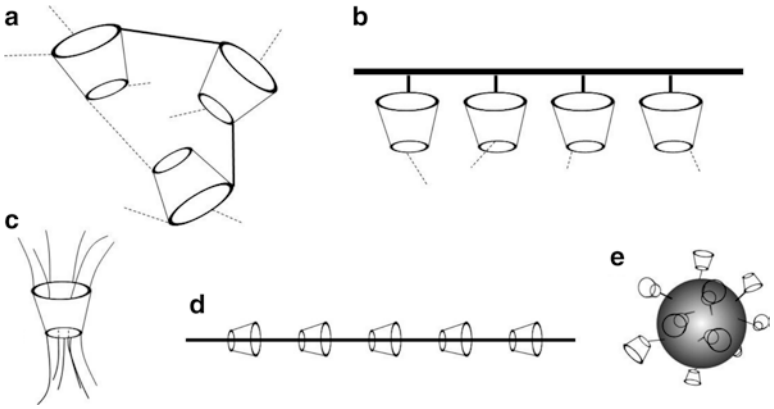

Fig. 6.2 Scheme representation of cyclodextrin-containing macromolecular systems: **(a)** cross-linked cyclodextrin polymers (more than three units); **(b)** linear polymers (either grafted-cyclodextrin polymers or monomeric cyclodextrin (co)polymers); **(c)** amphiphilic and star-like unimeric cyclodextrins; **(d)** (pseudo)polyrotaxanes; **(e)** nanocomposites and immobilized cyclodextrins

alcohol) using epichlorohydrin and epoxy ethers in the late 1970s. Poly(vinyl alcohol) was intended to provide a "skeleton" for the cyclodextrin polymer, in order to improve the mechanical properties of the resin. This procedure cannot be fully considered as a grafting modification, but it is not exactly a cross-linking process either since the cyclodextrin units are attached to a previously formed polymer. Hirayama et al. (1984) used epichlorohydrin to prepare a β-cyclodextrin/starch composite gel. The tosylation of cyclodextrins does produce reactive units that can be attached to pre-existing polymers by grafting. Thus, poly(allylamine) with cyclodextrin pendant groups was produced in the late 1980s and 1990s. In the 1990s, Pöpping and Deratani (1992) reported the production of monochlorinated cyclodextrins, and, later on, other derivatives containing heterocycles were synthesized (Reuscher et al. 1998). Earlier, in 1981, Tanaka and co-workers had immobilized derivatives of α- and β-cyclodextrin on polyurethane and also onto a polyacrylamide support after activating it with succinyl hydrazide (Tanaka et al. 1981, 1982) with the aim of obtaining stationary phases for the separation of benzene derivatives. About 20 years ago, Crini's group used cyclodextrin tosyl derivatives to produce macroporous polyamines (Crini et al. 1998a) or to modify poly(ethyleneimines) in order to coat silica beads (Crini et al. 1995). Cyclodextrin side-chain polyesters were also obtained in those years, for instance, by reacting poly(N-vinyl-2-pyrrolidone-co-maleic anhydride) with deprotonated β-cyclodextrin (Weickenmeier and Wenz 1996), and the interaction of this polymer with anionic or cationic adamantyl guests was studied. The authors also reported the synthesis of interesting associative thickeners based on the specific interaction between complementary cyclodextrin polymers and guest polymers (Weickenmeier and Wenz 1996).

So far, we have presented some examples of cyclodextrin polymers produced during the first years after the first announcement of this particular type of cyclodextrin derivatives. A more comprehensive collection can be found, for instance, in the review of cyclodextrin-containing adsorbents by Crini and Morcellet (2002). In the last two decades, more complex cyclodextrin polymer structures have been produced, namely, interpenetrated networks, molecular imprinted polymers, dendrimers, nanogels, polymer assemblies, and nanocomposites. The following subsection will be devoted to describe in detail each of these types of structures, with some examples found in the literature of the evolution of the synthetic procedures and the characterization techniques employed to analyze them, irrespective of their potential applications in food and pharmacy, separation technologies, chemical recognition, or other areas. The especial cases of the feasible uses of these materials in these two sectors will be the goal of the last section of this chapter.

6.2.2 Covalent and Supramolecular Architectures

Cyclodextrin Cross-Linked in Covalent Networks

Cyclodextrin cross-linked with epichlorohydrin polymers, the most abundant in the literature, were also the first type known, synthesized by Solms and Egli (1965). Epichlorohydrin is one of the oldest and most widely used cross-linking agents in

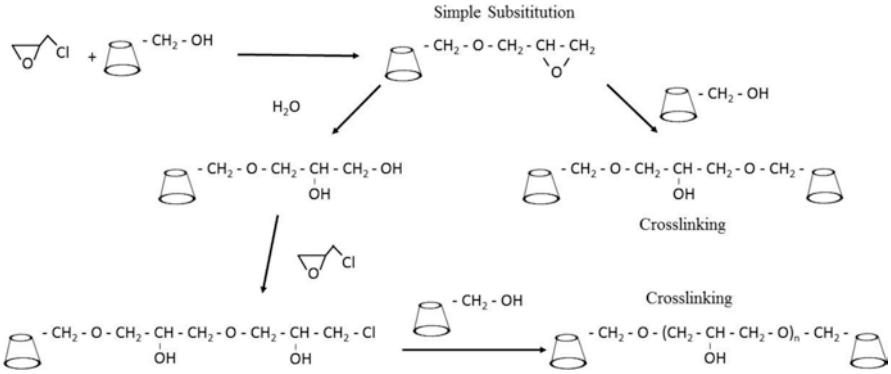

Fig. 6.3 Synthesis of cyclodextrin polymers using epichlorohydrin as a cross-linking agent. The self-polymerization of epichlorohydrin creates cross-linked bridges of variable lengths between cyclodextrin units. A 3D network is produced because of the high functionality (hydroxyl groups) of the cyclodextrin moieties

polymer synthesis. Its two reactive functional groups (epoxide group and a chlorine atom) can react with the cyclodextrin hydroxyls to yield ether linking units. In addition, epichlorohydrin can easily react with itself due to the inductive effect of chlorine. Thus, in the synthesis of these cyclodextrin polymers, several possible reactions can take place, as shown in Fig. 6.3 (where only the reactions of the primary hydroxyls of cyclodextrins have been considered).

The reaction of saccharides such as glucose with epichlorohydrin is well-known (Dumitriu 1996) and proceeds with the initial opening of the epoxy ring by a nucleophilic attack and the subsequent displacement of chlorine. Unlike other epoxides, epichlorohydrin does not yield a hydroxide as a product of a simple substitution by reacting with the cyclodextrin molecule, but it is instead capable of forming an epoxide adduct that can either react with another cyclodextrin molecule or to yield the hydroxyl product. The primary product of the reaction of β-cyclodextrin with epichlorohydrin in alkaline media is a heterogeneous mixture of several ethers, of low molecular weight and viscosity, soluble in water. In this reaction, the self-polymerization of epichlorohydrin, which is favored at high temperatures, can also occur (Renard et al. 1997). The cross-linking reaction of cyclodextrin is relatively slow, so it is feasible to control the degree of polymerization. The final product is a material where there are two structural units: cross-linked cyclodextrin units and self-polymerized epichlorohydrin units. Both structural units possess hydroxyalkyl and ether groups, which makes hard to find differences that permit their correct characterization.

The bulk synthesis procedure of Solms and Egli (1965), already mentioned in the previous section, produced irregular polymer particles. A few years after that, Wiedenhof et al. (1969) proposed a two-phase emulsion polymerization with controlled stirring, in which the cyclodextrin dissolved in water is dispersed in a nonpolar organic solvent containing a nonionic surfactant and the cross-linker. In this way, the insoluble cyclodextrin polymer resins are obtained as uniform microspheres

(beads) with better physicochemical properties: they are easily swollen, being insoluble in water and organic solvents, and stable in alkaline solutions.

These networks become insoluble provided that the "gel point" has been reached during the cross-linking process, and, because of their hydrophilic character, they will have the ability to absorb high amounts of water. They can be considered, therefore, as hydrogels. Obviously, the presence of cyclodextrin units in these hydrogels makes them capable of forming inclusion complexes with suitable host molecules. Nevertheless, the structure of the polymer network needs now to be taken into account, looking at other factors that influence the diffusion of molecules. In order for the sorbate molecules to be trapped by the polymer, they must interact with the cyclodextrin cavity and/or with the polymer network. Therefore, the amount of cyclodextrin in the polymer, the amount and type of cross-linker used, the swelling capacity (a consequence of the latter), and the possible further chemical modifications thereof need to be considered. These cyclodextrin polymers, in addition to the "rigid" cavities of the cyclodextrin moieties, have other cavities constituted by the cross-linking bridges between the cyclodextrin units (secondary cavities). Those additional cavities can be considered more flexible than those of cyclodextrin, at least when the cross-linker is the self-polymerizable epichlorohydrin molecule. Sorption in these polymers takes place then by inclusion in the cyclodextrin cavities or by specific interactions in the secondary ones. In addition, the cross-linker tails are also capable of interacting with the sorbate molecules. As potential drug delivery devices, cyclodextrin-epichlorohydrin hydrogels made with a controlled geometry are useful to obtain kinetic parameters by fitting experimental data to mathematical models suitable for drug release and to obtain diffusion coefficients according to the contact surface of the polymeric matrix (Machín et al. 2012).

Among the most frequently used non-epoxide cross-linkers are diisocyanates, first introduced by Buckler and co-workers (1969), as mentioned above. Dihalogenated acid dihalides or dihalogenated dicarboxylic acids of different sizes have also been used as space arms (Buckler et al. 1969; Zemel and Koch 1990), besides other agents such as dihalogenated alkenes or, more recently, maleic anhydride (Girek et al. 2000). Shono's group prepared insoluble porous polymers with a high cyclodextrin content, polymerizing α- and β-cyclodextrin with diisocyanates as cross-linking agents in pyridine or dimethylformamide, and studied their capability to absorb aromatic derivatives (Mizobuchi et al. 1980; Tanaka et al. 1981). Since those initial investigations, the most commonly used diisocyanates to produce cyclodextrin polymers are hexamethylene diisocyanate and toluene diisocyanate. After those, other groups also prepared cyclodextrin polymers with these same cross-linkers and certain properties, and applications have been studied thereof: stationary phases in chromatography (Lee et al. 2002), artificial cholesterol receptors (Asanuma et al. 1998), solid phase for the extraction, and subsequent analysis of carcinogenic aromatic compounds (Bhaskar et al. 2004). Ma's group, which also used these two diisocyanates, postulated the presence of interconnected nanoporosity in these polymers (Li and Ma 1999; Ma and Li 1999), which increases the apparent inclusion constant with respect to other cyclodextrin polymers such as those cross-linked with epichlorohydrin. The use of difunctional cross-linkers with longer

spacers between their two reactive groups can lead to macromolecular networks with increased porosity, which are also more flexible and less compact. In these networks, smaller molecules can increase their diffusion rates, and bulkier substances may also become entrapped (Mocanu et al. 2001).

Even though the clean polymer resulting from the synthesis using toxic reagents, such as acid dichlorides, epichlorohydrin, or diisocyanates, should be harmless, the use of nontoxic cross-linkers like the polycarboxylic acids is also feasible. Martel's group described the synthesis of soluble and insoluble polymers (Martel et al. 2005) and the production of cotton-bound cyclodextrin using these cross-linkers (Martel et al. 2002).

Several parameters are of great interest when characterizing these materials: cyclodextrin and cross-linker amounts and ratios, water contents (intrinsic moisture of the polymer), the water sorption capacity (swelling processes), the particles size and shape and their porosity, e.g., for suspension of polymerized beads, and, obviously, the sorption capacity of organic molecules of interest. In the last years of the past century, a comprehensive bibliography concerning the synthesis and sorption studies for cyclodextrin polymers could be gathered, but, in contrast, not much information on their characterization was available at that time. The analysis of cyclodextrin polymers cross-linked with epichlorohydrin is complicated when it comes to infrared or Raman spectroscopic techniques (Crini et al. 2000) because, as mentioned above, both the cross-linked cyclodextrin units and the self-polymerized epichlorohydrin possess hydroxyalkyl and ether groups. Nevertheless, the interpretation of the infrared spectra of starch cross-linked with epichlorohydrin was resolved at that time (Dumoulin et al. 1998; Delval et al. 2004).

While the spectroscopic characterization of cyclodextrin-epichlorohydrin polymers is not easy, that of cyclodextrin polymers cross-linked with diisocyanates seemed to be simpler. Qualitative characterizations by infrared spectroscopy (Li and Ma 1999; Bhaskar et al. 2004) or Raman (Lee et al. 2002) were attempted, and the successful quantitative analysis was achieved, thanks to the intense carbonyl band of the cross-linker (García-Zubiri 2005). Thermal and thermogravimetric analysis were also used in most of those studies, as well as nuclear magnetic resonance spectroscopy (Asanuma et al. 1998; Lee et al. 2002). For polymers with other cross-linkers, such as maleic anhydride, there were also some nuclear magnetic resonance results of interest (Girek et al. 2000).

As for the cyclodextrin content of the polymer, the most common procedures used already in the 1990s were the colorimetric methods using chlorotetrazolium blue (Crini et al. 1995, 1998b; Janus et al. 1999) or iodometry (Renard et al. 1997) and phenolphthalein (Mäkelä et al. 1987). For soluble cyclodextrin polymers, proton nuclear magnetic spectroscopy could be used (Renard et al. 1997), and for the insoluble resins, ^{1}H or ^{13}C solid-state nuclear magnetic resonance were employed (Crini et al. 1998b, 2000). Thus, the β-cyclodextrin-epichlorohydrin (or, rather, 2-hydroxypropyl ether) ratio can be determined because the signal corresponding to the hydrogen atoms in the 2-hydroxypropyl ether segments is displaced below the two wide peaks of the glucopyranose units.

Another technique used to determine the cyclodextrin content in the polymers is CHN elemental analysis. This method is especially useful and simple for polymers cross-linked with diisocyanates, since the nitrogen content is directly proportional to the amount of cross-linker in the polymer (Lee et al. 2002). Nevertheless, it must be used with great care in the case of cyclodextrin-epichlorohydrin polymers due to the similar elemental composition of both constituents (Romo et al. 2006).

Other Novel Cyclodextrin Polymers

The reticulated cyclodextrins, also known as nanosponges, have evolved into more complex structures in the last 10–20 years. Four generations of nanosponges can be defined, according to the classification by Trotta's group (Caldera et al. 2017). First of all, a reticulation reaction using a simple molecule such as epichlorohydrin gave us the first generation of "nanosponges." Besides those ether linkages, ester, carbonate, and urethane are the main connectors investigated in the literature. The decoration of those primary nanosponges using a cross-linker plus a special functional group produced the second generation. If this extra space arm or the added functions react to external stimuli (such as temperature or pH), allowing the nanosponges to change their shape, swelling behavior, or sorption/release capabilities, then the new "smart material" synthesized is said to belong to the third generation. Finally, a fourth generation of nanosponges is feasible by creating molecular imprinting polymers using a template, in order to improve the selectivity of the matrix toward such molecules (Caldera et al. 2017).

From a historical point of view, the last three classes can be considered as those of the present days, although some of these new attractive features of novel cyclodextrin nanosponges have been known for a couple of decades. Thus, molecular imprinted polymers using cyclodextrin moieties were already produced in the late 1990s (Piletsky et al. 1998). Stimuli-responsive polymers based on cyclodextrins were prepared in 1995 using the ubiquitous N-isopropylacrylamide monomer (Nozaki et al. 1995). Interpenetrated networks containing cyclodextrins also appeared at that time (Sreenivasan 1997). Fenyvesi et al. (1996) encapsulated several cationic disinfectant agents, in chemically modified (carboxymethylated) nanosponges, based on cyclodextrin linked to polyvinyl alcohol, to be used in the prolonged treatment of wounds.

Nanogels combine the advantages of hydrogels and nanoparticles into a single carrier that can be tailored for specific therapeutic molecules, such as low molecular weight drugs, peptides, or proteins, and target them to specific tissues or cells (Moya-Ortega et al. 2012). Liu et al. (2004) prepared cyclodextrin microgels, including one interpenetrated network, by inverse-emulsion polymerization. About 10 years ago, nanoparticles with differing charge densities were synthesized by a one-step condensation polymerization of β-cyclodextrin, choline chloride, and epichlorohydrin by Gil et al. (2009). The top-down approach can break bigger networks into the nanoscale size by using ultrasounds (Swaminathan et al. 2010). The water-in-oil emulsion method has been thoroughly employed in the last decade to

produce cyclodextrin nanogels, but their direct synthesis by polymerization of cyclodextrin monomers is more rare (Moya-Ortega et al. 2012).

Another interesting method of producing nanogels was designed by Gref et al. (2006) and consists on supramolecular nanoassemblies between a cyclodextrin-epichlorohydrin polymer and an alkyl-grafted dextran. Other potential uses of cyclodextrins as "smart" components of polymer nanoparticles were reviewed by Gref and Duchêne (2012), including nanoparticles made of cyclodextrin-based copolymers using various polyesters and polypeptides prepared in the 2000s. In the field of drug delivery, cyclodextrins had already been added in their monomeric form to improve the drug-loading capacity of polymeric nanoparticles, but the use of cyclodextrin polymers opened new perspectives. Thus, a variety of cyclodextrin-based architectures (linear, dendrimers, stars, polyrotaxanes) were used in the preparation of polycomplexes for gene delivery (Mellet et al. 2011). In 1997, β-cyclodextrin was attached to dendrimer poly(ethyleneimines) (Suh et al. 1997). Two years later, linear cationic alternate copolymers capable of binding deoxyribonucleic acid with transfection efficiency were prepared by the group of Mark E. Davis (Gonzalez et al. 1999). Later on, Choi et al. (2005) prepared polyplexes grafting cyclodextrin to poly-L-lysine instead of using poly(ethyleneimine). Besides the aforementioned cyclodextrin-coated dendrimers, cyclodextrin-centered dendrimers (i.e., star-shaped), polyrotaxanes, and polycationic amphiphilic cyclodextrins also present many interesting capabilities in the field of gene delivery, but, as mentioned above, those architectures are not the subject of this review.

Electrospun nanofibers have been used as drug delivery materials due to their high specific area, and, obviously, various formulations including cyclodextrins have been tested in the last 5 years (Costoya et al. 2017). Cyclodextrin polymers have been also explored as components of electrospun nanofibers very recently, firstly by mixing cyclodextrin-epichlorohydrin polymers with poly(methacrylic acid) inter-cross-linked at high temperature to render them insoluble in water (Oliveira et al. 2015). Nevertheless, the design of electrospinnable cyclodextrin polymers should be still improved.

6.3 Applications in the Food and Pharmaceutical Areas

6.3.1 Cyclodextrin Polymers in Food Science

In the food industry, cyclodextrins have been studied for different applications as sorption/release agents or, more recently, for packaging purposes. Many of these involve the use single cyclodextrins incorporated into different types of products as fibers (Celebioglu et al. 2018) or films (Plackett et al. 2006). Cross-linked cyclodextrins were firstly proposed for food-related applications as early as the 1960s with the patent of Bucker et al. One of the possible applications of those novel materials was related to their suitability as agents for concentration of organic molecules such

as flavors or aromas in the food industry (Buckler et al. 1969). As explained above, in order to form the cyclodextrin polymers, reagents that possess two or more functions capable of reacting with hydroxyl groups are needed to form an insoluble resin that can be used as a sorbent matrix.

Some years after the abovementioned patent was filed, a cyclodextrin polymer made with epichlorohydrin was developed to reduce the bitterness of fruit juices (Shaw et al. 1984). The purpose of that investigation was to improve the taste of orange or grapefruit juices using α- or β-cyclodextrin polymers as sorbents to form a complex with limonin, narangin, and nomilin, three natural bitter components. Their results were conclusive showing a good absorption of the bitter molecules and a taste preference of the new bitterless juice over the control juice, without absorbing other flavor or valuable components such as ascorbic acid, and with the possibility to regenerate the cyclodextrin polymer sorbent. A couple of years after that, the selectivity of these cyclodextrin polymers was tested (Shaw and Buslig 1986), using γ-cyclodextrin polymer as well, with other juice containing the same bitter components and also caffeine, and proved that cyclodextrin polymers do not complex with the latter. In the same research paper, they studied the importance of the cross-linking agent used to prepare the cyclodextrin polymers. Their study concluded that naringin removal was more effective when using β-cyclodextrin polymer resins, compared to α- and γ-cyclodextrin polymers or a standard Amberlite XAD-4 resin, which did remove caffeine or limonin in turn.

Two decades later, β- or γ-cyclodextrin were linked to chitosan through succinyl or maleyl bridges to improve the sorption of bitter compounds (Binello et al. 2004). This bitter-masking potential was measured by analyzing the bitterness of different solutions composed of either a single model molecule (caffeine) or natural extracts. Pure chitosan possesses a good sorption capacity of bitter compounds, better than those of the α-, β-, or γ-cyclodextrin monomers. However, the chitosan β-cyclodextrin adducts improve the bitter-masking power in all cases. Besides the batch procedures, Wagner Jr. et al. (1988) reported, also in the 1980s, on the result of a pilot-plant fluidized-bed procedure, where the β-cyclodextrin polymer was regenerated over 20 times without apparent loss of capacity. The debittering of other juices has also been reported later on (Szejtli and Szente 2005).

In the last decade, another area of application searched in food science and cosmetics is the retention of fragrance or aroma molecules. For example, the encapsulation of two molecules (linalool and camphor) composing *Lavandula angustifolia* essential oil using cross-linked cyclodextrin-epichlorohydrin polymers and their subsequent liberation was studied using a static headspace gas chromatography technique both in gaseous and aqueous phases and compared to those of the parent and derivative cyclodextrins (Ciobanu et al. 2012). Cyclodextrin polymers present different retention profiles depending on cyclodextrin/cross-linker ratios, the phase, and the volatile compound.

In 2009, cyclodextrin polymers were used in solid-phase extractions to determine additives in food (Li et al. 2009). Epichlorohydrin was used to cross-link β-cyclodextrin with soluble starch to evaluate the content of brilliant blue in food. The detection is feasible between 0 and 12 ppm. As solid-phase extraction research

continues, molecular imprinted cyclodextrin polymers also arrived in this field. As in the previous example, the determination of dyes in food is in order. For instance, monomeric cyclodextrin reacts with maleic acid, and then, in presence of a template, such as Congo red, the polymerization takes place with N,N′-methylenebisacrylamide as the cross-linker (Liu et al. 2015). Thanks to this type of synthesis procedures, the molecular imprinted cyclodextrin polymer shows a high selectivity and a remarkable sorption power for its target. Also in recent years, cyclodextrin polymers have been prepared with some especial characteristics. A few examples are a cyclodextrin polymer with a higher specific area (Li et al. 2018), grafted onto metallic graphene (Li et al. 2016a), added to ionic liquids (Feng et al. 2015), or imprinted on carbon nanotubes (Liang et al. 2019). Many of these new materials are designed in order to be used in solid-phase extractions, and the main interests are their capabilities for the removal and/or the determination of organic molecules present in food.

Among their many possible applications, cyclodextrin monomers are also common for food packaging, and they began to be exploited for that purpose since the end of the past century (Szente and Fenyvesi 2018). In those first uses, cyclodextrins are present in a polymer network but without being cross-linked to it. The first reported use of a cyclodextrin polymer in packaging dates back from a decade ago. At that time, β-cyclodextrin and polyvinyl alcohol were cross-linked with glyoxal, following different procedures, to remove an undesirable product in food such as cholesterol (López-De-Dicastillo et al. 2011).

On the other hand, active films are designed to liberate chemicals encapsulated in them. In this case, cyclodextrin units are, for instance, grafted onto a modified polyamide, both by a non-covalent and a covalent cross-linking; in the presence of a template, two different synthetic polymers mixed produced a film capable to release chemicals using UV stimuli (Tan et al. 2016). One of the most sought characteristics for a packaging film is its antibacterial power. In order to achieve this potential, it is also feasible to integrate ZnO nanoparticles into polymer films (Andrade-Del Olmo et al. 2019). In this investigation, anionic cyclodextrin is added with chitosan layer by layer onto a poly-L-lactic acid-ZnO film to provide it the antibacterial ZnO properties but also with the ability to release carvacrol, plus the hydrophobicity from poly-L-lactic acid and the biodegradability provided by all the polymeric components. Another path to create an antibacterial film is to cross-link a sorbate/cyclodextrin complex, such that with sodium benzoate (Yang et al. 2019). By a green synthesis procedure, xylan, hydroxyethyl cellulose, and the complexed cyclodextrin molecules are cross-linked using citric acid. The resulting film possesses the desired mechanical properties, besides a low oxygen permeability and good antibacterial properties.

6.3.2 Cyclodextrin Polymers in Drug Delivery

The first reviewing of the potential applications of cyclodextrin polymers in the pharmaceutical industry was written by Fenyvesi (1988), and it was mainly based on cyclodextrin cross-linked with epichlorohydrin. The soluble cyclodextrin-epichlorohydrin

polymers were used for promoting the solubilization of several drugs. The first bioavailability study using a soluble cyclodextrin polymer was reported in the mid-1980s (Uekama et al. 1985). The absorption-promoting effect of the soluble cyclodextrin polymer on the sublingual route was also demonstrated in the case of steroids (Pitha et al. 1986). Karadake et al. (1982) showed that the drug release was retarded and the stability against oxidation and degradation was greatly increased when penicillin complexed with soluble cyclodextrin polymer was microencapsulated. In those years, the safety of these new materials was obviously a concern, so its innocuity was checked. Practically no hemolytic effects were observed when compared to natural or methylated cyclodextrins.

On the other hand, some applications of the insoluble cross-linked cyclodextrin polymer were also investigated. For instance, its effect on wound healing was tried on tissues of rats (Felméray et al. 1996). In addition, the cyclodextrin-epichlorohydrin sorption capabilities were tested for the removal of phenylalanine from a protein hydrolysate in order to make it digestible for children suffering from phenylketonuria (Specht et al. 1981). Also at that time, the effectiveness of a cyclodextrin polymer as a tablet disintegrant was studied in direct compression systems (Fenyvesi et al. 1984).

Those first attempts to show their capabilities in the sorption and release of aromatic model molecules pointed to the use of cyclodextrin polymers as controlled release agents (Friedman et al. 1989). Specifically, the release of cetylpyridinium chloride (an antimicrobial agent) and iodine, using cyclodextrin polymers, was patented in the late 1980s (Friedman 1988; Szejtli et al. 1988). An earlier example of a cyclodextrin polymer as a macromolecular carrier in the field of antitumor chemotherapy was published also in the mid-1980s (Kaji et al. 1985). In that work, a bifunctional delivery system composed of mixed micelles and a complex between the drug (1-hexylcarbamoyl-5-fluorouracil) and cyclodextrin polymer was tested.

The following decade showed only a few other distinct examples of the applicability of cyclodextrin polymers in the field of drug delivery. Thus, drugs complexed in cyclodextrin polymers were entrapped into liposomes. The latter present some problems in the accommodation of water-insoluble drugs in their lipid bilayers, so the new formulation using cyclodextrin polymer could circumvent such limitations (McCormack and Gregoriadis 1994). On the other hand, the need to prepare degradable materials for medical applications, including drug delivery, associating networks using cyclodextrin-epichlorohydrin polymers and degradable copolyesters containing adamantyl groups were tested and were shown to be pH sensitive (Cammas et al. 1999).

Cyclodextrin-based nanosponges, prepared by cross-linking reactions using either condensation or interfacial polymerization reactions, are biocompatible nanoporous nanoparticles. They have been designed in the last years to increase the dissolution rate, the solubility, and stability of drugs, to prolong the release time, and also applied in semisolid formulations for skin delivery (Ansari et al. 2011; Shende et al. 2013; Conte et al. 2014).

As mentioned above, cyclodextrin moieties can be incorporated to pre-existing polymeric materials via grafting reactions. In most of the drug delivery applications, cyclodextrins are attached to polysaccharides (Luzardo-Alvarez et al. 2014), such as

chitosan, for which the adsorption and release of a model drug (ketoprofen) were evaluated some time ago (Prabaharan and Mano 2005). Although cyclodextrin adds new drug inclusional properties to the polycationic polymer, a decrease in mucoadhesion of cyclodextrin-chitosan was observed, an effect attributed to the increase in the chain compaction caused by the cyclodextrin grafting (Venter et al. 2006). More recently, cellulosic substrates (uncoated and crepe paper and a medical bandage) were grafted by a cyclodextrin polymer to sustain the release of antibacterial agents (Cusola et al. 2013). Besides those polysaccharides, other materials such as poly(hydroxyethylmethacrylate) have also been grafted with β-cyclodextrin for its application in soft contact lenses conservation liquids and to sustain drug delivery in the lacrimal fluid (dos Santos et al. 2009). The use of some cyclodextrin polymers for therapeutics delivery was patented in 2013 (Cheng et al. 2013).

In the turn of the century, a new class of polymers for the delivery of macromolecular therapeutics arose (Gonzalez et al. 1999). Polymeric vectors for gene delivery and gene therapy, in contrast to viral vectors, avoid an immune response, and, in addition, they are capable of carrying nucleic acids of virtually any size. Thus, cationic cyclodextrin polymers used to bind deoxyribonucleic acid showed comparable or even better results to those obtained for polyethyleneimine. Thus, low molecular weight poly(ethylenimine) cross-linked by (2-hydroxypropyl)-β-cyclodextrin or (2-hydroxypropyl)-γ-cyclodextrin demonstrated its lower cytotoxicity and higher transfection efficiency for the delivery of plasmid deoxyribonucleic acid compared with those of poly(ethylenimine) (Huang et al. 2006). Another significant achievement has been, for instance, the use of a specific functional group such as folic acid grafted to poly(ethyleneimine)-cyclodextrin carriers, to target the tumor cells (Yao et al. 2009). Intranasal mRNA vaccination with the aid of a cationic cyclodextrin-poly(ethyleneimine) conjugate, capable of overcoming the nasal epithelial barrier, has also been recently proposed (Li et al. 2016b).

Drug release behavior can be modulated with the aid of stimuli-responsive polymers. Among them, poly(N-isopropylamide) has attracted much attention in the recent past because of its sharp and somewhat tuneable phase transition close to 32 °C, ideal for injectable clinical applications. Moreover, the design of interpenetrated networks permits to combine the temperature responsiveness of poly(N-isopropylamide) gels with the inclusional capabilities of cyclodextrin networks. For instance, a semi-interpenetrated network was prepared incorporating a water-soluble cyclodextrin-epichlorohydrin polymer into the poly(N-isopropylamide) hydrogel to find that the release rate of the model drug (ibuprofen) from the β-cyclodextrin containing gel was slower and the release time was greatly prolonged (Zhang et al. 2005). Another semi-interpenetrated network was prepared by the radical polymerization and cross-linking of N-isopropylacrylamide in the presence of β-cyclodextrin-grafted polyethylenimine. The propranolol release rate from the semi-interpenetrated network matrix was retarded because of the formation of complexes between the drug and the β-cyclodextrin moieties, and the release kinetics could be tuned by controlling the environmental temperature (Zhang et al. 2008). Interpenetrated

networks can also be used to develop new selective and synergistic sorption capacities for specific purposes such as a combined drug release (Fujiyoshi et al. 2019).

A remarkable pH-responsive behavior can be achieved using acrylic acid containing polymers. Thus, highly hydrophilic pH-sensitive networks which load large amounts of hydrophobic drugs with sustained release capabilities were prepared over 10 years ago by the copolymerization of cyclodextrin with acrylic monomers (Siemoneit et al. 2006). Other examples have been reported in the recent literature: highly pH-dependent swelling in graft cyclodextrin/acrylic acid copolymers for the delivery of ketoprofen (Wang et al. 2009) or mucoadhesive hydrogels by the cross-linking of poly(acrylic acid) with cyclodextrins for the controlled release of diflunisal and fluconazole (Kutyła et al. 2013). A biocompatible system based on guar gum, poly(acrylic acid) and β-cyclodextrin using a nontoxic cross-linker, and tetraethyl orthosilicate, for intestinal delivery of dexamethasone, has also been reported (Das and Subuddhi 2015).

In the last decade, triple-response (pH, temperature, and glucose) semi-interpenetrated hydrogels were prepared by polymerization in the presence of the magnetite (Fe_3O_4) nanoparticles, a cyclodextrin-epichlorohydrin polymer, and a cross-linker (Huang et al. 2012). These targeting hydrogels could control the release of quercetin by adjusting both the pH value and glucose concentration of the release media. More recently, a carboxymethyl-β-cyclodextrin polymer was grafted on the surface of chitosan-coated magnetite NPs by an emulsion chemical cross-linking method (Ding et al. 2015). The loading and release of 5-fluorouracil from these magnetic composites showed that these were promising targeted anticancer drug carriers for tumor therapies.

Finally, cyclodextrin polymers have also recently found applications in the field of regenerative medicine (Alvarez-Lorenzo et al. 2017). Bone and cartilage diseases are each day more challenging because of the increasing number of people affected. Vascular polyester and polyamide prostheses can be coated with grafted cyclodextrins that can be loaded with an antibiotic in order to reduce the risk of postoperative infections (Blanchemain et al. 2005). Polyvinylidene difluoride membranes can also be grafted with cyclodextrins to improve the capture and subsequent release of antiseptic agents (Tabary et al. 2007). Polyamide inguinal meshes (El Ghoul et al. 2008) or polypropylene abdominal wall implants for the prolonged delivery of ciprofloxacin (Laurent et al. 2011) have been prepared using citric acid as a cross-linker. Hydroxyapatite used in bone implants can also be functionalized with a cyclodextrin polymer for loading antibiotics (Hoang Thi et al. 2010; Taha et al. 2014). Recently, injectable hydrogels of polyelectrolyte complexes between chitosan and cyclodextrin polymers (both soluble and insoluble) have been rheologically tested to select those with a better performance in biomedical applications (Palomino-Durand et al. 2019).

As in the case of "monomeric" (both natural and derivative) cyclodextrins, an increasing number of publications can be found in the recent literature concerning cyclodextrin polymers. As Table 6.1 shows, many reviews have been published in the last 5 years, and the interested reader is referred to them to acquire a better idea of the goals this field of research is heading and the paths, or approaches, taken. In

Table 6.1 Recent reviews (2015–2019) on the applications of cyclodextrins and cyclodextrin polymers in pharmacy and biomedicine

Reference	Review title
Simões et al. (2015)	Supramolecular cyclodextrin-based drug nanocarriers
Osmani et al. (2015)	Cyclodextrin-based nanosponges: impending carters in drug delivery and nanotherapeutics
Wei and Yu (2015)	Cyclodextrin-functionalized polymers as drug carriers for cancer therapy
Gidwani and Vyas (2015)	A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs
Gonzalez-Gaitano et al. (2016)	Drug carrier systems based on cyclodextrin supramolecular assemblies and polymers: present and perspectives
Mejia-Ariza et al. (2017)	Cyclodextrin-based supramolecular nanoparticles for biomedical applications
Peng et al. (2017)	Polymeric nanocarriers based on cyclodextrins for drug delivery: host-guest interaction as stimuli-responsive linker
Adeoye and Cabral-Marques (2017)	Cyclodextrin nanosystems in oral drug delivery: a mini review
Alvarez-Lorenzo et al. (2017)	Cyclodextrins as versatile building blocks for regenerative medicine
Topuz and Uyar (2019)	Electrospinning of cyclodextrin functional nanofibers for drug delivery applications
Yao et al. (2019)	Cyclodextrin-based polymer materials: from controlled synthesis to applications
Zhang et al. (2019)	Cyclodextrin-based delivery systems for cancer treatment

addition to the reported references, some other recent reviews on new materials for pharmaceutical and biomedical applications also include a section on cyclodextrin-based systems (Larrañeta et al. 2018; Levack et al. 2018; Solanki et al. 2018).

6.4 Conclusion

Carbohydrates molecules, one of the most abundant products in nature, are present in animals, plants, bacteria, or fungi. These molecules show an enormous diversity: starch, cellulose, alginate, guar gum and other hydrocolloids, chitin and chondroitin, etc. Some of them can be easily modified, such as chitin into chitosan, in order to achieve improved characteristics to make them suitable for biomedical of food-related applications. Cyclodextrins, these peculiar cyclic oligosaccharides of bacterial origin, have been also applied in these fields. It was soon realized that, because of its encapsulation capabilities, immobilized cyclodextrins could be used in the food industry to improve taste, extract some nutrients or flavors, or, more recently, as constituents of the smart packaging of comestible products. The capabilities of the parent and modified cyclodextrins as carriers of substances of low solubility, such as most drugs, were exploited for

pharmaceutical applications as well. Exploring cyclodextrin polymers in drug delivery was not immediate because of the obvious concerns on biocompatibility and toxicity of those new materials.

The challenges cyclodextrin polymers face today mostly have to do with safety and cost, if their promising features, conscientiously proven in the thousands of investigations published so far, are expected to cross the bridge between academia and industry. Even though many of the raw cross-linking agents needed to prepare these cyclodextrin polymers are toxic, once the product is finished, it can be considered "clean." This new material obviously needs yet to be tested following the protocols applicable in each case, depending on their uses.

In many pharmaceutical applications, the final cost of the produced carriers will not be a concern if they are designed as "high-tech" smart gels or vectors suitable for some particular purposes. On the other hand, for food-related applications, cost is a major concern. For instance, a higher efficiency in the removal of a certain bitter agent will not justify the replacement of a low-cost sorbent with a somewhat lower performance.

Finally, among the features required for the new cyclodextrin polymers to be designed in the near future, sustainability is a must. The new materials, especially those designed for large-scale applications, need to be as "green" as possible. Natural cyclodextrins themselves do fulfil this criterion, and polymers made from them should also be produced by means of the new ways of doing chemistry in the twenty-first century.

Acknowledgments The authors wish to thank University of Navarra (PIUNA 2018-15) for the financial support, and MP gratefully acknowledges *Asociación de Amigos* (Universidad de Navarra) for his grant.

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Chapter 7
Role of Cyclodextrins in Nanoparticle-Based Systems for Drug Delivery

Abhishek Pandey

Contents

Abstract Pharmaceutical products continue to be developed for improved patient compliance, but the issue of hydrophobicity, low permeability, short half-life, and stability of various drugs always has been a challenging task for formulation development. Conventional formulations lack the features of prolong release of drug over an extended period of time and site-specific action. To resolve these issues, cyclodextrin has emerged as an exceptional pharmaceutical excipient with the features of bioavailability, nontoxicity, inclusion ability, and water solubility. Additionally, nanoparticles overcome the drawbacks associated with conventional formulations such as prolong release and site-specific action of active molecules. Cyclodextrins and chemically altered cyclodextrins in combination with certain polymers have sparked various researchers for exceptional advancements in the field of novel drug delivery. More recently, these substances have been incorporated in polymer systems to develop nanoparticles. Cyclodextrin conjugated nanoparticles offer synergistic advantages such as enhanced drug solubility, served as drug carriers to a

A. Pandey (✉)
School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_7

specific target site such as cancer cells with minimum toxicity to normal cells, greater surface area over microparticles, and higher stability over liposomes. Accordingly, nanoparticles based on cyclodextrins have gained notable interest, and a variety of nanoparticles have been developed since the last two decades.

This chapter review major critical research on cyclodextrin-based nanoparticles to explain their versatility and high potential for advanced drug delivery, protein and peptide drug delivery, and gene delivery. This chapter also highlights the role of cyclodextrins in specific types of nanoparticles such as gold, silver, and magnetic, polymeric, and lipid-based nanoparticles. Finally, pharmaceutical applications of amphiphilic cyclodextrin nanoparticles and miscellaneous administration routes of cyclodextrin-based nanoparticles are also discussed.

Keywords History · Nanoparticles · Pharmacy · Drug delivery · Protein · Peptides · Amphiphilic materials

Abbreviations

DNA	Deoxyribonucleic acid
MCF-7	Michigan Cancer Foundation-7
MDR1	Multidrug resistance protein 1
mRNA	Messenger ribonucleic acid
RNA	Ribonucleic acid
siRNA	Small interfering ribonucleic acid

7.1 Introduction

The presence of the hydrophobic cavity renders cyclodextrins able to form inclusion complexes. These molecules contribute distinguished advantages due to their novel architectural features to form inclusion complexes with several kinds of molecules like ions, protein, and oligonucleotides (Lysik and Wu-Pong 2003). Inclusion complexes are formed when the "guest" molecule usually a drug is partially or fully included inside the "host's cavity" (Szente and Szejtli 1999). Owing to the hydrophobic cavity, cyclodextrins as ghosts offer the guest a suitable environment for interaction (Fig. 7.1). The outer hydrophilic surface of cyclodextrins is compatible with water, which allows hydrogen bonding cohesive interactions (Challa et al. 2005).

In 1891, Villiers first discovered the cyclodextrins. He determined a crystal structure called "cellulosine" from the isolation of starch after the digestion by *Bacillus amylobacter*. Then, at the beginning of the nineteenth century, Schardinger described two crystalline dextrins (α-cyclodextrin and β-cyclodextrin), which were separated from bacterial digestion of potato starch (Schardinger 1903; Crini 2014).

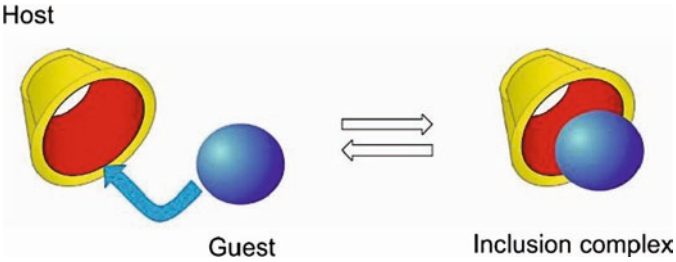

Fig. 7.1 Inclusion complex of cyclodextrins. A complex is formed when the "guest" molecule, such as a drug, is partially or fully included inside the host's cavity

Furthermore, Schardinger performed many experiments with cyclodextrins and was acknowledged as an originator of cyclodextrin chemistry by experts. In the decade of 1930, Freudenberg discovered γ-cyclodextrin, and he earned the credit of the first patent publication, including the first fundamental article on the role of cyclodextrins in drug formulations (Loftsson and Duchêne 2007). Till 1970 to present, cyclodextrin has been recognized as a valuable pharmaceutical excipient in the formulation development of numerous active pharmaceutical excipients, including novel drug delivery systems.

Therefore, to fulfill the need of the pharmaceutical industry for purified cyclodextrin, researchers have demonstrated several biotechnological techniques to obtain purified cyclodextrin products (Kurkov and Loftsson 2013). Literature reveals that cyclodextrins and their derivatives have been used in conventional and novel drug delivery systems such as emulsions, microspheres, liposomes, and nanoparticles. Following this, to overcome the issue of poor water solubility of natural cyclodextrins, several cyclodextrin derivatives were synthesized with the substitution of hydroxyl groups. Otherwise, cyclodextrins have been used to enhance the drug loading capacity of polymeric microspheres. Additionally, novel surface-active cyclodextrin derivatives have also been developed to impart a cutting edge in formulation development (Bilensoy et al. 2005).

Cyclodextrins and their derivatives have been successfully employed to create novel nanomaterials. More recently, these products have been incorporated in polymer systems to develop nanoparticles that are suitable in the solubility of the hydrophobic drug. Cyclodextrin conjugated nanoparticles offer numerous advantages such as enhanced drug solubility, serve as drug carriers to a specific target site such as cancer cells with minimum toxicity to normal cells, greater surface area over microparticles, and higher stability over liposomes.

This chapter discusses on cyclodextrin-based nanoparticles to explain their versatility and high potential for advanced drug delivery, protein and peptide delivery, and gene delivery. It also highlights the role of cyclodextrins in specific types of nanoparticles such as gold, silver, and magnetic, polymeric, and lipid-based nanoparticles. Additionally, pharmaceutical applications of amphiphilic cyclodextrin nanoparticles and miscellaneous administration routes of cyclodextrin-based nanoparticles are also discussed.

7.2 Cyclodextrin Nanoparticles as Drug Delivery System

Since the nineteenth century, extraordinary scientific work has been done to explore the pharmaceutical potential of cyclodextrins, and they have been the subject of numerous scientific literature; cyclodextrins have been used in the pharmaceutical industry since the 1970s with the first product prostaglandin E2/β-cyclodextrins (Prostarmon ETM sublingual tablet) marketed in Japan in 1976. Cyclodextrins offer notable advantages due to their unique ability to form inclusion complexes with a variety of organic and inorganic lipophilic molecules. Cyclodextrins act as true carriers by dissolving and delivering hydrophobic drug molecules through the aqueous exterior of lipophilic biological membrane barriers, e.g., mucosa. In general, only dissolved drug molecules can partition into the barrier and then penetrate through it. In addition, cyclodextrins are known to self-assemble to form nanosized aggregates in aqueous solutions and thus have the potential of being developed into novel drug delivery systems (Messner et al. 2010). This characteristic is promising for a broad range of nanotechnology domains such as drug delivery, cancer therapy, gene delivery, and biosensing.

Cyclodextrins are advantageous in drug delivery because the bucket-shaped cavity shields the drug from degradation and irritation is lessened at the administration site. Cyclodextrin-based nanoparticles facilitate a novel drug delivery system with the advantages of both components: the cyclodextrin molecules offer enhanced water solubility and drug loading, while the nanoparticles afford targeted drug delivery. Additionally, cyclodextrins can surmount the constraints of nanoparticles such as low encapsulation efficiency and drug loading. Cyclodextrin-based nanoparticles yield a novel drug delivery system with the advantages of both components: the cyclodextrin molecules offer enhanced water solubility and drug loading, while the nanoparticles afford targeted drug delivery.

7.2.1 Anticancer Drugs

Oral administration of paclitaxel is still considered one of the most suitable and safe modes of delivery. Hamada et al. (2006) studied the aqueous solubility behavior of anticancer agent paclitaxel employing 11 kinds of cyclodextrins and the bioactivity of the paclitaxel-cyclodextrin inclusion complex. They have reported that 2,6-dimethyl-β-cyclodextrin was most effective, and paclitaxel showed significant solubility in 2,6-dimethyl-β-cyclodextrin aqueous solution. Moreover, this inclusion complex revealed a 1.23-fold polymerization activity as paclitaxel in a tubulin assay. Cancer therapy is currently changing from a standardized systemic strategy to more personalized and precisely customized disease therapy. Such personalized treatments use multifunctional drugs in association with drug carrier systems to target the molecular level at a specific site.

Nanotechnology-based drug delivery system provides an exceptional platform for the delivery of anticancer agents in order to enhance their targeting ability and bioavailability. One of the main advantages of loading anticancer drugs into nanoparticles is to enhance their cellular uptakes by bypassing the different multidrug-resistant mechanisms. Nanoparticle-based targeting of tumor cells has emerged as a potential therapeutic arsenal against cancer. For example, paclitaxel isolated from *Taxus brevifolia* is a potent anticancer agent approved for the treatment of a large number of solid tumors. But its hydrophobic nature results in low bioavailability.

Therefore, to overcome the issue of hydrophobicity, Bilensoy and co-workers have developed amphiphilic cyclodextrin as a nanoparticulate carrier system for paclitaxel drug delivery. This yielded nanospheres via nanoprecipitation technique with good cytotoxicity against L929 cells and was well studied using atomic force microscopy micrographs (Bilensoy et al. 2008a, b). Further studies demonstrated high encapsulation efficiency and a threefold increase in the loading capacity of nanoparticles when formed directly from the inclusion complex. Prolonged release rates for the drug were obtained: 12 h for nanospheres and 24 h for nanocapsules. In another approach Agüeros et al. (2009) investigated the concept of utilizing cyclodextrin-polyanhydride nanoparticles for oral delivery of paclitaxel. The addition of cyclodextrin increases the solubility by developing an inclusion complex, and the use of polyanhydride enhances the intestinal permeability. Additionally, they have also performed oral bioavailability studies in rodents by producing a synergistic effect using three distinct cyclodextrins, particularly β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and 6-mono-deoxy-6-monoamino-β-cyclodextrin in the combination of polyanhydride nanoparticles.

7.2.2 Proteins and Peptides

Various problems associated with the practical use of therapeutic peptides and proteins are their chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, peculiar dose-response curves, and immunogenicity. Cyclodextrins, because of their adaptability in pharmaceutical use and ability to interact with cellular membranes, can act as potential carriers for the delivery of proteins, peptides, and oligonucleotide drugs (Irie and Uekama 1997). The combination between cyclodextrins and nanoparticles can also be of interest for the delivery of proteins and peptides. Cyclodextrin complexation represents an effective strategy for improving protein therapy by stabilizing them against aggregation, thermal denaturation, and degradation. Proteins are mostly hydrophilic and too bulky to be wholly included in the cavity of cyclodextrins. Nevertheless, the hydrophobic side chains in the peptides may penetrate into the cavity of the oligosaccharide, leading to the formation of non-covalent inclusion complexes, which improves the stability of proteins.

Da Silveira et al. (1998) have prepared and evaluated nanoparticulate systems of progesterone composed of poly(isobutyl cyanoacrylate) and cyclodextrins for enhancing the loading of the particles with substances. The nanoparticles were synthesized by polymerization of isobutyl cyanoacrylate in the presence of cyclodextrins or progesterone/hydroxypropyl-β-cyclodextrin complex. The particle size, zeta potential, and loading capacity of the particles were determined. The authors have demonstrated that nanoparticles could be efficiently prepared in the presence of cyclodextrins. Additionally, an increase in hydroxypropyl-β-cyclodextrin concentration resulted in small nanoparticles of size less than 50 nm. It was also observed that the addition of a higher concentration of cyclodextrins yields a 50-fold increase in progesterone loading compared to nanoparticles prepared without cyclodextrins. The poly(isobutyl cyanoacrylate)-cyclodextrin nanoparticles were delineated by the presence of many lipophilic sites belonging to the cyclodextrins which were tightly attached to the structure of the particles.

Sajeesh and Sharma (2006) reported the formulation development and evaluation of an oral insulin delivery system based on hydroxypropyl-β-cyclodextrin insulin complex encapsulated in polymethacrylic acid-chitosan-polyether (polyethylene glycol-polypropylene glycol copolymer). They have formulated the nanoparticles by the free radical polymerization of methacrylic acid in the presence of polymer chitosan and polyether in a solvent-/surfactant-free medium. Hydroxypropyl-β-cyclodextrin was incorporated to prepare a non-covalent inclusion complex with insulin. Furthermore, hydroxypropyl-β-cyclodextrin complexed insulin was entrapped into nanoparticles by diffusion filling technique, and their in vitro release profile was assessed at different pH. They found that nanoparticles exhibited satisfactory insulin encapsulation efficiency and pH-dependent release profile. An enzyme-linked immunosorbent assay study illustrated that insulin encapsulated inside the particles was biologically active. The mucoadhesive study of prepared nanoparticles was conducted using freshly extracted rat intestinal mucosa, and the nanoparticles were observed fairly adhesive to the mucosal membrane.

Recently, researchers have been focused on the nasal mucosa as an alternative route to the oral and parenteral routes, because it offers advantages such as large absorptive surface area and the high vascularity of the nasal mucosa, which facilitate direct passage of drug into the systemic circulation, thereby bypassing first-pass liver metabolism. However, the bioavailability of intranasally administered peptide and protein drugs may be low due to their high molecular weight and hydrophilicity (Merkus et al. 1991). Cyclodextrin has the ability to form non-covalent inclusion complexes with a large variety of drugs/proteins. Moreover, cyclodextrins are believed to enhance nasal absorption of peptides by opening tight junctions and/or solubilizing membrane components (Merkus et al. 1999).

Hyperbranched polyglycerols are readily available, highly water soluble, biocompatible, and stable polymer. Therefore, to explore these properties of hyperbranched polyglycerols, Zhang et al. (2011) fabricated a cyclodextrin and hyperbranched polyglycerols coupling based novel nanoparticle system to enhance the nasal transport of insulin. Insulin-loaded hyperbranched polyglycerol-β-cyclodextrin nanoparticles of size ranging from 198 to 340 nm with a positive

charge were prepared. The nanoparticles showed a prominent capacity of incorporating insulin. In vitro release study showed significant release rate of insulin under acidic conditions than physiological conditions. In vitro cytotoxic evaluation against Caco-2 cells exhibited that hyperbranched polyglycerol-β-cyclodextrin had significant biocompatibility. Moreover, the capacity of hyperbranched polyglycerol-β-cyclodextrin nanoparticles to penetrate the nasal mucosal epithelia was proved by confocal laser scanning microscopy.

Three alkyl carbonates of γ-cyclodextrin (hexyl-,octyl-, and dodecyl-carbonate) have also been examined as a formulation additive to prepare solid nanoparticles for the effective delivery of progesterone. They have developed spherical nanoparticles in the size range of 80–200 nm. The prepared nanoparticles when subjected to evaluation showed negative surface charges and extended release rate of progesterone (Cavalli et al. 2007). Glutathione is the main thiolated small peptide in mammalian cells. It possesses reducing and nucleophilic properties which enable glutathione a key redox buffer to inhibit the oxidative damage caused by free radicals. Glutathione is used for the treatment of drug poisoning and protection against cytotoxic chemotherapy and radiation trauma. However, its clinical use encounters many hurdles associated with its low and variable oral bioavailability, non-enzymatic pH-dependent oxidation, and chemical and enzymatic degradation of the peptide in the jejunum. Hence, inclusion and preservation of glutathione into conventional pharmaceutical dosage forms are challenging tasks Currently, glutathione is only available on the market as parenteral dosage forms (Gluthion) (Langie et al. 2007). Therefore, to resolve these issues, Trapani et al. (2010) have developed new nanoparticles containing chitosan or cyclodextrin and evaluate their potential for oral delivery of the peptide glutathione. More precisely, nanoparticle formulations composed of chitosan, chitosan/alpha-cyclodextrin, and chitosan/sulphobutylether-β-cyclodextrin were investigated for this application. They have demonstrated that by selecting the most suitable cyclodextrin, physicochemical characteristics of the nanoparticles and their ability to load glutathione can be altered. Chitosan nanoparticles containing the anionic cyclodextrin sulfobutylether 7 m-β-cyclodextrin seem to be significant potential oral glutathione carriers, as they combine enhanced glutathione loading along with the ability to improve glutathione permeabilization through the intestine, as observed in a frog intestinal sac model.

Zhang et al. (2009) have demonstrated the feasibility of chitosan bearing β-cyclodextrin nanocomplexes for controlled protein release. Briefly, chitosan bearing β-cyclodextrin nanocomplexes was fabricated by a single-step scheme with *N*-succinylated chitosan and mono(6-(2-aminoethyl)amino-6-deoxy)-β-cyclodextrin along with water-soluble carbodiimide. The results of in vitro cytotoxicity against NIH 3 T3 cells confirmed that prepared nanocomplexes have not cytotoxic effect. In conclusion, these results proved chitosan bearing β-cyclodextrin copolymer as a novel carrier for controlled protein release.

More recently, He et al. (2019) reported a novel oral protein delivery system of ovalbumin with improved intestinal permeability and enhanced antigen stability. The delivery system based on the combination of chitosan nanoparticles and antigen-cyclodextrin inclusion complex was prepared by a precipitation/

coacervation method. Results of the in vivo study of nanoparticles revealed that ovalbumin-loaded cyclodextrin/chitosan nanoparticles possess the capacity to induce an intestinal mucosal immune response.

7.3 Cyclodextrin Nanoparticles as Gene Delivery Systems

Gene therapy as an option to conventional drug therapy paves the new way for the treatment of both genetic and inherited diseases, such as hemophilia, cystic fibrosis, and cancers. The efficacy of a viral or non-viral vector directly determines the benefit of gene therapy. Gene therapy offer advantages over conventional protein therapy such as improved bioavailability and reduced systemic toxicity. Therefore, to avoid the toxicity issue of viral vectors, researchers have developed cyclodextrin-based nanoparticles as non-viral vectors. The unique characteristic of the presence of two well-differentiated faces in the cyclodextrins, specifically the narrower rim owning the primary hydroxyl groups and the wider rim positioning two chemically distinct sets of secondary hydroxyls, is an intrinsic characteristic of this family of cyclo-oligosaccharides that classifies them as genuine Janus (the Roman god of doorways and passages, depicted with two faces on opposite sides of his head) molecular nanoparticles.

In 1999, Gonzalez et al. (1999) published the first report of the synthesis of the cationic cyclodextrin polymers and the characterization of the cationic cyclodextrin nanoparticles loaded with plasmid DNA including their in vitro transfection efficiency. Teijeiro-Osorio et al. (2009) first reported the potential of a new generation of hybrid polysaccharide nanocarriers composed of chitosan and anionic cyclodextrins for gene delivery to the airway epithelium. They investigated hybrid polysaccharide nanocarriers to evaluate their ability to penetrate epithelial cells and improve gene expression in the Calu-3 cell culture model. Furthermore, hybrid chitosan and anionic cyclodextrin nanoparticles were developed and loaded with plasmid DNA model that encodes the expression of secreted alkaline phosphatase. Results of cellular uptake studies revealed that the nanoparticles were efficiently internalized by the cells and confirm their potential as gene vectors. The transfection ability of the various nanoparticle formulations showed a significantly higher response than the naked DNA (control). This resulted in enhanced delivery of DNA and reduces the otherwise high levels of protein expression in the respiratory mucosa.

Similarly, cyclodextrin-based polycations have also been studied for nucleic acid delivery. Park et al. (2006) have demonstrated a new strategy for surface-mediated gene delivery based on inclusion complex formation between the solid surface and delivery carrier. The complexation ability of β-cyclodextrin molecule was utilized to especially immobilize cyclodextrin-modified polyethylenimine nanoparticles, on adamantane-altered self-assembled monolayers. Cyclodextrin-modified polyethylenimine nanoparticles are particularly immobilized on the chip surface by cyclodextrin-adamantane inclusion complex formation. The results of competition studies with free cyclodextrins showed multivalent interactions between

cyclodextrin-modified polyethylenimine nanoparticles and the adamantane-modified surface results in tremendous binding affinity. Therefore, the ability of cyclodextrin-modified polyethylenimine nanoparticles to form inclusion complexes can be employed to achieve specific, high-affinity loading of delivery carriers onto solid surfaces.

Huntington's disease is an uncommon autosomal neurodegenerative disease provoked by the expression of a toxic huntingtin protein. The huntingtin gene renders instructions for producing a protein called huntingtin. This protein plays a vital role in neurons in the brain and is essential for healthy growth before birth. The application of short interfering RNAs (siRNAs) is a promising approach to restrict the mutation of protein. The main hindrance in siRNA-based strategies is the lack of efficient and nontoxic transportation vectors to ensure target delivery to the nervous system. This stimulated Godinho et al. (2013) to develop modified amphiphilic β-cyclodextrins as novel siRNA neuronal carriers. The results showed that the cyclodextrin formed nanosized particles were stable in artificial cerebrospinal fluid. Furthermore, these complexes significantly reduced the expression of the *huntingtin* gene in rat striatal cells and human Huntington's disease primary fibroblasts. These findings firmly support the utility of modified β-cyclodextrins as safe and effective siRNA delivery vectors (Godinho et al. 2013).

Since the past few years, several strategies of low and high molecular weight polyethylenimines have been attempted for safe and effective DNA and siRNA delivery but were limited by transfection and cytotoxic activity. Therefore a copolymer-based delivery system has been developed by researchers. Ping et al. (2011) synthesized chitosan-graft-polyethylenimine-β-cyclodextrin copolymers for DNA and siRNA delivery. These two hydrophilic cationic copolymers were fabricated by a reductive amination reaction between oxidized chitosan and low molecular weight polyethylenimine-modified β-cyclodextrin. Furthermore, the characterization of nanoparticles was carried out by proton nuclear magnetic resonance spectroscopy and gel permeation chromatography. These polycations displayed significant ability to condense both plasmid DNA and small interfering RNA into compact and spherical nanoparticles. Additionally, both polymers delineate improved gene transfection activity performance in comparison with native CTS in HEK293, L929, and COS7 cell lines.

In the past decade, low and high molecular weight polyethylenimines have been extensively studied for DNA and siRNA delivery but have faced challenges of transfection and cytotoxic activity. A new strategy was suggested where polyplexes formed between polymers and DNA were further enhanced by the addition of β-cyclodextrin. In another laboratory work to facilitate the delivery of siRNA, cationic cyclodextrin conjugated with poly(ethylene glycol) (PEG) chain to expedite the attachment of targeting group anisamide. Parenteral administration of anisamide-tagged PEGylated cyclodextrin nanoparticles presented notable tumor inactivation with diminished toxicity when investigated preclinically in a rodent prostate tumor model. Hence, serving as an excellent drug delivery system of siRNA delivery for prostate cancer therapy (Guo et al. 2012). The siRNAs generally exhibit weak cell

penetration with limited stability; the inclusion of cyclodextrins as a key excipient can aid in the delivery of oligonucleotides.

Accordingly, in light of these facts, Méndez-Ardoy et al. (2011) developed and evaluated polycationic amphiphilic cyclodextrins along with nucleic acids as therapeutic gene vectors for in vivo purpose. Briefly, a tetradecacationic structure consisting of 14 primary amino groups and 7 thioureido groups in the primary face of the cyclodextrin core and 14 hexanoyl chains in the second face was assessed for therapeutic gene delivery. The results obtained delineate that polycationic amphiphilic cyclodextrins having the capacities of self-assembling as a nanosystem for gene delivery, and when evaluated on HeLa and HepG2 cells, exhibited significant cell death with reduced toxicity. Furthermore, in vivo experiments performed on rats correlated with previous results that revealed high transfection levels in the liver with reduced toxicity. Usually, acquired resistance to a cytotoxic agent is mediated by overexpression of a membrane-associated protein that encodes via multidrug resistance gene-1.

Zokaei et al. (2019) recently developed chitosan β-cyclodextrin complexes as a tropical agent. These polymer cyclodextrin complexes loaded with the mRNA-cleaving DNAzyme that targets the mRNA of the multidrug resistance protein 1 (MDR1) gene in the doxorubicin-resistant breast cancer cell line. Results proved the downregulation of MDR1 mRNAs in MCF-7/DR/DNZ by a real-time polymer chain reaction, compared to the MCF-7/DR as control. Additionally, the results of the water-soluble tetrazolium salt 1 (WST1) assay displayed a significant decrease in drug resistance in mRNA-cleaving DNAzyme-treated cells 24 h after transfection. To sum up, results substantiate chitosan β-cyclodextrin complexes in association with chemotherapy drug for cancer therapy as well as notably valuable at the delivery of DNAzyme in reviving chemosensitivity.

7.4 Role of Cyclodextrin in Magnetic Nanoparticles

The most common class of substances used in the fabrication of theranostic nanostructures is carbon nanotubes, graphene, up-converting nanoparticles, and gold nanostructures. Nevertheless, the issue of nanotoxicity, complicated and time-consuming synthetic procedures, and poor stability represents the main obstacles for the therapeutic application of these nanomaterials. Therefore, magnetic nanoparticles offer several advantages over other types of nanomaterials, such as narrow size distribution, high colloidal stability, low toxicity, and high specific surface area to render them suitable for biomedical applications (Ahmed et al. 2014). Additionally, magnetic nanoparticles displayed the phenomenon of superparamagnetism: they are promptly magnetized under the influence of the external magnetic field and vice versa. This unique characteristic facilitates easy magnetic separation, removal, and recovery of magnetic nanoparticles. The before-mentioned magnetic property allows the nanoparticles to localize at the targeted site in vivo in response to the externally applied magnetic field. Silica is generally added to the surface of the

nanoparticles to prevent their oxidation which leads to demagnetization which subsequently maintains the stability of magnetic nanoparticles.

Furthermore, to explore the versatility of magnetic nanoparticles, cyclodextrins are added into the silica-coated surface of the magnetic nanoparticles via linkers such as 3-aminopropyltriethoxysilane. Thus, allowing cyclodextrin to function as a carrier for numerous active pharmaceutical ingredients, proteins, and cell-targeting ligands on the surface of the magnetic nanoparticles. Moreover, it also prevents premature drug release into non-target regions. Wang et al. (2003) first proved the role of cyclodextrin to enhance the stability of magnetic nanoparticles in an aqueous medium. They have modified the surface properties of these nanoparticles through the formation of an inclusion complex between surface-bound surfactant molecules and α-cyclodextrin, thus improving its dispersion for a longer period in water. Furthermore, Xia et al. (2007) reported a simple pathway to synthesize water-soluble Fe_3O_4 nanoparticles with a surface-surrounded layer by incorporating cyclodextrin, polyethylene glycol, and nonylphenol ether in water. Additionally, a method for fabricating cyclodextrin concentration-dependent nanostructured spherical aggregates from individual magnetic nanoparticles was also described. This method is very significant because it instantly produces water-soluble magnetic nanoparticles and is useful for biomedical applications of magnetic nanoparticles.

To investigate the efficiency of cyclodextrin-based magnetic nanoparticles as a carrier for hydrophobic drug delivery, Banerjee and Chen (2007) have developed cyclodextrin-citrate-gum Arabic modified magnetic nanoparticles. Briefly, magnetic nanoparticles were synthesized by grafting the citrate-modified cyclodextrin along with gum Arabic modified magnetic nanoparticles through carbodiimide activation. The cyclodextrin grafting was validated by Fourier transform infrared spectroscopy. The practicability of using this novel formulation as a vehicle for hydrophobic drug delivery was described by examining the formation of the inclusion complex and the in vitro release profile using ketoprofen as standard hydrophobic drug delivery. The results of the experimental study showed that cyclodextrin-citrate-gum Arabic modified magnetic nanoparticles exhibited a considerable adsorption capability for ketoprofen as compared to gum Arabic modified magnetic nanoparticles. Therefore, this system seems to be a very promising vehicle for the administration of hydrophobic drugs.

A decade later, Chen et al. (2017) have amalgamated double-layer polymer-coated magnetic targeted nanoparticles (coated with β-cyclodextrin and polymer chitosan) to ensure stability and biocompatibility of the nanoparticles and effective drug delivery of ibuprofen, a hydrophobic drug delivery. They noted that nanocarriers exhibited sufficient magnetic properties, high drug loading capacity, and significant in vitro drug release. In conclusion, the cyclodextrin chitosan-coated magnetic nanoparticles represent a promising nanocarrier for the delivery of hydrophobic drugs. Recently, the same authors have proposed a new approach for the production of β-cyclodextrin-based magnetic nanocarriers via a molecular docking technique. Fe_3O_4 magnetic nanoparticles surface-modified with β-cyclodextrin and its derivatives, carboxymethyl-β-cyclodextrin, and maleated-β-cyclodextrin, respectively, were manufactured via a layer-by-layer approach, incorporating carmofur, an

antineoplastic agent, as a model drug. The results of loading and release studies were similar to the previously reported literature. Herein the introduction of the molecular docking technique establishes a method to fast select an effective β-cyclodextrin-based surface coating for the development of high-performance magnetic nanoparticles (Chen et al. 2019).

During the last decade, researchers published numerous designings and preparation techniques of cyclodextrin-functionalized superparamagnetic nanoparticles by conjugating cyclodextrin units onto the surface of magnetite nanoparticles. Similarly, in one of the notable contributions, Lu and co-workers have explained an innovative protocol for the development of cyclodextrin-based magnetic nanoparticles intending to establish their wide variety of biomedical applications as targeted drug delivery vehicles. Briefly, Li et al. (2011) fabricated superparamagnetic β-cyclodextrin-functionalized composite nanoparticles with core-shell compositions via cross-linking reaction (by using epichlorohydrin as cross-linking agent) on the surface of carboxymethyl β-cyclodextrin-modified magnetite nanoparticles. This strategy ensures that the innermost magnetite nanoparticles could sense and react to an externally applied magnetic field. Additionally, the outermost cyclodextrin moiety represents an inclusion site for drugs. Luo et al. (2012) developed a novel redox responsive controlled drug release system based on magnetic nanoparticles to provide efficient intracellular anticancer drug delivery. Disulfide bonds are employed as intermediate linkers to immobilize polyethylenimine/β-cyclodextrin molecules as nanoreservoirs for drug loading onto magnetic nanoparticles. The endocytotic pathway and endosomal escape of the smart controlled drug release system are proposed as an end result. Badruddoza et al. (2013) synthesized highly uniform silica-coated iron oxide (Fe_3O_4) magnetic nanoparticles and cross-linked them with carboxymethylated-β-cyclodextrin, intending to equip magnetic nanoparticles with drug storage and delivery carrier. These magnetic nanoparticles contributed quadruple features of magnetism, luminescence, cell targeting, and hydrophobic drug delivery. These magnetic nanoparticles included functionalities of fluorescence labeling by fluorescent dye-conjugated and a common cancer-targeting ligand, folic acid, that Banerjee's magnetic nanoparticles lacked. Preliminary outcomes of this study recommend that such magnetic nanoparticles can be a smart *theranostic* candidate for an optically trackable, cancer cell-targeting, and delivery vehicle of the hydrophobic drug delivery (all-trans-retinoic acid), loaded in cyclodextrin moiety. Ding et al. (2015) developed a novel hydrogel of poorly soluble drug 5-fluorouracil, based on chitosan-cross-linked carboxymethyl-β-cyclodextrin polymer-modified Fe_3O_4 magnetic nanoparticles intending to explore the inclusion abilities of cyclodextrin hydrophobic cavity with this insoluble anticancer drug through host-guest interactions. Experimental results showed that the nanocarriers displayed a high loading efficiency and pH-dependent swelling and diffusion-controlled drug release. This report tentatively proposed the mechanism of 5-fluorouracil encapsulated into the magnetic chitosan nanoparticles.

The literature reveals that the Food and Drug Administration has approved more than 150 chemotherapeutic agents for cancer treatment. But, most of these drugs exert cytotoxic action on tumors as well as normal cells and cause severe adverse

effects on the patients. Additionally, numerous anticancer agents have poor solubility and stability in the aqueous and biological system. Several researchers have developed some novel approaches to ensure the safe and effective delivery of such chemotherapeutic agents. Cyclodextrins can be associated with iron oxide magnetic nanoparticles to increase their stability and dispersion in water. Anirudhan et al. (2015) have developed magnetic nanoparticles of anticancer drug 5-fluorouracil, which is used to treat breast, stomach, and lung cancer and has detrimental effects on normal cells, as it is not targeted specifically for the tumor cells. The authors prepared 3-methacryloxypropyltrimethoxysilane-coated magnetic nanoparticles polymerized with glycidylmethacrylate-grafted-maleated cyclodextrin in the presence of ethylene glycol dimethacrylate as cross-linker and a′-azobisisobutyronitrile as initiator. The prepared nanoparticles exhibited significant antimicrobial activity against gram-positive and gram-negative bacteria. The cytotoxicity studies were also performed using MCF-7 (human breast carcinoma) cells and observed that prepared nanoparticles are biocompatible and provide sustained and controlled release of drugs to the targeted site. To overcome the hindrances of earlier reported methods of targeted drug delivery, Enoch et al. (2018) synthesized β-cyclodextrin-based magnetic nanoparticles. Briefly, manganese ferrite nanoparticles were synthesized by coating with β-cyclodextrin-modified polyethylene glycol as a vehicle for the anticancer drug camptothecin. The fabricated nanoparticles showed superparamagnetic behavior. Further research showed that coating the magnetic nanoparticles with the cyclodextrin-tethered polymer improves the drug loading capacity and sustained drug release. Additionally, cytotoxicity is also enhanced when the drug is incorporated in the polymer-coated magnetic nanoparticles.

Nowadays mild acid response nanodrug delivery system has been gaining attention in the research of drug delivery based on the responsive property to the abnormal physiological environment and to the normal physiological environment. However, it lacks the site-specific action. In light of these facts, Wang et al. (2018) fabricated a magnetic and pH-sensitive composite nanoparticulate system prepared by double emulsion technique (Fig. 7.2) and incorporating acetylated β-cyclodextrin as a key ingredient to recognize the pH response and Fe_3O_4 as a component to realize magnetic response. Results showed irreversible pH response property and reversible magnetic responsive properties at different pH environment for the

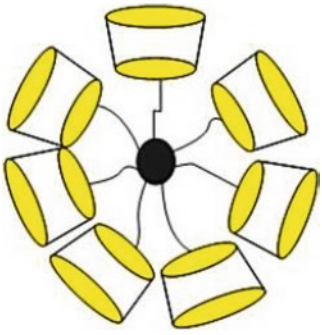

Fig. 7.2 Cyclodextrin-based metal gold and silver nanoparticles. Cyclodextrin attached to a metallic core using a linker such as adamantane which forms a strong stable complex with the cyclodextrin molecules

composite nanoparticle. Mrówczyński et al. (2018) developed polydopamine-coated magnetic nanoparticles of doxorubicin combined with mono-6-thio-β-cyclodextrin for cancer therapy. The hepatic cancer cellular uptake of doxorubicin-loaded nanoparticles was investigated by confocal imaging microscopy, and the significant anticancer effect of magnetic nanoparticles was observed.

7.5 Role of Cyclodextrin in Polymeric Nanoparticles

Polymeric nanoparticles are both biocompatible and biodegradable, so the fate of the nanoparticles in biological system is not a concern. Examples of natural and synthetic polymers used in the nanoparticles are chitosan, polyethylene glycol, poly (lactic acid), and poly (lactic-co-glycolic acid) poly(cyanoacrylates). The inclusion property of cyclodextrin renders polymeric nanoparticles to conveniently deliver hydrophobic molecules to the targeted site by encapsulating the drugs in the hydrophobic cyclodextrin cavity. The polymeric nanoparticles have cyclodextrin casting outer shells, while the core of the polymeric nanoparticles is composed of natural or synthetic polymer. Thus, the drugs can be loaded in the core of the polymeric nanoparticles, or it can be conjugated with the cyclodextrin in the outer shell. Nanoparticulate systems can be prepared either by dispersion of preformed polymers or polymerization. Among the polymers used in the nanoparticle preparation is poly(cyanoacrylates) which are particularly interesting, because of their biodegradability and very simple polymerization process. One of the major drawbacks of this type of nanoparticle is related to the difficulty of entrapping in hydrophobic drugs.

Da Silveira et al. (1998) first proposed cyclodextrin to overcome this problem. The authors proposed possibility of preparing nanoparticles of poly(isobutyl cyanoacrylate) in the presence of hydroxypropyl-β-cyclodextrin by anionic polymerization of isobutyl cyanoacrylate. Later, Ren et al. (2009) dissolved adamantane-end-capped poly(ε-caprolactone) and poly(vinylpyrrolidone)-cyclodextrin in *N*-methyl-2-pyrrolidone, a common solvent for both polymers. Further addition of this mixed polymer solution in solvent results in self-assembled polymeric nanoparticles. The same year, Zhang and Ma (2009) reported synthesis of polymeric core-shell assemblies based on inclusion complexes of a wide variety of poorly soluble drugs such as indomethacin and coumarin as guest molecules with a polyaspartamide copolymer composed of a block carrying cyclodextrin units and a polyethylene glycol block (polyethylene glycol-β-cyclodextrin). Subsequently incubation of these assemblies in buffer medium provides a prolong release of these compounds. The chronological summary of various major cyclodextrin-based polymeric nanoparticles is illustrated in Table 7.1.

Table 7.1 Formulation of various cyclodextrin-based polymeric nanoparticles loaded with pharmaceuticals including natural compounds and techniques of drug inclusion to facilitate the improved drug stability and sustained, controlled, and targeted drug delivery including encapsulation of hydrophilic and hydrophobic compound

Polymer	Cyclodextrin	Pharmaceuticals	Technique	Outcomes offered by cyclodextrin-based polymeric nanoparticles	Reference
Chitosan	Hydroxypropyl-β-cyclodextrin	Triclosan and furosemide	Ionic cross-linking of technique	Potential for transmucosal delivery of hydrophobic compounds	Maestrelli et al. (2006)
Chitosan	Carboxymethyl-β-cyclodextrin	Insulin and heparin	Ionotropic gelation technique	Facilitate fast or sustained delivery of macromolecules	Krauland and Alonso (2007)
Chitosan	Carboxymethyl-β-cyclodextrin and sulphobutyl ether-β-cyclodextrin		Mild ionic cross-linking technique	Improved stability and ability to encapsulate hydrophilic and hydrophobic compound	Trapani et al. (2008)
Glycol chitosan	Beta-cyclodextrin and derivatives	Laser dye 6-coumarin	Mild ionic gelation technique	Promising for studying intracellular nanoparticle uptake	Trapani et al. (2009)
Chitosan	β-Cyclodextrin	Glutathione	Complex formation	Facilitate oral administration of small peptides.	Trapani et al. (2010)
Chitosan	Cationic β-cyclodextrin	Insulin	–	Facilitates slow-release oral delivery of insulin and protection from gastric environment	Zhang et al. (2010)
Chitosan-polyacrylic acid	β-Cyclodextrin	Paclitaxel	Polymerizing acrylic acid and β-cyclodextrin substituted acrylic acid in chitosan solution	Controlled release of the drug at different pH range	Wang et al. (2012)

(continued)

Table 7.1 (continued)

Polymer	Cyclodextrin	Pharmaceuticals	Technique	Outcomes offered by cyclodextrin-based polymeric nanoparticles	Reference
Chitosan	Carboxymethyl-β-cyclodextrin	Sulindac	Ionotropic gelation technique	Encapsulation of sulindac and continuous release of the drug throughput 24 h	Ammar et al. (2012)
Chitosan	Sulfobutylether-β-cyclodextrin	Econazole nitrate	Ionotropic gelation technique	Controlled delivery of drug to the eye	Mahmoud et al. (2011)
Chitosan	Carboxymethyl-β-cyclodextrin	Indomethacin	–	Controlled drug release and biodegradability	Anirudhan et al. (2013)
Chitosan	Mono-6-deoxy-6-(p-toluenesulfonyl)-β-cyclodextrin	Ketoprofen	Ionic gelation technique	Controlled release of poorly water-soluble drugs with pH-responsive capability	Yuan et al. (2013)
Chitosan	Sulfobutylether-β-cyclodextrin	Quercetin	Conotropic gelation technique	Anti-quorum sensing or antibacterial activities	Nguyen and Goycoolea (2017)
N-maleoyl chitosan	β-Cyclodextrin	Ketoprofen	Ionic gelation method	Sustained release of poorly water-soluble drugs	Hou et al. (2017)
Chitosan	β-Cyclodextrin	Carvacrol and linalool	Kneading method	A promising carrier for botanical pesticides	Campos et al. (2018)
Chitosan	β-Cyclodextrin	Ovalbumin	Precipitation/coacervation method	A promising antigen delivery system for oral vaccination	He et al. (2019)
Polyethylene glycol and polyethylenimine	β-Cyclodextrin	5-Fluorouracil		Anticancer drug delivery in tumor therapy.	Prabha and Raj (2016)
Polyethylene glycol	Amphiphilic cyclodextrins	Short interfering RNA		Improved stability and reduced clearance	Godinho et al. (2014)
Polyethylene glycol	Modified β-cyclodextrin and derivatives	Short interfering RNA		Efficient cellular uptake, gene-knockdown ability	Gooding et al. (2015)

Poly lactic acid	Mono (6-(2-aminoethyl) amino-6-deoxy)-beta-cyclodextrin	Bovine serum albumin	Double emulsion method and nanoprecipitation method	Improved encapsulation and stability of bovine serum albumin	Gao et al. (2005)
Poly lactic acid	β-Cyclodextrin	–	Nanoprecipitation method	Well-defined core-shell nanoparticles with a shell able to protect the hydrophobic PLA core	El Fagui et al. (2011)
Poly lactic acid	Hydroxypropyl-β-cyclodextrin	Doxorubicin	Double emulsion method and nanoprecipitation method	Significant anticancer activity	Wang et al. (2011)
Poly (lactic acid and glycolic acid)	β-Cyclodextrin	Oxaprozin	Double-emulsification method	Cyclodextrin complexation promotes and regulates drug release	Mura et al. (2010)
Poly (lactic acid and glycolic acid)	β-Cyclodextrin	Docetaxel	Double-emulsification method	Targeted delivery of docetaxel to cancer cells	Bu et al. (2015)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Puerarin	Emulsion solvent evaporation technique	Targeted delivery of puerarin nanoparticles to brain injury induced by ischemic reperfusion	Tao et al. (2013)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Fisetin	Simple coacervation technique	Improved anticancer activity and oral bioavailability	Kadari et al. (2017)
Poly (lactic acid and glycolic acid)	Hcyclodextrin	Erlotinib	Multiple emulsion solvent evaporation	Improved therapeutic efficacy against non-small cell lung cancer cells	Vaidya et al. (2019)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Methotrexate	Double emulsion method	Controlled drug release	Gorjikhah et al. (2017)

(continued)

Table 7.1 (continued)

Polymer	Cyclodextrin	Pharmaceuticals	Technique	Outcomes offered by cyclodextrin-based polymeric nanoparticles	Reference
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Formononetin	Neutralization agitation method	Promising carrier for poor lipophilic and poor hydrophilic drugs	Guo et al. (2017)
Poly (lactic acid and glycolic acid)	β-Cyclodextrin	–	Emulsion evaporation process	Enhanced internalization of nanoparticles into the Caco-2 cells	García-González et al. (2016)
Poly (ethylene glycol)-poly (ε-caprolactone)	Hydroxypropyl-β-cyclodextrin	Zinc (II) phthalocyanine as drug carrier	Melting/sonication procedure	Novel vehicle for the skin delivery of highly lipophilic compounds	Conte et al. (2015)

7.6 Cyclodextrin-Based Lipid Nanoparticles

Lipid-based cyclodextrin nanoparticles represent numerous examples such as liposomes, nanoemulsions, solid lipid nanoparticles, or nanostructured lipid carriers. The association of cyclodextrin into lipid nanoparticle formulations not only promotes the hydrophobic drug loading within the aqueous components of the lipid cyclodextrin nanoparticles but also maintains the targetability of nanoparticles. It has been confirmed from earlier investigations that highly lipophilic molecules included in the liposome membranes are released rapidly after in vivo administration (Maestrelli et al. 2005).

To ensure stable encapsulation, McCormack and Gregoriadis (1994a, b) suggested an approach wherein cyclodextrin/drug inclusion complexes are embedded into liposomes. This strategy identified a novel drug delivery system consisting of liposomes and cyclodextrin complexes of lipophilic drugs and designated as drug-in-cyclodextrin-in-liposome. In liposomes, cyclodextrin complexation competes with liposomal membrane binding, which strengthens the potential benefit of complexation in increasing hydrophobic drug retention. This concept was applied to dexamethasone retinol and retinoic acid included in hydroxypropyl-β-cyclodextrin (McCormack and Gregoriadis 1994a, b, 1996). Arima et al. (2006) developed PEGylated liposomes entrapping the doxorubicin complex with γ-cyclodextrin and evaluated the antitumor effect of doxorubicin in rodents bearing colon-26 tumor cells. The findings of the study displayed retardation in tumor growth and an increase in drug retention. From the historical point of view, a number of lipophilic drugs have been encapsulated in the drug-in-cyclodextrin-in-liposome system. They include Ca^{2+} channel blocker drug nifedipine (Škalko et al. 1996); anti-inflammatory drugs such as prednisolone (Fatouros et al. 2001), ketoprofen (Maestrelli et al. 2005), betamethasone (Piel et al. 2006), celecoxib (Jain et al. 2007), and indomethacin (Chen et al. 2007); anesthetic drugs such as benzocaine, butamben (Maestrelli et al. 2010), and prilocaine (Bragagni et al. 2010); and anticancer drugs such as ß-lapachone (Cavalcanti et al. 2011) and tretinoin (Ascenso et al. 2013).

Curcumin is well known for its therapeutic effects such as antibacterial, anti-inflammatory, antioxidant, and antitumor. But, it exhibits instability and poor solubility. Therefore, to improve the cytotoxic effect and to resolve the issue of instability and solubility, Dhule et al. (2012) fabricated curcumin-loaded cyclodextrin-based liposomal nanoparticles and studied to treat osteosarcoma. The resulting 2-hydroxypropyl-γ-cyclodextrin/curcumin-liposome complex exhibits promising cytotoxic potential and represents themselves as a potential delivery vehicle for the treatment of cancers of different tissue origin.

Ji et al. (2016) practiced the use of cyclodextrin to enhance the tumor-targeting ability of the lipid nanoparticles on the outside of the liposomal wall. The surface of the liposome consisted of pirfenidone-loaded β-cyclodextrin linked with a cleavable peptide, along with arginyl glycyl aspartic acid peptide (most common peptide motif responsible for cell adhesion to the extracellular matrix) to target pancreatic tumor cells, while the interior of the liposome carried the chemotherapeutic agent

gemcitabine. Solid lipid nanoparticles represent an alternative carrier system to conventional colloidal carriers due to their specific features such as the use of natural fabrication components, size and related narrow distribution, enhanced stability, and increased permeation through biological barriers. Additionally, increased solubility, biocompatibility, ease of manufacture, and different possible administration routes enable solid lipid nanoparticles a frontline drug delivery system.

Skiba et al. (1993) first proposed the concept of employing cyclodextrin in the solid nanoparticulate system and filed a patent for this invention. This invention described the development and application of a novel cyclodextrin-based dispersible colloidal system in the form of spherical particles of matrix type with size ranging from 90 to 900 nm (nanospheres), which might contain an active pharmaceutical ingredient. This nanoparticulate system was used as a carrier for numerous pharmaceuticals and cosmetic agents.

Similarly, Cavalli et al. (1999) developed inclusion complexes of hydrocortisone and progesterone with β-cyclodextrin or 2-hydroxypropyl-β-cyclodextrin to modulate the release kinetics. The inclusion complexes were incorporated into two types of solid lipid nanoparticles. The results showed that using the β-cyclodextrin complexes, the incorporation of the more hydrophilic drug, hydrocortisone, was higher than that of progesterone. The release of hydrocortisone and progesterone from solid lipid nanoparticles was lower when they were incorporated as inclusion complexes than as free molecules. To study the morphology of cyclodextrin-based solid lipid nanoparticles, Dubes et al. (2003) have performed scanning electron microscopy and atomic force microscopy for the imagery of solid lipid nanoparticles developed from an amphiphilic cyclodextrin, 2,3-di-o-alkanoyl-β-cyclodextrin, β-cyclodextrin 21C6. The results of the study reveal that the vacuum drying technique used in sample preparation for scanning electron microscopy causes shrinkage in the size of the solid lipid nanoparticles, whereas the deposition method used for atomic force microscopy produces small clusters of solid lipid nanoparticles.

Chirio et al. (2011) formulated solid lipid nanoparticles of curcumin, composed of different triglycerides with or without various modified α- and γ-cyclodextrins. The synthesized nanoparticles showed significant entrapment efficiency, improved hydrolytic stability, and a notable reduction in curcumin photodegradation when the drug was incorporated in tristearin solid lipid nanoparticles. Moreover, the results of the skin uptake study displayed an improvement in curcumin skin accumulation when curcumin was incorporated in solid lipid nanoparticles obtained with all cyclodextrin derivatives, particularly with most lipophilic ones. Solid lipid nanoparticles act as a protection to bioactive molecules.

To explore this unique feature of solid lipid nanoparticles, Carlotti et al. (2012) evaluated the potential of solid lipid nanoparticles as a protective carrier of resveratrol, against photosensitivity. A notable decline in photodegradation was recorded in drug-loaded solid lipid nanoparticles in comparison to tetradecyl-γ-cyclodextrin. Moreover, significant in vitro skin accumulation and an enhanced antioxidative efficacy were also observed in resveratrol-loaded nanoparticles.

Spada et al. (2012) formed diclofenac sodium-loaded solid lipid nanoparticles composed of different ratios of Compritol AT088 and 2-hydroxypropyl-β-

cyclodextrin via an oil/water hot homogenization method for colon-specific drug delivery. In vitro and ex vivo investigations confirmed solid lipid nanoparticles as a prominent carrier for colonic drug delivery. Additionally, in vitro toxicity studies showed that the solid lipid nanoparticles are well tolerated. Furthermore, Baek and Cho (2013) developed the surface-modified paclitaxel-filled solid lipid nanoparticles with hydroxypropyl-β-cyclodextrin. This cyclodextrin has been recognized to solubilize the drugs and inhibit the oxidation of lipids (Zafar et al. 2013). The formulated solid lipid nanoparticles showed a paclitaxel encapsulation percentage of 71% with a mean size of 251 nm. The Caco-2 cell uptake of paclitaxel from solid lipid nanoparticles was 5.3-fold greater than the Taxol formulation.

Nanostructured lipid carriers represent an upgraded generation of lipid nanoparticle, which overcome the major drawback of solid lipid nanoparticles, particularly the tendency of discharge of the drug during storage as an outcome of their highly ordered crystalline composition. Nanostructured lipid carriers composed by a solid lipid matrix are developed from a mixture of biocompatible solid and liquid lipids and an aqueous phase containing a surfactant or a blend of surfactants. Recently, several reports have been published demonstrating the strategy of simultaneously utilizing the advantages of both cyclodextrin and nanolipid carriers by locking them in a novel drug delivery system, by incorporating the drug-cyclodextrin inclusion complex into the lipid nanoparticles. A brief summary of recently developed cyclodextrin-based solid lipid nanoparticles and lipid nanoparticles loaded with various drugs used as anticancer, antihypertensive, diuretic, and anti-inflammatory is illustrated in Table 7.2.

7.7 Role of Cyclodextrin in Gold and Silver Nanoparticles

In recent years, gold and silver nanoparticles have been widely investigated for nanomedicine due to their superior optical, chemical, and biological properties which make them ideal for molecular imaging, drug/gene delivery, biosensors, and therapeutic agents. Furthermore, silver nanoparticles have antibacterial properties that make them desirable for drug delivery systems as they provide additional antimicrobial action. When combined with cyclodextrins, these metallic nanoparticles can become more targeted. Gold and silver cyclodextrin nanoparticles are commonly produced by connecting cyclodextrin to the metallic core using a linker, such as adamantane, which forms a strong stable complex with the cyclodextrins (Fig. 7.2). Sometimes the cyclodextrins are added by using cyclodextrin-loaded macromolecules (cyclodextrin-modified hyaluronic acid).

Liu et al. (1998) first developed a novel technique for the surface derivatization of gold colloidal particles to prepare gold colloidal particles of diameter > 10 nm. They demonstrated aqueous solubilization of aliphatic thiols by α-cyclodextrin, which effectively binds to the aliphatic chains and carries the hydrophobic thiol

Table 7.2 Formulations of cyclodextrin-based solid lipid nanoparticles and lipid nanoparticles loaded with various drugs, utilizing the advantages of both cyclodextrin and nanolipid carriers by incorporating the drug-cyclodextrin inclusion complex into the lipid nanoparticles

Type of lipid nanoparticle	Cyclodextrin	Active ingredients	Therapeutic use	Reference
Solid lipid nanoparticles	2-Hydroxypropyl-β-cyclodextrin	Paclitaxel	Anticancer agent	Bake and Chao (2013)
Solid lipid nanoparticles	Hydroxypropyl-β-cyclodextrin	Indomethacin	Nonsteroidal anti-inflammatory drug	Hippalgaonkar et al. (2013)
Solid lipid nanoparticles	γ-Cyclodextrin	Stearic acid	Inclusion complex of stearic acid and gamma cyclodextrin	Negi et al. (2014)
Solid lipid nanoparticles	2-Hydroxypropyl-β-cyclodextrin	Paclitaxel	Anticancer agent	Baek et al. (2015)
Solid lipid nanoparticles	Hydroxypropyl-beta-cyclodextrin and sulfobutyl-ether-beta-cyclodextrin	Hydrochlorothiazide	Antihypertensive and diuretic	Cirri et al. (2017)
Solid lipid nanoparticles	Carboxymethyl-β-cyclodextrin	Famotidine	H_2 receptor (antagonistic effects on gastric secretion)	Mady et al. (2010)
Solid lipid nanoparticles	β-Cyclodextrin	Simvastatin	Antihyperlipidemic	Vakhariya et al. (2017)
Nanostructured lipid carriers	β-Cyclodextrin-epichlorohydrin polymer	Ketoprofen	Nonsteroidal anti-inflammatory drug	Cirri et al. (2012)
Nanostructured lipid carriers	Cyclodextrin and derivatives	Vinpocetine	Protective and anti-aging agent	Lin et al. (2014)
Nanostructured lipid carriers	Methylated-β-cyclodextrin	Oxaprozin	Nonsteroidal anti-inflammatory drug	Mennini et al. (2016)
Nanostructured lipid carriers	Hydroxypropyl-β-cyclodextrin and sulfobutyl-ether-β-cyclodextrin	Hydrochlorothiazide	Antihypertensive and diuretic	Cirri et al. (2018)
Nanostructured lipid carriers	Hydroxypropyl-β-cyclodextrin	*Lippia origanoides* (essential oil)	Follicular accumulation and controlled delivery	Pires et al. (2019)

molecules to the surface of the gold particles. Two years later, the same authors developed cyclodextrin-modified gold nanospheres by reduction of $AuCl_4$ in the presence of perthiolated cyclodextrin receptors resulting in gold nanospheres modified with attached cyclodextrins. It is proposed that cyclodextrin-modified gold nanospheres represent multisite hosts in aqueous media. The most common application of cyclodextrin-gold nanoparticles is in biosensor technology.

Holzinger et al. (2009) developed a single-walled carbon nanotube with β-cyclodextrin-functionalized gold nanoparticles attached to the surface, loaded with polymerized adamantane. The association between the polymerized adamantane and the β-cyclodextrin-functionalized gold nanoparticles ideally simulates the biological interactions of biotin and avidin. To explore the potential of gold nanoparticles for photothermal release of drug, Sierpe et al. (2015) carried out the synthesis of a 1:1 β-cyclodextrin-phenylethylamine inclusion complex and the adhesion of gold nanoparticles onto microcrystals of this complex. Wang et al. (2016a, b) described an easy method to produce the host-guest assembly of gold nanoparticles induced by intracellular glutathione. Briefly, gold nanoparticle aggregates were developed from dispersive gold nanoparticles by host-guest interactions between ferrocene and β-cyclodextrin and triggered by intracellular glutathione. It is well known that ferrocene develops an inclusion complex with β-cyclodextrin and detaches upon ionization (Fc+). Results showed that the synthesized aggregates are retained for a long time in cancer cells and provoke apoptosis of cells when exposed to near-infrared irradiation. It has been proven from several scientific investigations that β-cyclodextrin-functionalized gold nanoparticles are more efficient in anticancer therapy when incorporated with anticancer agents. For example, Ha et al. (2013) formulated gold nanoparticles decorated with polyethylene glycol and poly (*N*-isopropyl acrylamide) linked via complexation between β-cyclodextrin and adamantane groups. It has been observed that exposure of these gold nanoparticles to low temperature facilitates the release of the doxorubicin as well as transports it directly to the cancer cell nucleus by dismantling.

Furthermore, Bakar et al. (2015) reported decreased breast cancer cell (MCF-7) proliferation by complexing various ligands (pinoresinol, lariciresinol, and secoisolariciresinol) with thiolated-β-cyclodextrin and decorating them on the exterior of gold nanoparticles. Conventional anticancer molecules such as doxorubicin, paclitaxel, and docetaxel were incorporated into the β-cyclodextrin-functionalized gold nanoparticles and targeted to cancer cells. Findings of cell line studies showed that the doxorubicin-loaded β-cyclodextrin gold nanoparticles enhanced the cellular uptake and exerted a significant antiproliferative effect. Similarly, Wang et al. (2016a, b) constructed a twofold nanoparticulate delivery system based on host-guest nanoplatforms loaded with anticancer agent docetaxel and genetic material siRNA using gold nanorods coated with polyethylenimine-grafted β-cyclodextrin. The developed gold nanoparticles, upon exposure to near-infrared laser irradiation, generate a significant hyperthermia effect to trigger siRNA and docetaxel release from the cyclodextrin, and it has been observed that developed gold nanoparticles in combination with laser irradiation remarkably inhibit lung metastasis of 4T1 breast tumors.

A general method to improve the dispersity of oleic acid-stabilized silver nanoparticles was proposed by Wang et al. (2016a, b). The authors have modified the surface properties of the nanoparticles by the configuration of an inclusion complex between surface-bound surfactant particles and α-cyclodextrin. Results showed that initial cyclodextrin concentration is a key factor responsible for the phase transfer of nanoparticles to the aqueous solutions (Wang et al. 2016a, b). To explore this concept of phase transfer of silver nanoparticles in aqueous solvents, George et al.

(2011) synthesized antibacterial water-soluble, silver nanoparticles encapsulated in β-cyclodextrin. The β-cyclodextrin-encapsulated silver nanoparticle revealed remarkable stability and antimicrobial effect when tested in vitro against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. One year later, the same researcher's group synthesized silver nanoparticles by reducing silver acetate with a long-chain aliphatic amine stabilized with β-cyclodextrin. This formulation revealed significant results when evaluated for antifungal activity against various human pathogens such as *Aspergillus fumigatus*, *Mucor*, and *Chrysosporium* species.

Gannimani et al. (2016) coupled the antibacterial properties of silver nanoparticles and hydrophobic drug carrier characteristic of cyclodextrin to fabricate supramolecules to provide cutting edge for antibacterial efficacy of chloramphenicol. Likewise, Gaurav et al. (2015) exploited an interesting mechanistic feature of metal nanoparticles for multiple therapeutic targets. They utilized β-cyclodextrin to solubilize clotrimazole, an antifungal agent, and then attach to albumin-stabilized silver nanoparticles; here albumin facilitates to reduce the interaction between the silver nanoparticles and the cyclodextrin-clotrimazole complex. These hybrid nanoparticles exerted a synergistic effect when evaluated for antifungal activity against candida yeast cells. β-Cyclodextrin-capped silver nanoparticles also have a notable contribution to cytotoxic therapeutic applications. Jaiswal et al. (2015) proved the ability of β-cyclodextrin silver nanoparticles to regulate biofilm growth and lessen the cytotoxic effect. The cytotoxicity of silver nanoparticles in human HaCat skin cells was eliminated due to the shielding capping of β-cyclodextrin. These nanoparticles particularly target cancerous cells and bypass uptake in normal cells. Zhai et al. (2017) reported the formulation and therapeutic application of biocompatible nanoparticles for the examination of the uptake of nanoparticles into viable cells in a microfluidic chip by utilizing surface-enhanced Raman spectroscopy, which modified the surface of β-cyclodextrin-capped silver nanoparticles using para-amino thiophenol and folic acid. The para-amino thiophenol molecules serve as the Raman reporter, while the folic acid fragments have a high proclivity for folate receptors that are overexpressed on the surface cancerous cells so that the nanoparticles can penetrate the cells and be observed by the Raman reporter.

Like gold nanoparticles, silver nanoparticles represent valuable attributes such as high functionalization and good catalytic activity, which make them suitable for biosensor applications. Therefore, with an aim to explore this characteristic of silver nanoparticles, Gao et al. (2015) developed a novel sandwich-type electrochemical immunosensor based on host-guest interaction for the detection of alpha-fetoprotein (a protein made in the liver of a developing baby). The developed immunosensor displays a wide linear calibration range from 0.001 to 5.0 ng/mL with a low detection limit (0.2 pg/mL) for the detection of alpha-fetoprotein. This method has a large-scale application promise in the clinical domain. Hui et al. (2015) explored β-cyclodextrin as a reducing agent between silver nitrate and graphene oxide in a guanine and adenine biosensor. In this study, β-cyclodextrin acts as a stabilizer as well as a dispersant for the silver nanoparticles and graphene oxide. This property

of β-cyclodextrin offered a microenvironment that produced a rapid absorption of guanine and adenine leading to faster electrocatalysis.

7.8 Pharmaceutical Applications of Amphiphilic Cyclodextrin Nanoparticles

The potential use of cyclodextrin in a biological system needs amphiphilic properties because natural cyclodextrin has relatively low solubility both in water and organic solvents, thus limiting their uses in pharmaceutical formulations. Amphiphilic or ionizable cyclodextrins can modify the rate or time of drug release and bind to the surface membrane of cells that may be used for the enhancement of drug absorption across biological barriers. Improvement of the interaction of cyclodextrins with hydrophobic drugs renders self-assembly capacity in aqueous solutions (Bilensoy and Hincal 2009). Amphiphilic cyclodextrins are obtained by grafting of 6-C aliphatic chains linked with ester or/and amide groups of different length on the primary/secondary face of the glucopyranose units (Duchêne et al. 1999a). The major advantage of amphiphilic cyclodextrins is their self-assembly properties which are sufficient to form different nanosized carriers spontaneously without the presence of surfactants. This superiority gives them amphiphilic properties resulting in the formation of supramolecular aggregates in the nanometer range (Duchêne et al. 1999b).

According to the chemical structure of the amphiphilic cyclodextrin, different carrier systems could be obtained such as solid lipid nanoparticles, bilayer vesicles, liposomes, and nanoparticles (Donohue et al. 2002; Dubes et al. 2003). According to the groups conjugated onto cyclodextrins, amphiphilic cyclodextrin-based systems can be classified as nonionic, cationic, and anionic materials (Zhang and Ma 2013). Amphiphilic cyclodextrins have been synthesized to overcome the drawbacks of natural cyclodextrins. In addition, they have the ability to form self-assembled nanoparticulate systems. Their unique properties can improve the drug loading capacity, cellular interaction and tumoral penetration, drug release profiles, and cytotoxicity of drug delivery systems. Skiba et al. (1996) synthesized an amphiphilic β-cyclodextrin-based nanosphere drug delivery system prepared by uniform dispersion of an organic solution of modified β-cyclodextrin in the hydrophilic phase with or without surfactant. A preliminary study for the effect of surfactant on the size, physicochemical properties, and stability of the nanospheres was carried out. Furthermore, in a similar study, the authors reported the synthesis and characterization of amphiphilic cyclodextrin-based new nanosphere drug delivery system consisted of fatty acid chain of either 6 or 12 or 14 carbon atoms assembled at the 02 and 03 positions of the β-cyclodextrin molecule. Table 7.3 summarized the various potential pharmaceutical applications of amphiphilic cyclodextrin-based nanoparticles such as anticancer, cholesterol-targeted, folate-targeted, and amphiphilic cyclodextrin nanoparticles for gene delivery.

Table 7.3 The historical landmarks of amphiphilic cyclodextrin-based nanoparticles containing anticancer and antimicrobial drugs including gene delivery to facilitate improved drug loading capacity, significant cytotoxicity, and vectorized gene delivery

Drug/ mechanism	Amphiphilic cylodextrin	Indication	Outcomes offered by amphiphilic cylodextrin nanoparticles	Historical landmarks	References
Bifonazole and clotrimazole	6-*N*-capro-β-cyclodextrin	Antifungal	Improved drug loading capacity	First report on antifungal drug with amphiphilic cyclodextrin	Memişoğlu et al. (2003)
Tamoxifen citrate	β-Cyclodextrin	Anticancer	Improved loading capacity and cytotoxicity		Bilensoy et al. (2005)
Amphiphilic β-cyclodextrin nanosphere	β-Cyclodextrin	In vivo tissue distribution	No particular sign of toxicity	First report of in vivo behavior of amphiphilic cyclodextrin nanoparticles	Gèze et al. (2007)
Paclitaxel	Cyclodextrin derivatives	Anticancer	No effect on cell proliferation and no hemolysis of red blood cells		Bilensoy et al. (2008a, b)
Camptothecin	β-Cyclodextrin	Anticancer	Improved release profiles and significant antitumor efficacy	First comparison of amphiphilic cyclodextrin nanoparticles with polymeric analogues	Çirpanli et al. (2009)
Camptothecin	Cyclodextrin	Anticancer	Significant anticancer efficacy		Çirpanli et al. (2011)
Docetaxel	Cyclodextrin heptakis	Anticancer	Prolonged cell arrest in mitosis		Quaglia et al. (2009)
Acyclovir	Fluorinated alpha-cyclodextrin hexakis	Antiviral	Improved encapsulation efficiency, sustained release of acyclovir	First report on antiviral drug nanoparticles based on amphiphilic cyclodextrin	Ghera et al. (2009)
Plasmid DNA	Polycationic cyclodextrin	Transfection capability	Vectorized gene delivery		Díaz-Moscoso et al. (2011)

(continued)

Table 7.3 (continued)

Drug/ mechanism	Amphiphilic cylodextrin	Indication	Outcomes offered by amphiphilic cylodextrin nanoparticles	Historical landmarks	References
Nucleic acid	Polycationic cyclodextrin	Gene therapy	Efficiently mediated serum-resistant transfection in HeLa and HepG2 cells		Méndez-Ardoy et al. (2011)
Plasmid DNA	Polycationic amphiphilic cyclodextrin	Gene therapy	Efficiently mediated transfection	First preforming self-assembled nanocomplexes from a polycationic amphiphilic cyclodextrin and plasmid DNA	Aranda et al. (2013)
Doxorubicin	Star-like polymers composed of a β-cyclodextrin	Anticancer	pH-responsive sustainable drug release	A new generation of drug delivery systems	Xu et al. (2015)
Short interfering RNA	Cyclodextrins	Brain cancer	Enhanced gene silencing efficiency		Gooding et al. (2015)
Cholesterol targeted	Nonionic or cationic β-cyclodextrin	Cholesterol-targeted anticancer effects	Apoptosis of cancer cells via cholesterol extraction		Varan et al. (2016)
Paclitaxel (folate-targeted)	β-Cyclodextrin	Anticancer	Reduced cell proliferation		Erdogar et al. (2017)
Doxorubicin	β-Cyclodextrin	Anticancer	Inhibit the growth of MDA-MB-231 cancer cells	First report on nanoparticles equipped with multivalent mannose target units	Ye et al. (2016)
Short interfering RNA	Cationic cyclodextrin	Prostate cancer	Transfect prostate cancer cells in a 3D model of bone metastasis	First report of targeted cyclodextrin to transfect prostate cancer cells in a 3D model of bone metastasis	Evans et al. (2017)

(continued)

Table 7.3 (continued)

Drug/ mechanism	Amphiphilic cylodextrin	Indication	Outcomes offered by amphiphilic cylodextrin nanoparticles	Historical landmarks	References
Iodinin	β-Cyclodextrin	Anti-leukemic activity	Significant cytotoxicity & improved water solubility	First report on iodinin amphiphilic β-cyclodextrin nanoparticles	Prandina et al. (2018)
Paclitaxel	β-Cyclodextrin	Anticancer	Stronger antitumoral activity in the 3D multicellular tumor mode	First report on the 3D multicellular tumor mode	Varan et al. (2018)

7.9 Miscellaneous

Nowadays, numerous types of neutral, amphiphilic, modified cyclodextrins are incorporated in the formulation development of novel drug delivery systems that can enable effective delivery of drugs across mucosal or dermal membranes. As per the biopharmaceutical classification system of drugs, poor drug solubility or poor mucosa permeability attributes of drugs limit their pharmaceutical applications. These cyclodextrin-based polymeric nanoparticles represent a more reliable drug delivery system when compared with control nanoparticles; they displayed homogeneous bioadhesive interactions with the gastrointestinal mucosa due to the presence of several hydroxyl groups in cyclodextrin nanoparticles, which would promote hydrogen bonding with the gut, subsequently enhancing the bioadhesive potential (Agüeros et al. 2011). Furthermore, Luppi et al. (2011) examined the potential of different cyclodextrins in nasal drug delivery using albumin nanoparticles for the treatment of the most common neurodegenerative disorder Alzheimer's disease to validate their effect on the drug release, mucoadhesiveness of nanoparticles, and permeability of model drug tacrine. In another approach, β-cyclodextrin was conjugated with chitosan and further quaternized with glycidyltrimethylammonium chloride for mucoadhesive drug delivery system.

Transdermal delivery of drugs has always been a challenging task due to barrier property of skin; due to unique properties of cyclodextrin-based nanoparticles, they represent an alternative choice for effective transdermal delivery of drugs. Maestrelli et al. (2006) synthesized chitosan nanoparticles in the presence of cyclodextrin as a nanocarrier system for the triclosan (an antifungal agent) and furosemide (a diuretic). This nanocarrier system showed immediate drug release, followed by a delayed-release of drug. It confirms the inclusion of the drug inside the cyclodextrin cavity and later encapsulation inside the chitosan polymer. Thus, representing an ideal nanocarrier system for transdermal drug delivery. Similarly, Khalil et al.

(2012) formulated nanoparticles of warfarin, an anticoagulant drug, by loading it in chitosan-cyclodextrin-complexed nanoparticle systems for transdermal drug delivery. The results of in vitro release studies and ex vivo permeation studies of warfarin-cyclodextrin-complexed nanoparticles paved the new way for the delivery of hydrophobic drugs. To improve the percutaneous absorption, Kwon and Kim (2010) fabricated mono-olein cubic phase nanoparticles comprising of 2-hydroxypropyl-b eta-cyclodextrin, complexed with minoxidil (a vasodilator drug), which were prepared by hydrating molten minoxidil with the inclusion complex solution. The cubic phase transparent gels were obtained in the presence of pluronic F127 as a dispersant that showed significant in vitro skin permeability when compared with native delivery carriers. Econazole nitrate, a poorly soluble antifungal agent for ocular drug delivery, was developed as the chitosan nanoparticles in the presence of sulfobutyl-ether-beta-cyclodextrin. Mucoadhesiveness property of chitosan enabled nanoparticles to interrelate with the ocular mucosa; besides the use of an anionic, sulfobutyl-ether-beta-cyclodextrin magnified the solubility and delivery of econazole to the cornea (Mahmoud et al. 2011).

Gil et al. (2009) synthesized the novel quaternary ammonium β-cyclodextrin nanoparticles as drug delivery carriers for doxorubicin to improve the permeability of doxorubicin, a hydrophobic anticancer drug across the blood-brain barrier. When quaternary ammonium β-cyclodextrin was experimented in different in vitro studies, it was found to be nontoxic at a concentration of up to 500 mg/ml in bovine brain microvessel endothelial cells and showed great potential for safe and effective delivery of doxorubicin and other therapeutic agents across the most complexed blood-brain barrier. Nanoparticle-based biomedicine has gained enormous acceptance for theranostic applications, due to their advantage features over conventional therapy. Therefore, in search of a novel theranostic material, Datz et al. (2018) have synthesized a new β-cyclodextrin-based biocompatible and multifunctional substance that cross-linked with rigid organic linker molecules to yield thermostable, readily water-dispersible particles having a nanosize range (∼150 nm). In the next step, these nanoparticles covalently linked with dye molecules to enable effective tracking of them during in vitro cell experiments. Results showed the successful nuclei staining with Hoechst 33342 dye, including effective cell killing with the doxorubicin cargo molecules. Concludingly, these findings represent a promising approach for the development of novel theranostic systems.

7.10 Conclusion

The application of cyclodextrin-based nanomaterials is beginning to confirm an effective degree of control in drug delivery and other therapeutic applications, although their safe, effective, and economical delivery is yet not significantly demonstrated. The chemical modification of cyclodextrin polymers is a promising strategy to extend their pharmaceutical applications. Some nanoparticles, such as CRLX101 and CALAA-01, are tumor-targeted and siRNA delivery

nanopharmaceuticals respectively, they contain a cyclodextrin-containing polymer. These nanoparticles formulated with a polyethylene glycol steric stabilization agent, are among the most appropriate nanotherapeutics in clinical phase II trials for cancer diseases (Weiss et al. 2011; Zuckerman et al. 2014).

There is a flourishing discussion about the inherent advantages, characteristic features, and potential therapeutic applications of cyclodextrin-based nanoparticles reported by the scientist fraternity in the past decades to date. These cyclodextrin-based nanoparticles are enriched with various properties of an ideal novel drug delivery system. Moreover, they overcome the limitations of other carrier systems as well. Cyclodextrin-based nanoparticles have emerged as a very promising carrier system for high molecular weight compounds such as peptides, proteins, DNA, and other genetic materials. Nanoparticles containing cyclodextrins have shown their potential to improve the loading capacity of carriers such as liposomes, nanoparticles, and solid lipid nanoparticles. This review also highlights the new-generation cyclodextrin-based nanocarrier for the delivery of associated DNA or proteins with remarkable cytotoxicity against various cancer cell lines. Amphiphilic cyclodextrins represent unique properties of ideal pharmaceutical excipients, such as the ability to form nanoparticles spontaneously. Moreover, they possess the advantages of natural cyclodextrins suitable for drug delivery, together with the advantages of delivery of drugs through various administration routes such as oral, transdermal, nasal, ocular, and across the biological membranes including the blood-brain barrier.

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Chapter 8
Water-Insoluble Cyclodextrin-Epichlorohydrin Polymers

Grégorio Crini

Contents

Abstract Proposed and studied in the mid-1960s, water-insoluble cyclodextrin-epichlorohydrin polymers are of continued interest to the scientific community, particularly for their environmental applications. The most characteristic feature of these materials is their ability to form inclusion complexes with various contaminants through host-guest interactions. This leads to many environmental applications, including water and wastewater treatment, soil remediation, air purification, and the concentration or elimination of target substances such as cholesterol.

In the early 1990s, our group began working on the synthesis of water-insoluble cyclodextrin-based materials, their structural characterization, and their application

G. Crini (✉)
Chrono-environnement, UMR 6249, UFR Sciences et Techniques,
Université Bourgogne Franche-Comté, Besançon, France
e-mail: gregorio.crini@univ-fcomte.fr

G. Crini et al. (eds.), *The History of Cyclodextrins*, Environmental Chemistry for a Sustainable World 52, https://doi.org/10.1007/978-3-030-49308-0_8

in the removal of pollutants present in wastewater. One of the first results published in 1995 concerned the fact that this material was not a true polymer but a copolymer with a particular structure with two different molecular mobilities. In 1997, this was demonstrated for the first time by solid-state NMR spectroscopy. These materials were composed of a relatively dense, rigid, and hydrophobic cross-linked core and a more hydrophilic surface, less cross-linked containing long and highly mobile hydroxyalkylated polymer chains through the homopolymerization of the cross-linking agent. In 1998, cyclodextrin-based materials were used as adsorbents to efficiently remove organic contaminants from contaminated water. One year later, a more surprising result showed that a high proportion of cyclodextrin was not necessary to have useful performance in terms of pollutant removal. In 2000, using cross-polarization magic angle spinning with dipolar decoupling and high-resolution magic angle spinning spectra, we concluded that the mechanism of adsorption can be explained by the presence of two main interactions: the formation of an inclusion complex due to the cyclodextrin molecules and the physical adsorption in the polymer network. In 2005, a patent was filed on a process for the synthesis of cross-linked polysaccharides with ionic functional groups for the simultaneous removal of metals and organic contaminants present at low trace levels in polycontaminated effluents. At the end of the 2000s, we carried out the first pilot studies demonstrating that a single cyclodextrin material with amphoteric and ion-exchange properties could replace two conventional adsorbents to effectively treat multi-contaminated effluent. In the early 2010s, our group proposed for the first time biomonitoring tests using plants as bioindicators to determine and compare the toxicity of industrial effluent from wood, pulp and paper, textile, and surface treatment industries before and after treatment with a cyclodextrin material. In the mid-2010s, we confirmed the feasibility of implementing materials for the treatment of discharge waters from surface treatment industries on an industrial scale.

The purpose of this chapter is to summarize the research conducted over the past 30 years by our research group on water-insoluble cyclodextrin-epichlorohydrin polymers used as complexing materials to remove contaminants present in aqueous solutions. It shows the progress of our work and our contribution to a better understanding of these materials. These years were devoted to the synthesis of a series of water-insoluble materials with different functionalities in the form of gels or beads, their characterization by innovative solid-state NMR techniques, the demonstration of their effectiveness as adsorbents in wastewater treatment, and the explanation of contaminant removal mechanisms according to the type of material used.

Keywords History · Cyclodextrin polymers · Synthesis · Characterization · Complexation · Adsorption · Industry

Abbreviations

CPMAS	Cross-polarization magic angle spinning with dipolar decoupling
ECP	Cyclodextrin-epichlorohydrin polymers
HRMAS	High-resolution magic angle spinning
NMR	Nuclear magnetic resonance

8.1 Introduction

In 1990, I was a young student in organic chemistry and macromolecular chemistry at the *Laboratoire de Chimie Organique et Macromoléculaire* (University of Lille 1, France) under the supervision of Professor Michel Morcellet.

In the same year, a French company (Roquette Frères, Lestrem) asked Morcellet's group to produce a series of cross-linked cyclodextrin gels using epichlorohydrin as cross-linking agent for applications in chromatography at industrial scale. The main objective was to verify if the polymer cyclodextrins were suitable chromatographic supports for gel inclusion chromatography, e.g., for the separation of caffeine, phenylalanine, naphthols and derivatives, benzaldehyde, nucleic acids, etc. This project was also carried out in collaboration with Professor Yahya Lekchiri of the University of Mohamed 1st, Oujda (Morocco).

Our first approach was to review the literature, an activity that we have been doing continuously since then (Crini et al. 2001; Crini and Morcellet 2002; Crini 2005a, 2006, 2014, 2015a, b; Badot et al. 2007; Sancey and Crini 2012; Morin-Crini and Crini 2013; Euvrard et al. 2015; Fourmentin et al. 2015; Crini et al. 2018a, b, 2019a; Morin-Crini et al. 2018a, b, 2019a). In 2002, we published a first comprehensive review on the synthesis, characterization, and applications of cross-linked cyclodextrin-based materials (Crini and Morcellet 2002). This review was updated 11 years later (Morin-Crini and Crini 2013).

Then we started working on the synthesis of water-insoluble cyclodextrin-based materials, thanks to industrial and European grants. With the first results obtained, I supported a Master of Science in Organic Chemistry in 1990, a Master of Science in Macromolecular Chemistry in 1992, and then a PhD in Organic Chemistry and Macromolecular Chemistry in 1995 (Crini 1995).

In 1994, my interest extended to solid-state nuclear magnetic resonance (NMR) characterization of these cyclodextrin polymers with a 1-year visit to the NMR Department of the G. Ronzoni Institute for Chemical and Biochemical Research (Milan, Italy), invited by the Research Director Giangiacomo Torri. Interesting results have been obtained both from the point of view of synthesis and characterization and applications in chromatography and oil removal and petroleum industry (Crini et al. 1995a, b, 1996, 1998a, b; Shao et al. 1996; Vecchi et al. 1998). However, for several reasons, such as the variability of polymer characteristics, the difficulty of producing materials with the same cross-linking density, lack of porosity, lack of reproducibility of the chromatographic results, etc., the industrial project initiated in

the early 1990s on cyclodextrin-based polymers for chromatographic applications was abandoned 1 year later.

At the same period, Professor Gerhard Wenz asked Professor Morcellet and Professor Casu to participate in the implementation of a European project on cyclodextrin polymers. In 1995, the project, focusing on the "Development from cyclodextrin derivatives to polymeric materials for selective transport, separation and detection of active substances" (FAIR Program 1995–1999, European Commission DGXII, contract no. CT 95-0300), was accepted. This was my entrance to the world of oligosaccharides and polysaccharides for environmental applications. As part of this project, after obtaining my PhD in 1995, I spent 2 years as a postdoctoral fellow at the Chemical Unit of G. Ronzoni Institute, under the direction of Dr. Torri and Professor Benito Casu, to work on the synthesis and NMR characterization of cyclodextrin-epichlorohydrin polymers, two of the objectives of the FAIR Program. At that time, the Institute's internationally recognized chemistry unit played a leading role in the pure and applied chemistry of carbohydrates and biopolymers. During the FAIR project, I had the opportunity to work with academics, including Dr. Anna-Maria Naggi, Dr. Carmen Vecchi, Dr. Marco Guerrini, Dr. Cesare Cosentino, Dr. Edwin Yates, Dr. Bernard Martel, Professor Wenz, Professor Wilfried König (Fig. 8.1), Dr. Bruno Perly, Professor Jacques Defaye, and Professor David Reinhoudt, and industrialists, e.g., Wacker Chemie, Bruker Italy, Chiesi Pharmaceutical, and *Stazione Sperimentale per i Combustibili*.

In September 1995, "after a long evening of fruitful exchanges at the *Galleria Vittorio Emanuelle II* in the Centre of Milan" with Giangiacomo Torri on the problems of the textile and paper industries, I had the idea to use cyclodextrin-based materials to remove dyes from aqueous solutions. Back at the Ronzoni Institute, I started working on the subject under the supervision of Dr. Torri, Professor Casu, and Professor Morcellet. The first results were presented at the Eight International Cyclodextrin Symposium in Budapest, March 31–April 2, 1996 (Fig. 8.1). At this Symposium, we first introduced the term "cyclodextrin microsponges" and proposed these materials as non-conventional adsorbents for the removal of target contaminants such as dyes and aromatic and phenolic compounds. However, this term

Fig. 8.1 Left: An evening organized by Professor König (with the red sweater) in Hamburg in 1996 during the FAIR project; Right: G. Crini with Professor M. Morcellet and Dr. G. Torri at the Eighth International Symposium on Cyclodextrins, Budapest, Hungary, March 31–April 2, 1996, where we introduced for the first time the term "cyclodextrin microsponges"

has generated much negative debate and criticism, although Professor József Szejtli, one of the prestigious researchers who contributed to the development of cyclodextrins, accepted it and congratulated our work. At the time, we abandoned it and then used the terms cyclodextrin polymer, cyclodextrin material, or simply gel/hydrogel. A few years later, the term "microsponges" was adopted over by other researchers.

In 1996, my interest also extended to starch, cellulose, and chitosan biopolymers, after two fruitful meetings in Milano, the first with Dr. Torri, Dr. Carmen Vecchi, and Professor Piero Sozzani organized at the *Stazione Sperimentale per i Combustibili* and the second with Professor Casu, Professor Bonaventura Focher, and Professor Kjell Vårum at the *Stazione Sperimentale per la Cellulosa, Carta e Fibre Tessili*. A year later, I joined the University of Franche-Comté where, with Professor Joël Vebrel, I created a research group working on adsorption processes based on oligosaccharides and polysaccharides for pollutant removal. At that time, our work focused mainly on the use of cyclodextrin-epichlorohydrin polymers and chitosan-based materials used as adsorbents for the removal of dyes from industrial effluents. Our current research focuses on the design of new functionalized macromolecular networks based on oligosaccharides (linear or cyclic dextrins), polysaccharides (starch, chitosan, cellulose), or agricultural fibers (hemp) for applied research for environmental purposes.

The purpose of this chapter is to present a review of some 30 years of research within my team as part of a scientific and industrial strategy. Our main area of research focused on the design and use of cyclodextrin-based materials for the removal of trace contaminants from polycontaminated industrial effluents from the textile, pulp and paper, wood, and surface treatment industries. The work involved the production of a series of water-insoluble cyclodextrin-epichlorohydrin polymers with different physical and textural properties, their chemical modification and solid-state NMR characterization, and their use as complexing agents in wastewater treatment. An important part of the work has also focused on explaining the contaminant removal mechanisms according to the type of cross-linked material used.

8.2 Synthesis of Water-Insoluble Cyclodextrin-Epichlorohydrin Polymers

8.2.1 Cross-Linking Reaction

Chemical cross-linking using epichlorohydrin as cross-linking agent is the most straightforward method to produce water-insoluble cyclodextrin-based polymers. These cyclodextrin-epichlorohydrin polymers known as ECP materials were first proposed in 1964 by the Swiss chemist Jürg Solms (Research Laboratory of the Nestlé Group, Vevey), who patented their chemical synthesis by block polymerization and their analytical applications as "inclusion resins" in chromatography and separation science (Solms and Egli 1964, 1965; Solms 1966, 1967, 1969).

The Dutch group of Niels Wiedenhof (Laboratory of General Chemistry, Eindhoven) at the end of the 1960s (Wiedenhof 1969; Wiedenhof et al. 1969, 1971; Wiedenhof and Trieling 1971), the American group of Jerald L. Hoffman (University of Louisville, Kentucky) in the early 1970s (Hoffman 1970, 1972, 1973), and the Hungarian group of József Szejtli (Chinoin Chemical and Pharmaceutical Works, Budapest) in the late 1970s (Szejtli et al. 1978; Szejtli 1980, 1982, 1984, 1988; Szemán et al. 1987) are also known for their many contributions to the cross-linking of cyclodextrins with epichlorohydrin. In the late 1990s, our group also studied ECP polymers and contributed to a better understanding of their synthesis. We used the same the procedure as described by Solms and improved by Hoffman but with some modifications, in particular in the molar ratios of the reagents.

The reaction that leads to the cross-linking of cyclodextrin molecules by epichlorohydrin, 1-chloro-2,3-epoxypropane (Fig. 8.2), is an easy method for preparing cyclodextrin-based materials (Solms and Egli 1964; Wiedenhof 1969; Hoffman 1970). Their one-step synthesis in water is simple and easy to set up in a lab and only requires mild reaction conditions (water-based chemistry, mild temperatures between 50° and 80 °C, and at atmospheric pressure). However, to obtain beads with porosity, it is necessary to use organic solvents. Figure 8.3 shows the reactor used in our laboratory to prepare up to 50 kg of material in a single step. The reagents involved are easy to find and inexpensive. The only compounds are water, caustic soda, and epichlorohydrin.

Cyclodextrin molecules are cross-linked by direct reaction between their hydroxyl groups with epichlorohydrin (abbreviated ECH or EPI in the literature) in an alkaline medium to form polymeric structures or ECP materials. Depending on the experimental conditions, in particular the degree of cross-linking, the ECP materials may be cross-linked polymers that are soluble or insoluble in water (Shao et al. 1996; Crini et al. 1998a). Due to its high reactivity in basic medium, the cross-linking agent can form bonds with cyclodextrin molecules (cross-linking step) and/

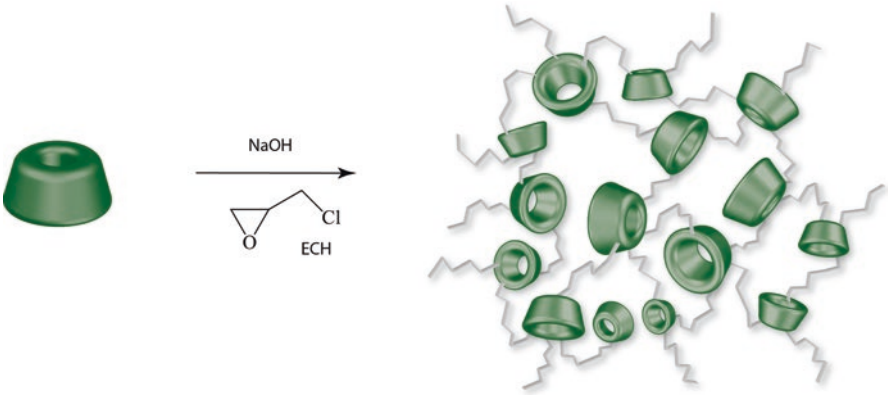

Fig. 8.2 Chemical reaction between a cyclodextrin molecule and epichlorohydrin (ECH) in basic medium to give a cyclodextrin-epichlorohydrin polymer

Fig. 8.3 Pilot used for the synthesis of cyclodextrin-epichlorohydrin polymers in our lab

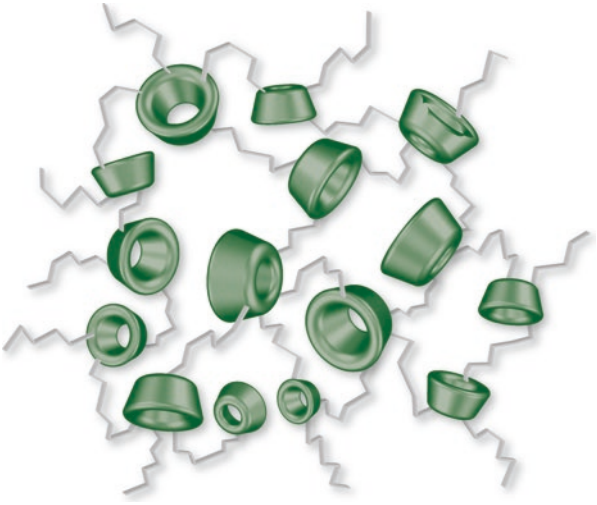

Fig. 8.4 Structure of a cyclodextrin-epichlorohydrin polymer known as ECP material in the literature

or itself (polymerization step). A number of cyclodextrin rings are interconnected, and a three-dimensional polymer network is formed. In 2002, our group proposed the structure of an ECP material described in Fig. 8.4, inspired on the 1972 Hofmann structure.

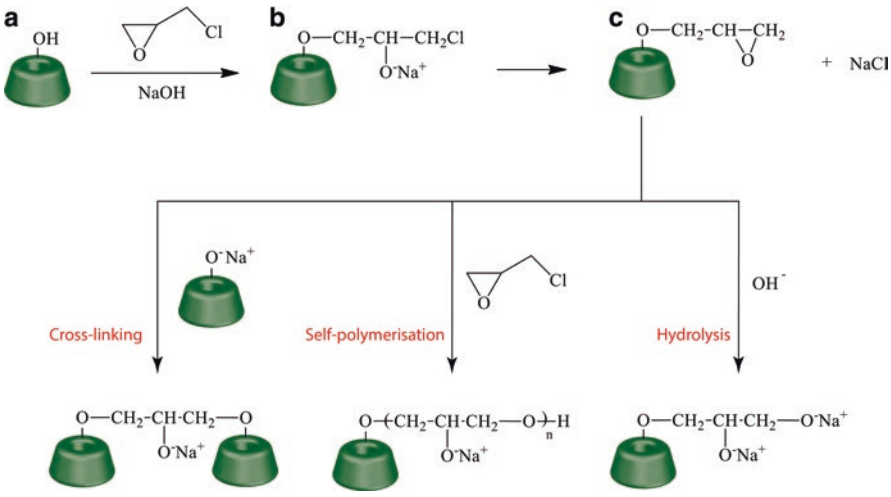

Fig. 8.5 Possible reactions between a cyclodextrin molecule and epichlorohydrin: (**a**) cross-linking to form a polymer; (**b**) self-polymerization of the cross-linker, and (**c**) formation of a glycerol monoether derivative by hydrolysis

To explain the cross-linking reaction (Fig. 8.2), Professor Szejtli adopted the mechanism described in Fig. 8.5, first proposed in the 1960s by Professor Hofmann, in the 1980s. This mechanism is divided into three main steps that take place simultaneously. The first step, cross-linking, consists in creating a three-dimensional structure using the bridging agent that binds the cyclodextrin molecules by strong covalent bonds. This is the main reaction and is responsible for creating a macromolecular network with a variable proportion of cross-links. The second step is the polymerization of the cross-linking agent, due to the high reactivity of epichlorohydrin, which allows it to polymerize with itself in basic medium, particularly with an excessive concentration of epichlorohydrin. This results long hydroxyalkyl macromolecular chains that function both as bridges and as side chains in the network. This is why some authors consider these materials as copolymers with two distinct components. In the last reaction (hydrolysis in Fig. 8.5), glycerol monoether polymer subunits are considered undesirable by-products. This reaction is not easy to control, which is why epichlorohydrin is often used in the synthesis in excess, usually 10 mol/mol cyclodextrin (Morin-Crini et al. 2013, 2018a).

A cyclodextrin-epichlorohydrin polymer, in water-insoluble or water-soluble form, is an O-alkylated polymeric resin. However, this is not a true polymer but a copolymer, first suggested in the 1970s by Professor Hoffman and taken up by Professor Szejtli in the 1980s. The concept is to consider cyclodextrin as a first monomer and epichlorohydrin as a second monomer in the synthesis. By modifying the molar ratio of the two monomers, the resulting copolymer is richer in one or the other of the monomers. In 1998, our group demonstrated that changes in the relative mole ratio of cyclodextrin (monomer A) to epichlorohydrin (monomer B) modify the repetitive structure of monomer units from an A-B-type copolymer to an

A-B_n-type copolymer; the latter type contains epichlorohydrin-rich domains that are hydrophilic by nature with an amorphous structure. This was demonstrated using NMR data (Crini et al. 1998b; Bertini et al. 1999) and later confirmed by the Spanish group of Professor José Ramon Isasi at Navarra University (Romo et al. 2004, 2006, 2008; García-Zubiri et al. 2006; Vélaz et al. 2007).

At the time, in accordance with Szejtli's results, our group also reported that it was important to select the optimal synthesis conditions to obtain the desired product characteristics, such as the degree of swelling and cyclodextrin content (Shao et al. 1996; Vecchi et al. 1998; Crini et al. 1998a). By varying the synthesis conditions, for example, the amounts of the different reagents, the molar ratio of cyclodextrin to epichlorohydrin, the NaOH concentration, the reaction temperature, and the reaction time, it was possible to induce structural modifications in the hydrogel networks in terms of surface area and porosity and also to obtain gels or beads with different cyclodextrin contents (Crini et al. 1998a, b). We have reported that a high polymerization temperature promoted a high degree of polymer swelling. The introduction of rigid structures into a material has been beneficial to create porosity and has increased the surface area, as well as the co-presence of an organic solvent during synthesis. Later, similar conclusions were reported by Professor Isasi (Romo et al. 2004, 2006, 2008; García-Zubiri et al. 2006; Vélaz et al. 2007), by the Turkish group of Professor Mustafa Yilmaz at Selçuk University (Yilmaz Ozmen and Yilmaz 2007, 2008), and by the Canadian group of Professor Lee D. Wilson at the University of Saskatchewan (Mohamed et al. 2010, 2012; Pratt et al. 2010; Wilson et al. 2010).

The cross-linking step has always been the subject of debate in the literature. Two "schools of thought" have been established (Crini 2005a; Morin-Crini and Crini 2013): one promoting a low cross-linking leading to hydrogel-type products and the other promoting a high cross-linking leading to organic bead-type products. However, as Professor Szejtli has pointed out, this distinction may result from different end uses. For wastewater treatment, gel-type systems are appropriate but not for use in high-pressure chromatography, as the particles must have some mechanical resistance (Szejtli 1982, 1988).

8.2.2 NMR Characterization

The mechanism described in Fig. 8.5 was studied in detail by Professor Bernard Sébille (*Université de Paris XII*, France) in 1997 for water-soluble epichlorohydrin-cross-linked cyclodextrin polymers (Renard et al. 1997). The same year, our group demonstrated for the first time the structure of water-insoluble ECP polymers by NMR spectroscopy. These results were presented at the IXth European Carbohydrate Symposium at Utrecht (The Netherlands, 6–11 July 1997) and published 1 year later in the journal *Carbohydrate Research* (Crini et al. 1998b). Using cross-polarization magic angle spinning with dipolar decoupling (CPMAS) and high-resolution magic angle spinning (HRMAS) spectra, we demonstrated that, in the materials, two kinds of structures existed with different molecular mobility: cyclodextrin cross-linked by

epichlorohydrin due to the cross-linking reaction between the cyclodextrin molecules and epoxide and polymerized epichlorohydrin due to the homopolymerization of epichlorohydrin with itself. These two components were analyzed in terms of relaxation parameters, i.e., ^{13}C spin lattice relaxation and ^{1}H spin lattice relaxation in the rotating frame (Crini et al. 1998a, b, 2000).

In spite of the facile synthetic conditions for the preparation of ECP-based polymers, the polymer networks may adopt variable structural variability. Since cyclodextrin molecules contain several glucose units and hydroxyalkyl groups present at positions 2, 3, and 6 in each glucose unit, the structure of the polymer network is complicated because, during synthesis, many units can be interconnected as shown in Fig. 8.2. This structure has been demonstrated by solid-state NMR experiments and relaxation time techniques (Crini et al. 1998a, 2000). Figure 8.6 shows the CPMAS spectra of a β-cyclodextrin sample and a water-insoluble β-cyclodextrin-epichlorohydrin polymer. The CPMAS spectrum of a polymer is typical of a solid with an amorphous structure, but it resembles to a classical β-cyclodextrin spectrum. However, this spectrum permits only one well-defined signal, i.e., the resonance at 100 ppm due to the anomeric C-1, to be assigned because there is a large degree of signal overlap in the range 55–85 ppm (Crini et al. 1998a). The signals of polymerized epichlorohydrin are completely hidden by the C-2, C-3, C-4, and C-5 β-cyclodextrin peaks. Our group was the first to overcome this overlap problem with a comprehensive NMR study, including CPMAS, MAS, and HRMAS experiments and relaxation parameter measurements. These NMR data made it possible to assign

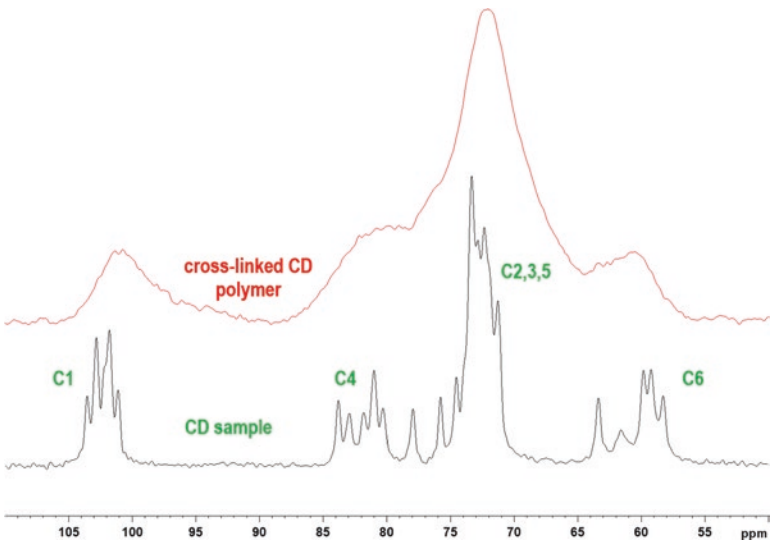

Fig. 8.6 Comparison of CPMAS spectra of a β-cyclodextrin sample and a water-insoluble β-cyclodextrin-epichlorohydrin polymer recorded by our team in 1994 on a Bruker AC-300 spectrometer and CXP-300 NMR spectrometer, respectively

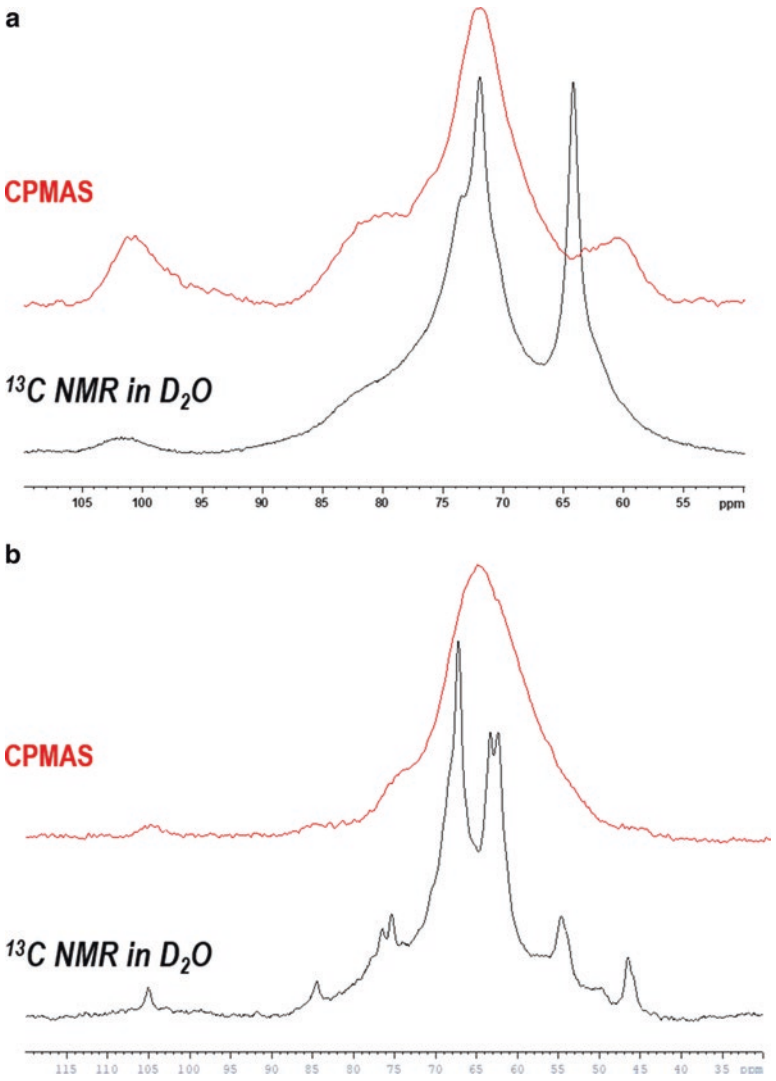

Fig. 8.7 Influence of the degree of cross-linking on CPMAS and ^{13}C NMR spectra of a water-insoluble β-cyclodextrin-epichlorohydrin polymer. (**a**) cross-linked polymer. (**b**) highly cross-linked polymer

the main ^{1}H and ^{13}C signals and to demonstrate the presence of two distinct components in the materials with different mobility.

As the degree of cross-linking increases, the resolution decreases in the CPMAS spectra as shown in Fig. 8.7; however, the resolution increases in the ^{13}C NMR spectra recorded in solution as revealed by the number of resonances. This highlights the mobility of the polymerized epichlorohydrin grafted onto the surface of the cross-linked polymer (Crini et al. 1998a). When the degree of cross-linking is high, the

sample is mostly amorphous, and cross-linking is not homogeneous. The amorphous character is caused by the loss of cyclodextrin crystallinity during the cross-linking reaction. The structure is heterogeneous and presents different regions with different mobility properties. For the first time, NMR studies have shown cyclodextrin gels are composed of a relatively dense, rigid, and hydrophobic cross-linked core and a more hydrophilic surface, less cross-linked containing long and highly mobile hydroxyalkylated polymer chains through the homopolymerization of the cross-linking agent (Crini et al. 1998a). Two years later, these conclusions were confirmed by HRMAS experiments (Crini et al. 2000). In 2012, Wilson's group reported similar interpretations using NMR experiments (Mohamed et al. 2012).

8.2.3 Swelling Properties of Cyclodextrin-Epichlorohydrin Polymers

Various types of materials can be obtained with physical textures and mechanical properties that can be varied by giving different shapes, such as gels/hydrogels or "small balls" (beads, resins). At the end of the 1960s, Professor Wiedenhof was the first to demonstrate that materials can easily be prepared as irregularly shaped particles or regular "balls" and that they had a remarkably high swelling capacity in water, depending on the conditions of synthesis, especially the degree of cross-linking. Under particular synthesis conditions, such as heterogeneous two-phase synthesis in the presence of a blowing agent, it is possible to obtain a well-defined spherical size and shape and a uniform and controlled distribution (Bertini et al. 1999; Vecchi et al. 1998). Other forms of such sponges or foams insoluble in water and in many other solvents can also be obtained, depending on the intended application (Crini and Morcellet 2002; Crini 2005a).

Among the most studied materials are gel polymers that can swell in water and absorb up to several times their weight. They simultaneously have properties characteristic of both liquids and solids. Their swelling properties become useful for the complexation of contaminants because they promote diffusion processes in the polymer network (Crini et al. 1998a). The macromolecular network also has a structure that is mainly amorphous with very few or complete absence of crystalline zone (Crini et al. 1998b, 2000; Vecchi et al. 1998). This amorphous character represents an additional advantage in wastewater treatment as it favors adsorption processes (Crini 2005a). Indeed, it is also important to note that the flexibility of the molecular chains makes them easily entangled with each other, resulting in a non-porous structure with a very low specific surface area (Crini and Morcellet 2002; Crini 2005a). Professor Szejtli was the first to study in detail the precise role of the solvent (water, organic solvents, or a mixture of both) in the formation of non-porous or porous gels and beads (Szejtli 1982). Since then, all highly porous cyclodextrin polymers have been synthetized in organic phase using customized cross-linkers, including epichlorohydrin (Morin-Crini et al. 2013, 2018a). Literature methods to produce

porous cyclodextrins polymers can require long reaction times, and the type of cross-linking agent strongly influences the pore diameter. Nevertheless, synthesis in aqueous media is generally preferred because of their simplicity and their more ecological nature (Crini and Morcellet 2002; Crini 2005a; Morin-Crini et al. 2013, 2018a). Xu et al. (2019) recently proposed for the first time the synthesis of an ultra-porous polymer in aqueous phase.

Nowadays, several materials with different characteristics in terms of cross-link density, surface area, pore structure, and physical and chemical properties can be obtained. They can be precisely tailored to have desired architectures and functionalities. This explains the fact that, although the cross-linking of cyclodextrin molecules with epichlorohydrin has been known for more than half a century, it continues to be of interest to the scientific community (Euvrard et al. 2017; Crini et al. 2018a, b; Morin-Crini et al. 2018a). Ongoing work is proposing innovative macromolecular architectures in the form of foams, nanoparticles, nanosponges, fibers (nanofibers/nanowebs), felts, membranes/nanomembranes, "intelligent" hydrogels, composites, or film-based products. These materials are developed for various applications not only in the environmental field, for example, the elimination of the so-called emergent pollutants (pesticides, drugs, endocrine disruptors, etc.) present in polluted water or soil and air filtration, but also in the pharmaceutical or medical fields (drug delivery, biomedicine) or in innovative fields (medical textiles, composites for packaging, encapsulation of essential oils and volatiles, nanocatalysis, nanoelectronics) (Crini et al. 2019a).

8.2.4 Chemical Modification of Cyclodextrin-Epichlorohydrin Polymers

The chemical modification of a cyclodextrin-based material is an interesting step to introduce specific properties in order to broaden the scope of its potential applications. This was first suggested by Professor French in the 1950s and then studied by Professor Casu in the 1960s (Crini 2014). In general, the objectives are to improve pollutant adsorption properties, to increase selectivity for target pollutants, and to prepare amphoteric polymers. For example, the functionalization of ECP materials can modify characteristics of this class of gel such as selectivity when forming inclusion complexes. By replacing one or more OH groups at a "desired" position and with an appositely designed substitution group, multisite recognition systems can be obtained (Crini and Morcellet 2002). The preparation of homogeneous, selectively derivatized ECP is, however, not an easy task, as reported by Professor Szejtli in the 1980s.

The literature suggests two main methods for modifying ECP materials. The first method was introduced by Professor French in the 1950s and adopted by Professor Wiedenhof in the 1960s and Professor Szejtli in the 1980s (Crini 2014; Morin-Crini et al. 2018a). It consists in grafting specific moieties onto the materials after

cross-linking using conventional modification reactions such as carboxymethylation and aminoalkylation. The main aim is to modify the surface chemistry of cross-linked materials by grafting ionic ligands (cationic and/or anionic) or neutral ligands (amine functions). These new ligands will then also behave as active binding sites and participate in the adsorption process (Crini and Morcellet 2002; Crini 2005b). These grafting reactions, which occur in heterogeneous media, are derived from the chemistry of polysaccharides such as cellulose. The second uses polymers such as carboxymethylcellulose or neutral or ionic reagents such as ammonia, glycidyl trimethylammonium chloride, etc. at the same time as epichlorohydrin in the cross-linking step of the same synthesis reactor. In this approach, the main objective is to control the structure of the materials (porosity, specific surface area, mechanical properties, etc.) while modifying the surface chemistry of the material (Crini and Morcellet 2002; Crini 2005b). Figure 8.8 shows that NMR techniques are also an interesting tool for demonstrating chemical grafting of carboxylic groups on an ECP material.

We have reported ECP materials with both cationic and anionic groups (Fig. 8.9), synthetized in two steps: cross-linking with epichlorohydrin in the presence of 2,3-epoxypropyltrimethylammonium chloride and carboxymethylation reaction (Crini 2005b). The degree of substitution (number of substituents in a cyclodextrin unit, DS) of hydroxyl groups by ionic functions was relatively low (DS < 0.2) but sufficient to exhibit chemisorption properties to remove pollutants from real polycontaminated effluents (Euvrard et al. 2015, 2017). When the cross-linked polymer

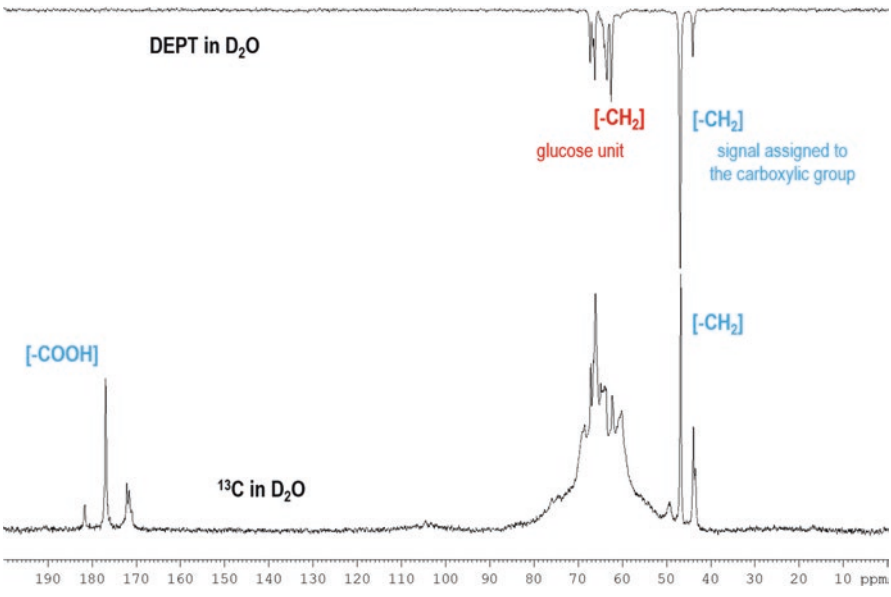

Fig. 8.8 ^{13}C NMR and DEPT spectra in D_2O showing the grafting of carboxylic groups onto the surface of a cross-linked polymer. The presence of two additional peaks at 48 and 180 ppm demonstrates carboxymethylation reaction

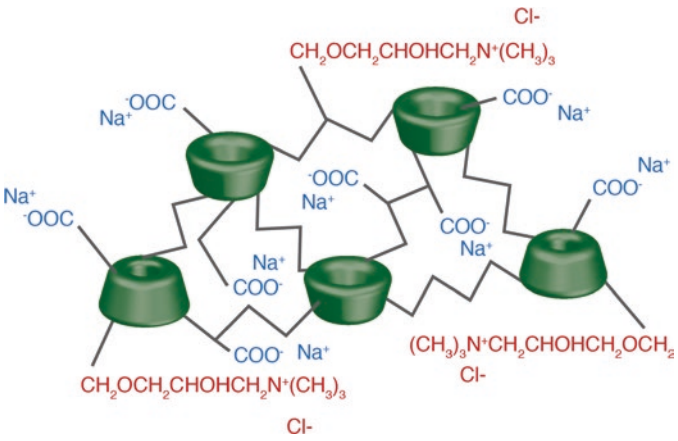

Fig. 8.9 A possible structure of a water-insoluble cyclodextrin-epichlorohydrin polymer containing both cationic and anionic groups

is modified or the cross-linking and modification are carried out simultaneously, the ionic substituents can then be located both on the rims of the cyclodextrins and on the network. This can be explained by the fact that the hydroxyl groups on the glyceryl bridges and on the side chains of the glyceryl monoether polymer are reactive (Szejtli 1982, 1988). Therefore, instead of degree of substitution, it is better to characterize the polymer by the concentration of substituents (mM)/g of the polymer adsorbent (Morin-Crini and Crini 2013). Modification by charged functional units can improve the binding affinity of cyclodextrin molecules for oppositely charged guests. This can be explained by the fact that, because one of the main driving forces for the formation of inclusion complexes by the cyclodextrin molecule in solution is hydrophobic interaction (Szejtli 1982, 1988), a more hydrophobic guest is apt to be accommodated in the cyclodextrin cavity and any hydrophobic functional groups on the guests tend to reduce the binding affinity (Crini and Morcellet 2002; Crini 2003). Other approaches proposed by our group focused on the reaction of epichlorohydrin in the presence of a chemical such as NH_4OH: this method is a convenient and inexpensive way to introduce weakly basic anion-exchange groups into the polymer network (Delval et al. 2005).

The main problem of epichlorohydrin is its toxicity. Other more environmentally and health-friendly cross-linking agents have been proposed. Recently, in collaboration with Professor Martel (University of Lille, France), we have demonstrated that polycarboxylic acids (cross-linking agents considered safe and environmentally friendly) can also be used to prepare bifunctionalized cyclodextrin-based materials, even if their performance is lower than polymers obtained with epichlorohydrin (Euvrard et al. 2016, 2017).

8.3 A Brief History of Water-Insoluble Cyclodextrin-Epichlorohydrin Polymers for Environmental Applications

The idea of preparing ECP materials for analytical purposes, such as gel chromatography, inclusion chromatography, and target substance complexation, has been the focus of attention of scientists worldwide for the past 60 years, but the most intensive studies on their use as adsorbents in wastewater treatment to remove toxic contaminants have only begun in the past two decades.

In the mid-1960s, Professor Solms was the first to demonstrate that α-, β-, and γ-cyclodextrin molecules have the ability to easily form cross-linked networks that could have industrial applications in the field of separation sciences such as chromatography (Solms 1966, 1967, 1969; Solms and Egli 1964, 1965). He has shown that cyclodextrin polymers exhibited strong adsorptive properties as inclusion resins for the separation of various molecules such as aniline, nitrophenols, benzaldehyde, pyridine, iodine, Congo red, and methylene blue and as chromatographic supports for the separation of phenylalanine, tryptophan, vitamins, and perfumes. To demonstrate the fundamental role of cyclodextrin cavities in the performance of ECP materials, Professor Solms compared the results with those obtained with a commercial cross-linking epichlorohydrin-dextran polymer, SEPHADEX®, which did not have inclusion properties. The results were interpreted in terms of the formation of inclusion complex or more simply complexation. Professor Solms also used the concept of "molecular encapsulation," introduced by Professor Cramer about 12 years earlier.

Professor Wiedenhof showed that α-cyclodextrin and β-cyclodextrin gels had a chromatographic behavior comparable to that of SEPHADEX G-25 resin in terms of swelling characteristics and heat resistance but with more interesting performances in terms of complexation. The results confirmed that ECP materials were suitable chromatographic supports for gel inclusion chromatography. Different separations using phenol, benzoic acid, aniline, chlorobenzoic acids, and tyrosine were obtained, and again the results were mainly interpreted using the complexation phenomenon. Professor Wiedenhof pointed out the fact that the ability of the cyclodextrin-based resins to separate different molecules was due to the fact that "each resin contained cyclodextrin voids which were able to form inclusion compounds." He introduced the term "inclusion isotherm" instead of adsorption isotherm.

Professor Wiedenhof was also the first to characterize ECP materials using infrared and NMR data (Wiedenhof 1969; Wiedenhof et al. 1969, 1971; Wiedenhof and Trieling 1971). Figure 8.10 shows the infrared spectrum of an ECP material with the following main bands: OH stretching, 3444 cm^{-1}; CH stretching, 2928 cm^{-1}; CH stretching, 2865 cm^{-1}; CH deformations, 1360 cm^{-1}; OH bending (water), 1629 cm^{-1}; OH bending, 1223 cm^{-1}; bending of COH group/CO stretching glycosidic bond, 1070–1150 cm^{-1}; CO/CC stretching, 1026 cm^{-1}; anomeric CH

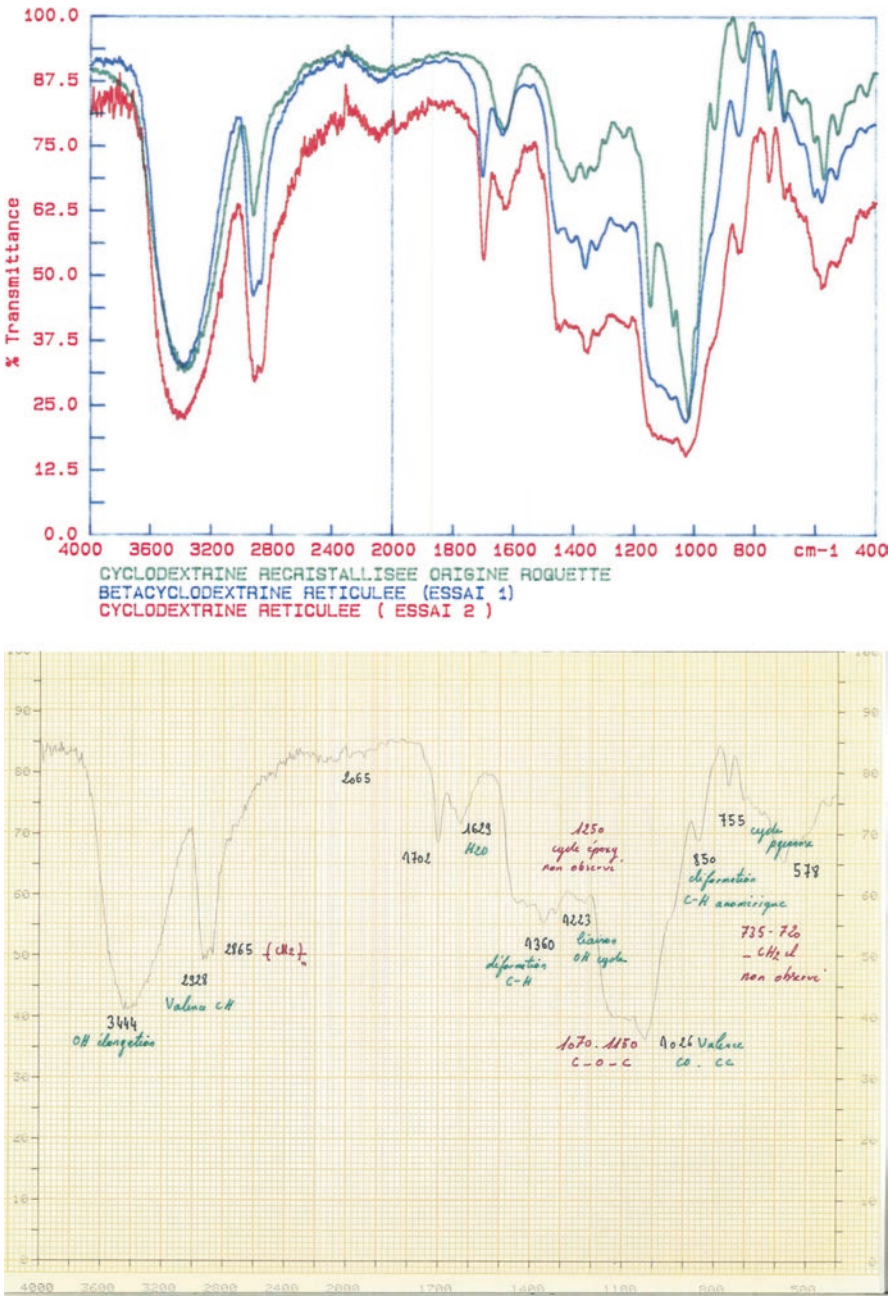

Fig. 8.10 Infrared spectra of a β-cyclodextrin sample and a water-insoluble β-cyclodextrin-epichlorohydrin polymer (above) recorded by our team in 1991 on a Perkin-Elmer spectrophotometer (powder sample using KBr pellet method) and the main assignments for the polymer spectrum (below)

deformation, 850 cm^{-1}; and pyranose ring vibrations, 755 cm^{-1}. This assignment of bands was in accordance with that of Professor Wiedenhof.

In 1970, Professor Hoffman proposed materials with high cyclodextrin contents in bead form for column chromatography. The materials were suitable chromatographic supports for the separation of nucleic acids, nucleotides, nucleosides, and oligonucleotides. Professor Hoffman also demonstrated that ECP materials were useful for separating various positional and optical isomers. The results were interpreted not only in terms of inclusion complexation but also by the presence of anion-exchange interactions, depending on the polymer structure (Hoffman 1970, 1972, 1973).

In the early 1980s, the Hungarian group of Professor Szejtli became very active in the field of ECP polymers for extraction, concentration, and purification of substances. Many significant results on chromatographic, environmental, and pharmaceutical applications have also been obtained (Szejtli 1980, 1982, 1984, 1988). Professor Szejtli has clearly demonstrated that cyclodextrin cavities retain their complexing properties despite the cross-linking reaction. In polymerized form, cyclodextrin molecules are enclosed in a network with loss of mobility, which, to some extent, "exacerbated steric hindrance at the entrance to cavities" (Szejtli 1988). However, this steric effect was "less important when the guest molecule was too large to be fully inserted into a single cavity because a second cyclodextrin molecule in the polymer network can then encapsulate its other extremity." This was the first time that this concept had appeared in the literature (Crini 2014). Professor Szejtli demonstrated that porous polymers had a high adsorption capacity due to their adsorption strength and large high surface area. The introduction of micro- and mesopores offered both abundant adsorption sites and open diffusion pathways for pollutants and thus contributed to improving the adsorption rate. Professor Szejtli was also the first to demonstrate that the presence of unreacted free epichlorohydrin (this cross-linking agent is toxic and far from being "green") in the materials was unlikely because epichlorohydrin was a highly reactive substance and underwent hydrolysis under alkaline reaction conditions. This was important for potential applications in the pharmaceutical field (Szemán et al. 1987; Fenyvesi 1988).

At the end of the 1980s, the main applications of the cyclodextrin polymers consisted of their use in low-pressure liquid chromatography to separate proteins, nucleic acids, mandelic acid derivatives, aromatic amino acids, vitamins, and perfumes (Szejtli 1980, 1982, 1988; Zsadon et al. 1981; Smolkova-Keulemansova 1982), in gas chromatography (Cserháti et al. 1983), in food industry to remove bitter substances from filtered orange and grapefruit juices using batch and column debittering procedures (Shaw and Wilson 1983, 1985; Wagner et al. 1988; Shaw 1990), and also in pharmacy (Szejtli et al. 1978; Szemán et al. 1987; Fenyvesi 1988). From the late 1990s onward, many patents and publications on environmental applications began to appear (Friedman and West 1988; Vanzo 1991; Cserháti and Forgács 1994). Over the past two decades, cyclodextrin polymers have gained considerable attention for their performance in environmental remediation-based applications. In an industry dominated by activated carbons and organic resins, in

which the main barrier of their use lies in the difficulty associated with their regeneration and rapid saturation, respectively, a large interdisciplinary effort has been devoted to the study of new materials including cyclodextrin-based products with unique adsorption and desorption mechanisms. In 2013, we published a historical review of this subject covering the last 50 years (Morin-Crini and Crini 2013).

8.4 Elimination of Environmental Contaminants Using Cross-Linked Cyclodextrin Polymers as Adsorbents

8.4.1 Early Works

As already mentioned, in the mid-1990s, thanks to a collaboration between the University of Lille (Professor Morcellet and Dr. Martel) and the G. Ronzoni Institute (Dr. Torri, Dr. Vecchi and Dr. Crini), our group has begun to focus on ECP materials. This Franco-Italian research program has been supported by several French and Italian industrialists. The objectives were to produce a series of ECP materials with the desired characteristics (e.g., a well-defined spherical size and shape, degree of swelling, cyclodextrin content) and to find applications in gel inclusion chromatography (separation of various natural products), the oil industry (complexation of aromatic pollutants), and textile (complexation of dyes), paper (incorporation in the pulp), tobacco (incorporation in the filters), and personal care and hygiene (superabsorbent polymers to treat odors) sectors (Shao et al. 1996; Crini et al. 1998a, b, 2000; Vecchi et al. 1998; Bertini et al. 1999). At the end of the 1990s, this work was continued at the University of Besançon (France) by Dr. Crini, and a friendly and fruitful collaboration was then established between the three research groups. In the mid-2000s, our research focused on the use of ECP materials in water treatment.

8.4.2 Organics and Dye Removal

For nearly 30 years, our group has been studying the use of ECP materials as adsorbents for the elimination of target contaminants (e.g., aromatic and phenolic substances, dye molecules, metals, anions, pesticides) from synthetic solutions or real effluents, for the treatment of multi-contaminated waters produced by industries such as textile, paper, wood, and surface finishing treatment and more recently for the cleanup of domestic waters and groundwater contaminated by so-called emerging chemicals such as endocrine disruptors.

Our first paper was published in 1996 (Shao et al. 1996) and presented the same year at the Eight International Cyclodextrin Symposium in Budapest. This work was the result of a collaboration between the G. Ronzoni Institute, the University of Lille, and the Textile Technology Center (Canada). We have shown that ECP

materials, mainly in the form of weakly cross-linked gels, can be used as complexing agents to interact with many dyes, e.g., acid, direct, mordant, and reactive dye molecules. The performance in terms of adsorption capacity, evaluated using batch experiments, depended mainly on the range of dye concentrations used in the experiments. Hydroxypropyl-β-cyclodextrin gels had a lower adsorption capacity than β-cyclodextrin gels. No correlation was observed between the performance of the gels and their respective degree of cross-linking. The presence of additives such as NaCl could improve the complexation of the dye, while sodium dodecyl sulfate had the opposite effect. Like Professors Solms and Wiedenhof, we explained these early results mainly by the formation of inclusion complexes and thus by the presence in the materials of cyclodextrin molecules' cavities. We used the notion of complexation by chemisorption and assumed that, in this mechanism, no covalent bonding occurred between the cyclodextrin and the dye. The reaction was a dissociation-association equilibrium, as in the case of the formation of inclusion complexes involving native cyclodextrin molecules in solution, in accordance with the conclusions published by Professor Szejtli (1982, 1988). The cross-linking did not change this property (Shao et al. 1996).

Two years later, in collaboration with an Italian institute, *Stazione Sperimentale per i Combustibili*, we proposed several materials with different cyclodextrin contents, ranging from 20% to 80% w/w (Crini et al. 1998a, b; Vecchi et al. 1998). We have modified the protocol of Professor Solms by increasing the amount of epichlorohydrin to obtain mechanically stable materials but with different mobility in terms of swelling properties and cyclodextrin content. The results demonstrated that ECP materials (particles of irregular shape or regular beads) could also be used as adsorbents to efficiently remove organic contaminants from contaminated water, whatever the quantity of cyclodextrin present in the gels (Crini et al. 1998b; Vecchi et al. 1998). ECP materials were able to interact with contaminants such as chlorophenols, nitrophenols, naphthols, and benzoic acids, in complex solutions, particularly those with hydrophilic properties. They were effective not only at trace levels of contaminants but also at high concentrations. Kinetics of contaminant adsorption were rapid: 2 h was sufficient for reaching the maximum adsorption capacity. The adsorption was much greater in the case of organic molecules which presented compatible size, steric arrangement, and hydrophobicity with the β-cyclodextrin molecules such as β-naphthol, p-nitrophenol, and 4-tert-butylbenzoic acid. However, small molecules such as phenol, known to be too small for the cyclodextrin cavity, were also complexed by the materials (Crini et al. 1998b; Vecchi et al. 1998; Bertini et al. 1999). Comparison with conventional adsorbents such as activated carbons and organic resins showed that ECP gels and beads were more selective and led to better results in terms of elimination, especially at trace levels. A more surprising and interesting result also showed that a high proportion of cyclodextrin was not necessary to have useful performance in terms of pollutant removal (Bertini et al. 1999). In the mid-2000s, Professor Isasi and Professor Christopher H. Evans (Ryerson University, Ontario) reported similar conclusions (Orprecio and Evans 2003; Romo et al. 2004, 2006; Zohrehvand and Evans 2005; García-Zubiri et al. 2006).

The performance of materials in terms of their ability to complex contaminants was strongly related to their structure and swelling properties and therefore to the experimental conditions used during cross-linking, notably the reaction temperature, the amount of caustic soda added, the epichlorohydrin dosage, the volume of water, and the use of a blowing agent or not. The stronger the cross-linking, the lower the swelling properties, and the less interesting the adsorption performance, whatever the quantity of cyclodextrin present in the gels. We also observed in our experiments that performance was independent of the concentration of the pollutant present in the solutions, as well as, more surprisingly, of the amount of cyclodextrin. As ECP did not alter the pH of the solutions to be depolluted (no variation during adsorption), it was not necessary to maintain the initial pH of the solutions during batch tests. However, performance depended on the pH used. Results obtained at pH 2 and pH 6 were similar but were different from those obtained at pH 11, suggesting that the inclusion complexes with cyclodextrin and aromatic and phenolic guests were less stable in basic than in neutral or acidic medium. The results were explained by the different ionization degree of the guest upon the various pH used (Crini et al. 1998b; Vecchi et al. 1998).

One of our objectives was to highlight a correlation between the structure of polymers and their adsorption properties. To do this, we used solid-state ^{13}C NMR spectroscopy techniques such as cross-polarization magic angle spinning with dipolar decoupling (CPMAS), magic angle spinning both with and without dipolar decoupling (DD-MAS and MAS, respectively) and CPMAS with dipolar dephasing (dd-CPMAS), and relaxation parameter measurements. Two components have been found, cross-linked cyclodextrin molecules and polymerized epichlorohydrin. We demonstrated that solid-state NMR techniques were useful to characterize insoluble cross-linked gels with a limited mobility (Crini et al. 1998a). Two years later, we confirmed these results by using high-resolution magic angle spinning with gradients (HRMAS) spectroscopy (Crini et al. 2000). ^{1}H spectra, ^{13}C CPMAS spectra at high temperature, and NOESY, TOCSY, HOHAHA, and $^{1}H/^{13}C$ HSQC spectra are published for the first time. The HRMAS experiments clearly demonstrated the presence of two types of structures in ECP materials, in accordance with the results obtained by CPMAS techniques. The NOESY experiments also demonstrated the interaction between the β-cyclodextrin molecules present in an ECP material and the pollutant adsorbed.

Adsorption results were then explained by taking into account just two important parameters: the presence of cyclodextrin molecules and their degree of cross-linking. The formation of inclusion complexes played the most important role in the mechanism. HRMAS experiments demonstrated not only the presence of two types of structures in ECP materials but also the adsorption mechanism by complexation due to the β-cyclodextrin molecules. NOESY and HOHAHA experiments clearly demonstrated the interaction between the β-cyclodextrin molecules present in an ECP material and the contaminant adsorbed. Our results also highlighted the importance of the structure of the 3D network (Crini et al. 1998b; Vecchi et al. 1998; Bertini et al. 1999). Using solid-state NMR data, we concluded that the mechanism of adsorption can be explained by the presence of two main interactions: the

formation of an inclusion complex due to the β-cyclodextrin molecules and the physical adsorption in the polymer network. In the mid-2000s, Professor Isasi's work also confirmed that the presence of cyclodextrin cavities cannot alone explain the adsorption results and stressed the importance of the polymer network structure and thus of the degree of cross-linking (Romo et al. 2004, 2006, 2008; García-Zubiri et al. 2006; Vélaz et al. 2007).

As the materials were relatively highly cross-linked, they could be used both in batch and column studies (Crini et al. 1998b; Vecchi et al. 1998; Bertini et al. 1999). The method proposed extended the potential applications of these materials because the use of cyclodextrin cross-linked gels in adsorption columns in general had limitations due to hydrodynamic problems and column fouling. Another advantage that has been mentioned was the regeneration of adsorbents after use (Vecchi et al. 1998; Janus et al. 1999). In the 1980s, Professor Szejtli stressed that the reversible nature of complex formation was essential in the case of water treatment (Szejtli et al. 1978; Szejtli 1980, 1982) since it enabled the ECP materials to be regenerated after use as first suggested by Professors Solms, Wiedenhof, and Hoffman. Our group has also confirmed this subsequently (Crini 2003; Crini and Peindy 2006; Crini et al. 2007). The ECP polymers could be easily regenerated, and column adsorption and desorption tests showed that the contaminants adsorbed on cross-linked polymers were successfully released by different types of aqueous alcohol solutions. Unlike for active carbons, the regeneration of these systems is simple and straightforward, which makes them more attractive (Crini et al. 2007, 2019b).

8.4.3 Pollutant Removal Using Modified Cyclodextrin Polymers

It is known that ECP polymers without modification had a low affinity for cationic dyes. An improvement can be obtained by introducing groups such as carboxyl or amino groups onto ECP materials able to complex target dyes. Some materials were prepared by reticulation in the presence of carboxymethyl cellulose. Due to the –OH and –COOH groups in the polymer network, the material was hydrophilic and easily swollen by water, but above all it had ion-exchange properties. Indeed, the gels exhibited more specific and higher adsorption of contaminants from water samples than other traditional ECP materials (Crini et al. 2002, 2003; Crini 2003). The presence of carboxymethyl cellulose also enhanced both accessibility and mobility of the cyclodextrin in the polymer by promoting the swelling of the material in water. However, the results confirmed that, despite identical experimental conditions, as for the performance of unmodified materials, the performances of two batches of modified ECP material may be different, mainly due to the exothermic nature of the cross-linking reaction, which makes it difficult to maintain the temperature in the reaction medium during the synthesis of the material. This last conclusion had previously been reported by Professor Szejtli (Szejtli et al. 1978; Szejtli

1980, 1982). To explain the adsorption results, the mechanisms integrated not only the presence of inclusion due to cyclodextrin cavities but also the effects of electrostatic interactions and van der Waals forces due to the presence of new reactive groups on the surface particles. We have also introduced the presence of pollutant-pollutant hydrophobic interactions that could explain the adsorption properties. However, depending on the experimental conditions used in the batch method, the mechanisms are more complex because other interactions such as ion exchange and chemical microprecipitation may also play a role (Crini 2005a, 2006). All these interactions have been discussed in two comprehensive reviews published in the journal *Progress in Polymer Science* (Morin-Crini and Crini 2013; Morin-Crini et al. 2018a).

In 2005, our group patented a process for the synthesis of cross-linked polysaccharides with ionic functional groups for the simultaneous removal of metals and organic contaminants present at low trace levels in polycontaminated effluents (Crini 2005b). The oligomer (cyclodextrin, linear dextrin) or polymer (starch) was mixed with an epoxy cross-linking agent (1,4-butanediol diglycidyle ether) and 2,3-epoxypropyltrimethylammonium chloride in the presence of NH_4OH at moderate temperature. During the cross-linking step with 1,4-butanediol diglycidyl ether, polymer chains were cationized with 2,3-epoxypropyltrimethylammonium chloride. The cross-linked polymer had both hydroxyl, tertiary amino, and quaternary ammonium groups with different degrees of substitution. The procedure gave beads with excellent physical (e.g., high surface area, 100–150 $m^2\ g^{-1}$) and chemical properties (amphoteric in nature) and uniform and regular shape. The beads were easily wettable, insoluble in water and in organic solvents, and stable in aqueous alkaline or acidic solution. The modified materials possessed a remarkably high swelling capacity in water due to the hydrophilic nature of its cross-linked units. Some porous polymers were capable of swelling in both acidic and basic media, without requiring modification of the pH. All these features were interesting for environmental applications (Crini 2005a, b; Delval et al. 2005; Renault et al. 2008; Charles et al. 2010; Sancey et al. 2010).

The aminoethylation and carboxymethylation of cationic cross-linked materials also enabled the preparation of amphoteric derivatives for possible use in the treatment of wastewater containing metals from surface treatment industries, dyes from textile industries, or organic matter from the paper industry (Renault et al. 2008; Charles et al. 2010; Sancey et al. 2010). The gels possessed typical amphoteric characteristics, due to the protonation and deprotonation of the backbone tertiary amine and pendant carboxyl groups in the polymer network. We proposed these new amphiphilic polymers as complexing resins for the removal of organic matter, turbidity, metals, and boron and fluoride ions from industrial wastewater. The gels could be used over a wide pH range due to their particular electrical character. The comparison with similarly prepared starch-based materials demonstrated the higher capacity for organic compound adsorption, due to the formation of inclusion complexes between cyclodextrins and pollutants.

8.4.4 *Treatment of Organic Substances and Metals Present in Industrial Discharge Waters*

It is extremely difficult to remove pollutants present at low concentrations in industrial discharge waters (Badot et al. 2007; Crini and Badot 2008). For this purpose, a sequential dual approach can be considered: firstly, adsorption onto commercial activated carbon to remove organics, e.g., oils, solvents, and organic load, combined with ion exchange by means of commercial organic resins to remove inorganic pollutants, e.g., metals and anions such as fluorides (Sancey et al. 2010, 2012; Crini 2015a). At the industrial scale, this type of sequence is acknowledged for its efficiency. However, it is an approach to water treatment that combines two methods of separation using two distinct commercial materials. Materials capable of combining the two functions are not yet available (Morin-Crini et al. 2019b).

With the exception of a few works, studies of real applications using cyclodextrin polymers are rare (Vélaz et al. 2007; Romo et al. 2008; Jurecska et al. 2014; Nagy et al. 2014; Crini et al. 2019b; Fenyvesi et al. 2020). Thanks to industrial grants and a French-Romanian research program, at the end of the 2000s, our group carried out the first pilot studies demonstrating that a single ECP with amphoteric and ion-exchange properties material could replace two conventional adsorbents (activated carbon and resins) to effectively treat multi-contaminated effluent (Sancey et al. 2010, 2011a, b, 2012; Sancey and Crini 2012). Coupled with an advanced oxidation preliminary step, adsorption on ECP materials was efficient for the treatment of water with multiple inorganic (e.g., metals, boron, fluoride) and organic (e.g., polycyclic aromatic hydrocarbons, volatile organic compounds, chlorophenols, and alkylphenols) contaminants both from a chemical and from an environmental point of view. The proposed process combined the advantages of oxidation (i.e., mineralization and/or degradation of part of the organic substances) with those of adsorption (i.e., physisorption and chemisorption of the pollutants by the cross-linked framework of the cyclodextrins). After use, the materials could be eliminated by incineration, thus avoiding the need for fastidious and expensive regeneration. This is the first time that such systems were able to treat both so-called emerging pollutants such as chlorophenols and alkylphenols and conventional pollutants such as metals, present in trace amounts in industrial effluents. We were talking about two-in-one materials (Sancey and Crini 2012), a term coined by Professor French in the 1950s and taken up by Professors Casu and Szejtli in the 1960s and 1980s, respectively (Crini 2014).

In the early 2010s, our group proposed biomonitoring tests with plants or animals used as bioindicators to determine and compare the toxicity of industrial effluent from wood, pulp and paper, textile, and surface treatment industries before and after treatment with an ECP material (Sancey et al. 2010, 2011a, b, c, 2012; Charles et al. 2010). For example, to evaluate the usefulness of this process, bioassays based on lettuce seed germination (*Lactuca sativa* L.) were proposed for the first time. The results showed that, after treatment, the impact on lettuce germination was significantly reduced, thanks to the reduction in effluent toxicity. These phytotoxicty tests

using plants such as *Lactuca sativa* were indeed good indicators of contaminant concentrations in wastewater before and after treatment. They were simple, quick, and reliable, being inexpensive and not requiring major equipment (Sancey et al. 2010, 2011a). Later, we also used another short-term bioassay based on the immobilization of a freshwater crustacean, *Daphnia magna*, for the ecotoxicological assessment of industrial discharge waters untreated or treated with ECP materials (Euvrard et al. 2015, 2017; Morin-Crini et al. 2019b). The two bioindicators, *Lactuca sativa* and *Daphnia magna*, were proved to be pertinent to assess the ecotoxicity of polycontaminated discharge waters.

In the mid-2010s, two European and international projects involving French, Italian, Romanian, and Canadian colleagues began on the possibility of using cyclodextrin polymers in water treatment on a semi-industrial scale. In a series of pilot-scale experiments, we confirmed the possible feasibility of its implementation on an industrial scale for the treatment of discharge waters from surface treatment industries (Charles et al. 2014, 2016; Euvrard et al. 2015, 2016, 2017). Chemical results in terms of pollutant abatement have confirmed that the combined use of oxidation and adsorption on a single bifunctionalized ECP material can achieve high levels of pollutant removal, well below regulatory values. Biological tests also demonstrated the efficiency of the adsorption process to radically decrease the effluent toxicity. From all these studies, we concluded that the removal of trace pollutants by an ECP polymer was an efficient tool to significantly decrease pollutant concentrations and water toxicity (Crini et al. 2019b).

Fenyvesi et al. (2020) recently reported a similar conclusion. Their study demonstrates the feasibility of ECP materials for the removal of dissolved micro-pollutants as a tertiary treatment of wastewater in a pilot-scale experiment using real municipal wastewater effluent in the adsorptive post-step of the investigated technology. For example, the measured removal efficiencies were >99% for hormones and bisphenol A and ~85% for ibuprofen and diclofenac in a few minutes of contact time. Bioassays also confirmed the environmental benefits obtained after ECP polymer treatment. The decrease in pollutant concentrations in wastewaters has resulted in a significant reduction in their impact on bioindicators. Their pilot-scale results in removing emerging pollutants such as pharmaceuticals and endocrine disruptors are very encouraging. Now it will be necessary to convince industry to use these materials in their wastewater treatment plants.

Currently, we are working on the treatment of certain industrial baths containing high loads of multiple organic and metallic contaminants through two national and European projects. These complex baths are difficult to treat. In general, they are eliminated by dilution in less loaded effluents and then by physicochemical treatment. A promising solution would be to pre-treat the baths with ECP particles of known size in order to decomplex the contaminants and insolubilize them more effectively. Another challenging application might be the removal of endocrine disruptors such as alkylphenols, alkylphenol polyethoxylates (Priac et al. 2017), and pesticides (Crini et al. 2017) from industrial and municipal discharges. These substances, which appear on a European priority list of potentially hazardous pollutants, are the subject of much research and policy debate. Results of adsorption in

batch mode showed that ECP materials are efficient adsorbents for the removal of fungicides present in polycontaminated solutions (Crini et al. 2017). Interesting affinities were found toward the mixture propiconazole + tebuconazole + epoxiconazole + bromuconazole + difenoconazole, five triazole fungicides. These contaminants are commonly used in the wood industry, vegetable cultivation, horticulture, and agriculture to protect various products against fungal decay.

8.4.5 Mechanisms of Sorption

In spite of the abundance of literature and conclusive results, interpreting the mechanisms of pollutant removal by ECP materials remains a source of debate and sometimes contradiction (Morin-Crini and Crini 2013; Gidwani and Vyas 2014; Cova et al. 2018; Morin-Crini et al. 2018a; Sikder et al. 2019; Liu et al. 2020). Recently, we published a review summarizing the different mechanisms proposed in the literature (Morin-Crini et al. 2018a).

Mechanisms are still being debated because they involve various interactions that can occur simultaneously, making it difficult to interpret the results. Until the 2000s, the literature reported a consensus on the adsorption/sorption mechanism which was mainly a chemical mechanism (chemisorption) via the formation of inclusion complexes (complexation concept introduced by Professor Cramer in the 1950s), as first suggested by Professor Solms in the 1960s to interpret its adsorption results, particularly the adsorption mechanism. At the same time, this concept was also taken up by Professors Wiedenhof and Hoffman. It was only demonstrated in the 1980s by Professor Szejtli (Crini 2005a; Morin-Crini and Crini 2013). Professor Szejtli also used the notion of association complexes (also suggested by Professor Cramer in the 1950s), i.e., the cooperation effect between cyclodextrin cavities during the adsorption process, in addition to the formation of inclusion complexes to interpret the adsorption mechanism (Crini 2014). Since the mid-2000s, studies have also highlighted the role played by the macromolecular network formed by the cross-linking agent. The performance of an ECP material depended not only on the presence of cyclodextrin units but also on its structure and therefore on the cross-linking step.

Since the 1980s, to explain the chemical effectiveness of ECP materials in water treatment, the concept of inclusion complex or more simply complexation was used by all researchers working on this subject, demonstrating the predominant role of the cyclodextrin molecules in the performance of an ECP material. This concept is mainly the formation of inclusion complexes between cyclodextrin and pollutant molecules. Our first studies also confirmed it (Crini et al. 1998b; Bertini et al. 1999; Janus et al. 1999). Kinetic studies have indicated longer contact times required to achieve equilibrium independently of polymer structure, suggesting chemisorption mechanism such as molecular encapsulation or complexation. During synthesis, the parameter that must be followed the most closely to obtain a material efficient for forming complexes was the quantity of cyclodextrin present per gram of material used. The greater this quantity (for a constant amount of adsorbent), the greater the complexing capacity of the material (Bertini et al. 1999). This first led to an important notion, namely, that a molecule of cyclodextrin corresponds to a guest

molecule. The complexation reaction depended also on the polarity of the guest molecule, stressing the major role played by the cyclodextrin in the mechanism (Crini et al. 2002, 2003; Crini 2003). It was the most hydrophobic part of the host molecule that was preferentially included in the cavity. The more hydrophobic the guest molecule, the greater the stability of the complex, and the more efficient the decontamination performance. Similar conclusions were previously reported by Professor Szejtli.

Later, studying the formation of complexes with low molecular weight model organic molecules such as phenol, benzene, and naphthol derivatives, up to more complicated chemical structures with higher molecular weights (dyes, polycyclic aromatic hydrocarbons), we have obtained four surprising results regarding the adsorption of bulky molecules (Crini and Peindy 2006; Crini et al. 2007; Crini 2008; Charles et al. 2010). The first showed that, even if the guest dye was too large, it could be complexed by the ECP polymers, irrespective of the size of the cyclodextrin ring. Even if the pollutant is too bulky, it could be immobilized in a complex, thanks to the cooperative effect of the cyclodextrin molecules of the macromolecular network. Several different cyclodextrin cavities could encapsulate different parts of a pollutant. This conclusion was in accordance with the notion of association complexes introduced by Professor Cramer for soluble native cyclodextrins in solution or solid state and demonstrated by Professor Szejtli for insoluble cyclodextrin polymers (Crini 2014). Two types of complexes are distinguished: complexes with simple model molecules for which inclusion is total – these they called inclusion complexes – and complexes with larger molecules for which inclusion would only be partial, which they called association complexes, and which can be the preponderant form of interaction or simply occur alongside inclusion complexes. This is why some bulky molecules are adsorbed by ECP polymers (Crini 2003, 2008; Crini and Peindy 2006; Crini et al. 2007; Charles et al. 2010; Sancey et al. 2010, 2011a). This was previously demonstrated using HRMAS experiments (Crini et al. 2000). Later, we also reported that there may be a cooperative effect not only between the cavities but also between the cyclodextrin cavities and the 3D polymer network, as shown in Fig. 8.11 (Euvrard et al. 2015, 2016, 2017).

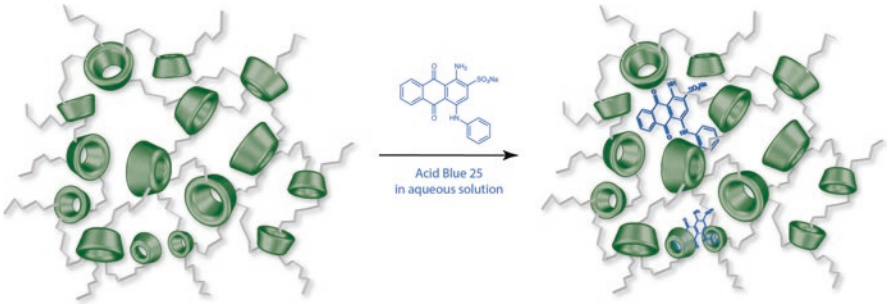

Fig. 8.11 Schematic illustration of the cooperative effect between cyclodextrin cavities and/or the role of the 3D polymer network during the removal of the Acid Blue 25 dye present in aqueous solution by an ECP material

The second result indicated that for polymers containing only a small proportion of cyclodextrin, the quantity of pollutant bound by the material was often much greater than the quantity of cyclodextrin present in the material, contradicting the notion that one molecule of cyclodextrin traps one pollutant molecule. For contaminants containing aromatic groups, we also introduced the occurrence of hydrophobic interactions leading to pollutant stacking (π–π interactions) and/or the formation of multilayers of contaminants at the surface of the polymers, in agreement with Freundlich's model. In the presence of phenolic derivatives with high dipole moments, electrostatic interactions of the dipole-dipole type between pollutant molecules were also possible, in particular at high concentrations (Crini and Peindy 2006; Crini et al. 2007). Another surprising result was the type of cyclodextrin incorporated into the gel. We prepared materials based on α-, β-, and γ-cyclodextrin using the same experimental conditions during the synthesis. The results showed that contaminants could be removed regardless of the type of cyclodextrin polymer used. For example, the cross-linked α-cyclodextrin polymer can adsorb Acid Blue 25 dye, which is too large to be a guest. For the three types of polymers (with a close cyclodextrin content but with different swelling properties), the performance could be comparable (Crini 2005a, b). A response was found in the structure of each macromolecular network. Similar conclusions have been published by Professor Yilmaz (Yilmaz Ozmen and Yilmaz 2007, 2008). The last result was related to the shape of the materials. As expected, the more regular the structure and spherical distribution of the beads, the higher their performance. However, the results were independent of the amount of cyclodextrin but dependent on the degree of cross-linking. With the beads, kinetic studies have indicated short contact times necessary to reach equilibrium, suggesting rapid adsorption surface. This led us to highlight the importance of physisorption in the process of pollutant removal by ECP polymers. This physisorption mechanism acts as a complement to chemisorption by complexation (Crini and Peindy 2006; Crini 2008).

We explained these four results mainly by the network structure of the materials and their shape and swelling properties, closely related to the degree of cross-linking, and also by the presence of cyclodextrin units (Morin-Crini and Crini 2012, 2013; Morin-Crini et al. 2015). For ECP materials, the question arises as to the predominance of inclusion complexes due to the cyclodextrin molecules or association complexes due to the polymer network. Currently, the consensus is rather for the latter, with the results being mainly due to the structure of the macromolecular network independent of the quantity of cyclodextrin actually present (Morin-Crini et al. 2018a).

The concept of association complexes is less simple since there can be a cooperative effect, not only between the cyclodextrin cavities themselves (particularly for large guest molecules) but also between the cyclodextrin cavities and those of the polymer network. To demonstrate this conclusion, we synthetized materials composed of non-cyclic oligosaccharides (linear dextrins, sugars such as sucrose which has similar dimensions and chemical composition to cyclodextrin moieties) and polysaccharides (starch fractions rich in amylose or amylopectin components, chitosan) under the same experimental conditions as the ECP polymers (Badot et al.

2007; Crini et al. 2007; Crini 2008; Sancey et al. 2010, 2011a, b, 2012). These cross-linked materials have been studied in pollutant complexing experiments, and their different performances were compared. It was found that, in some cases, cross-linked starches and cross-linked dextrins had higher adsorption capacities than cross-linked cyclodextrin polymers even if they did not have the type of cavity that participates in the inclusion complexes. The density of the cross-linking mainly explained these results. The cross-linking reaction creates a particular 3D macromolecular structure (recognized as difficult to control) forming a mesh that is also susceptible to bind pollutants (Fig. 8.11). The polymer network therefore offers cross-linked oligosaccharide and polysaccharide materials the possibility to sequester contaminants through effects of cooperation not only between cyclodextrin molecules but also via additional interactions in the mesh with diffusion into the network (Morin-Crini et al. 2013, 2015, 2018a). These mesh interactions have a greater role when the degree of cross-linking is lower, enabling the polymer to swell in water and thus enhance diffusion of the contaminants through the network. Professors Isasi and Yilmaz have carried out similar studies, which have led to similar conclusions.

8.5 Conclusions

This chapter reviews the research conducted over the past 30 years by our research group on water-insoluble cyclodextrin-epichlorohydrin polymers. It shows the progress of our work and our contribution to a better understanding of these materials. Table 8.1 summarizes all our contributions on cyclodextrin polymers during the period 1996–2019. Table 8.2 reports the ten most cited papers in the ISI Web of Science and Scopus databases since 1998 with "cyclodextrin polymer" and "pollutant removal" in the topic of our works.

Cyclodextrin-epichlorohydrin polymers can be used as complexing adsorbents to remove contaminants from polycontaminated effluents. They have several advantages: technological simplicity in their use, efficiency in the elimination of substances even at trace levels, easily recyclable (regeneration) or disposable (incineration), and beneficial to the environment to reduce the impact/toxicity of an effluent. However, as industrial production of cyclodextrin-epichlorohydrin polymers has not started, the materials produced at lab scale suffer from variability in their characteristics. There is also a non-negligible cost difference with conventional materials such as activated carbon used in wastewater treatment. Therefore, cyclodextrin polymer materials are basically at the laboratory study stage, and there is still a lot of work to be done to demonstrate their potential on an industrial scale.

On this subject, the first study on the industrial-scale use of cyclodextrin-epichlorohydrin polymers to remove emerging pollutants such as endocrine disrupters from wastewater treatment plant effluents has just been published (Fenyvesi et al. 2020). Chemical abatement and toxicity mitigation of wastewater have shown that adsorption on modified ECP materials can be an interesting additional

Table 8.1 Recap of the main results published by our group on water-insoluble cyclodextrin-epichlorohydrin polymers, from 1996 to 2019

Year	Result	Reference(s)
1996	The first paper on the complexation of dye molecules by ECP materials. β-cyclodextrin- and hydroxypropyl-β-cyclodextrin-based gels are able to adsorb acid, direct, mordant, and reactive textile dyes without specificity. Performance depends on the concentration range of the dye molecules in the experiments. The influence of pH is rather low, while that of ionic strength is important on their performance. The performance depends on the type of anionic surfactants and the salts present in the solution. Hydroxypropyl-β-cyclodextrin gels have a lower adsorption capacity than β-cyclodextrin gels. The results highlight not only the essential role of the cavities of cyclodextrin molecules but also of the macromolecular network of the gel. No correlation was observed between the performance of the gels and their respective degree of cross-linking	Shao et al. (1996)
1998	The synthesis of ECP materials is straightforward and facile; this is made possible by the high reactivity of cyclodextrin and of the cross-linking agent in basic media. The materials obtained are in the form of high molecular weight networks, without porosity and with a very low specific surface area. The 3D macromolecular network is composed of areas of cross-linked cyclodextrin units and areas of macromolecules corresponding to long chains of polymerized epichlorohydrin, with different molecular mobility: this structure is demonstrated for the first time using solid-state NMR measurements	Crini et al. (1998a)
	CPMAS technique and relaxation measurements are useful to characterize cross-linked gels with a limited mobility. The ^{13}C spin lattice relaxation values of the materials are very similar to those of the crystalline β-cyclodextrin form. The β-cyclodextrin trapped inside the network does not seem to change its mobility whatever the amount of epichlorohydrin. The addition of water to polymers results in better resolution in the NMR spectra and significantly increases the ^{13}C spin lattice relaxation values reflecting strong interactions between cyclodextrin molecules and water. The ^{1}H spin lattice relaxation values in the rotating frame are equivalent, indicating the homogenous nature of samples	
	Although the synthesis conditions that determine the properties of the ECP material are closely controlled, the cross-linking density remains difficult to predict. The structure of a macromolecular network depends directly on the degree of cross-linking: the higher the degree, the more the cross-linking increases, making the material rigid, which reduces both the ability of the material to swell in water and the concentration and accessibility of the CD cavities. The materials are amphiphilic, with both hydrophilic properties (owing to the presence of carbohydrate units and especially of their hydroxyl groups) and hydrophobic properties (due notably to the methyl groups of the cross-linking agent and to the ether bonds of cyclodextrin-glyceryl bonds)	

1998	For water treatment, especially in batch methods, particles that are not spherical and do not have regular shapes and sizes are sufficient to achieve satisfactory results in pollutant removal. ECP materials are effective materials for adsorbing aromatic compounds, particularly phenolic pollutants. Kinetics of pollutant adsorption on ECP materials are rapid: 2 h is sufficient for reaching the maximum adsorption capacity. The adsorption is much greater in the case of contaminants which present compatible size, steric arrangement, and hydrophobicity with the β-cyclodextrin molecules such as β-naphthol, p-nitrophenol, and 4-tert-butylbenzoic acid. The quantity of the retained compound depends on the concentration of the aqueous solution	Crini et al. (1998b) and Vecchi et al. (1998)
	Adsorption capacities obtained at pH 2 and pH 6 are similar but are different from those obtained at pH 11, suggesting that the inclusion complexes with cyclodextrin and aromatic and phenolic guests are less stable in basic than in neutral or acidic medium: the results can be explained by the different ionization degrees of the guest upon the various pH used. There is a close relationship between the degree of cross-linking and the complexation performance of the polymers, independent of the amount of cyclodextrin. A high proportion of cyclodextrin is not necessary to have useful adsorption results. The quantity of pollutant adsorbed is always higher than the content of cyclodextrin, suggesting that the macromolecular network participates in the complexation, independent of the method used (batch method or column setup). The mechanism of adsorption is physical adsorption in the polymer network and/or the formation of an inclusion complex and/or the formation of hydrophobic pollutant-pollutant interactions. ECP materials are chemically, thermally, and even mechanically stable when the degree of crosslinking is sufficient. For the complete regeneration of the material, it is necessary to use a mixture of water and ethanol	

(continued)

Table 8.1 (continued)

Year	Result	Reference(s)
1999	The presence of numerous hydroxyl groups gives ECP materials hydration properties of varying intensities depending on the degree of cross-linking. The macromolecular network is both hydrophilic and hydrophobic, a property that can be very useful for applications in aqueous media and that ECP materials can be used to efficiently remove pollutants, notably organics, from contaminated water, whatever the quantity of cyclodextrin present in the materials. Even for polymers containing few cyclodextrin units, the amount of pollutant retained by the adsorbent may be much greater than the amount of cyclodextrin present	Bertini et al. (1999) and Janus et al. (1999)
	β-Cyclodextrin polymers more effectively sequester pollutants, particularly those with hydrophilic properties. They have excellent performance even if they have specific surface areas that are much smaller than carbons. Contaminants with complex structures and high molecular weights are more easily complexed. It is much more advantageous to prepare materials in the form of regular, spherical beads with controlled swelling properties, especially for column setup	
	The increase of the β-cyclodextrin content increases the performance of the materials toward the aromatic compounds tested. A hydrophobic pollutant has a greater affinity for the ECP polymer with a higher cyclodextrin content, while the opposite behavior can be observed with a hydrophilic pollutant. However, a high proportion of cyclodextrin is not necessary to have useful adsorption results, and there is a relationship between the performance of the ECP materials and their molecular structure. When the degree of cross-linking is too high, the quantity of contaminants adsorbed decreases. Performances varies considerably from one batch of gels to another although the experimental conditions used in their synthesis are the same, due to their different degrees of swelling. The results obtained at basic pH are more in agreement with the association constants between β-cyclodextrin and the contaminants than those obtained in acidic conditions or in water. ECP materials can be regenerated without significant loss of adsorption capacity	
2000	HRMAS spectroscopy is useful to characterize insoluble cross-linked materials (gels or beads) with a limited mobility. ^{1}H spectra, ^{13}C CPMAS spectra at high temperature, and NOESY, TOCSY, HOHAHA, and HSQC $^{1}H/^{13}C$ spectra are published for the first time. HRMAS experiments demonstrate not only the presence of two types of structures in ECP materials but also the adsorption mechanism by complexation due to the β-cyclodextrin molecules. With the help of NOESY and HOHAHA experiments, it is possible to highlight the formation of an inclusion complex	Crini et al. (2000)
2001	Adsorption using ECP materials is a procedure of choice for the removal of organic compounds from wastewater. Cyclodextrin polymers exhibit high adsorption capacities toward phenolic compounds and dyes and high selectivity	Crini et al. (2001)
	The mechanism of adsorption can be explained by the presence of several interactions: the formation of an inclusion complex due to the β-cyclodextrin molecules, and/or the physical adsorption in the polymer network, and/or the formation of hydrophobic-hydrophobic pollutant-pollutant interactions	

2002	The first review on water-insoluble cyclodextrin-epichlorohydrin polymers published by our group. ECP materials are by far the most studied adsorbents due to their chemical effectiveness in removing a wide range of pollutants. These polymers are a versatile tool in separation science and for environmental purposes because cyclodextrin chemistry and polyfunctional character offer various possibilities for preparing different types of materials. However, it is difficult to find commercial sources of ECP materials with guaranteed reproducible properties. Although the role of the cyclodextrin is essential, a compromise must be found between the amount of cyclodextrin and the degree of cross-linking to obtain useful results in low-pressure chromatography and in adsorption-oriented processes	Crini and Morcellet (2002)
2002	ECP materials containing carboxylic groups are synthetized; these modified materials exhibit better adsorption capacities toward the same contaminants tested, pointing out the important role of the carboxylic groups. Grafting ionic or chelating groups on ECP materials can result in the modification of the polymer surface chemistry, which can then give rise to new interactions, in addition to inclusion in the cyclodextrin cavities during adsorption experiments. We also confirm the presence of pollutant-pollutant hydrophobic interactions which can explain the adsorption properties. For the first time, the notion of association complexes, i.e., cooperation between cyclodextrin cavities, introduced by Professor Szejtli, in addition to inclusion complexes, is proposed to explain the performance of the materials	Crini et al. (2002)
2003	The results confirm that, despite identical experimental conditions, the performances of two batches of ECP material can be different due to the exothermic nature of the cross-linking reaction which makes difficult to maintain the temperature within the reaction medium during the synthesis of the material. The particular macromolecular structure of the non-modified ECP polymers is composed of units that can also bind pollutants. Adsorption mechanism is also due to the presence of dye-dye interactions	Crini (2003)
2003	Grafting cationic groups on an ECP gel in well-controlled experimental conditions yields excellent adsorbents of acid, reactive, and direct dyes. Again the presence of cyclodextrin cavities cannot alone explain the adsorption results; we also stress the importance of the polymer network (the degree of cross-linking) and the chemical interactions via acid-base interactions, ion exchange, and hydrogen bonding due to the carboxylic groups. For modified ECP materials, the results are strongly dependent on the pH but independent on the cyclodextrin content	Crini et al. (2003)

(continued)

Table 8.1 (continued)

Year	Result	Reference(s)
2005	The complexation process results from a multitude of interactions between the three components of the adsorption system, i.e., the cyclodextrin molecules of the material, the contaminants, and the effluent to be treated. The role of cyclodextrins fundamentally occurs through the formation of inclusion and/or association complexes. We note the importance of the moieties at the surface of the ECP material rather than inclusion to explain the mechanisms	Crini (2005a, 2005b) and Delval et al. (2005)
	Materials composed of oligosaccharides (linear dextrins, sugars) or polysaccharides such as starches, prepared in the same cross-linking conditions as ECP materials, were studied in pollutant complexing experiments, and their different performances were compared. The results demonstrate that the most important parameter is the degree of cross-linking: the higher the degree of cross-linking, the lower the performance of the material. Cross-linked starches and cross-linked linear dextrins show adsorption capacities that are higher than those of ECP materials even though they do not possess the type of cavity that participates in inclusion complexes. Very high adsorption properties are described with respect to the same contaminants studied for several years. The materials are also capable of treating real effluents. For modified polymers, the mechanism is mainly due to electrostatic interactions, surface adsorption, and dye-dye interactions, which explain the rapid contact times	
	To obtain adsorbents able to efficiently process both minerals (including metals) and organics, it is necessary to modify or activate the networks by grafting different types of moieties (neutral or ionic): new bifunctionalized ECP materials with high porosity and surface area are synthetized	
2006	Contaminants with a complex structure and a high molecular weight are more easily complexed, due to an effect of cooperation between cyclodextrin molecules and the polymer network. The performance of the materials is strictly linked to the conditions of their synthesis: the degree of cross-linking is a key element in the same way as the presence of the cyclodextrin molecules. Adsorption kinetics are strongly dependent on the degree of cross-linking	Crini (2006) and Crini and Peindy (2006)
	Inclusion aside, various mechanisms are proposed depending on the type of function or ligand grafted, e.g., ion exchange, electrostatic attraction, chelation, and/or precipitation	
2007	The structure and the polarity of the contaminants studied as well as the experimental conditions (e.g., dosage of material, contaminant concentration, pH, ionic strength, etc.) of the batch used can contribute to complicating the interpretations on the adsorption mechanism. The reproducibility of the performances of cyclodextrin polymers used as adsorbents for the removal of dyes and the regeneration of the materials after saturation is reported	Crini et al. (2007)

2008	For non-modified materials, the cross-linking step not only influences the concentration and accessibility of the cyclodextrin molecules (the greater the accessibility of the cyclodextrin sites, the higher the adsorption properties) but also the swelling, which determines the diffusional properties of the gels. For modified ECP materials, the results also depend on the density of the cross-linking	Crini (2008), Gimbert et al. (2008), and Renault et al. (2008)
2010	A novel material, presenting amino, hydroxyl, and carboxylic groups coupled with the incorporation of cyclodextrins, ensures the simultaneous adsorption of different contaminants onto the surface material. The comparison with a similarly prepared starch-based material demonstrates the higher capacity for organic compound adsorption, due to the formation of inclusion complexes between cyclodextrins and pollutants	Charles et al. (2010) and Sancey et al. (2010)
	Our group proposes biomonitoring tests with plants or animals to determine and compare the toxicity of industrial effluent from wood, pulp and paper, textile, and surface treatment industries before and after treatment with an ECP material. The first study on the evaluation of the phytotoxicity of polycontaminated industrial effluents using the lettuce plant *Lactuca sativa* as a bioindicator is published. Both the chemical abatement and toxicity mitigation of wastewater show that adsorption on modified ECP materials can be an interesting additional treatment step for the detoxification of industrial effluents	
2011	The results confirm that the adsorption using an ECP material is a viable alternative for treating industrial wastewaters. Biological tests demonstrate the efficiency of the adsorption process to radically decrease the effluent toxicity. A modified ECP material can also interact with metals and anions such as fluoride ions present both in synthetic solutions and in real effluents. The comparison of its adsorption capacity with that of a similarly prepared starch material shows superior efficiency toward organic compounds, though maintaining the same efficiency toward inorganic species. Metal removal is dependent on the mass of material and contact time but independent of the pollutant load. Adsorption reaches equilibrium in 60 min irrespective of the metal considered	Sancey et al. (2011a, b, c)
2012	ECP materials remove residual turbidity and leads to a significant decrease in the residual chemical oxygen demand present in industrial water discharge. Adsorption on ECP materials represents an interesting tool for preventing or decreasing the environmental impact of industrial effluent: pilot-scale experiments confirm the possible feasibility of its implementation on an industrial scale. Plant biomonitoring tests are useful tools to evaluate and compare the toxicity of real effluents, presenting trace metal polycontamination. We indicate for the first time that the coupling of oxidation with adsorption on an ECP material allows the efficient removal of organic pollutant present in polycontaminated effluents. The proposed process combines the advantages of oxidation (i.e., mineralization and/or degradation of part of the organic substances) with those of adsorption (i.e., physisorption and chemisorption of the contaminants by the cross-linked framework of the cyclodextrins)	Sancey and Crini (2012) and Sancey et al. (2012)

(continued)

Table 8.1 (continued)

Year	Result	Reference(s)
2013	A comprehensive historical review on the ECP materials. The exact role of the cross-linking agent on the properties of the materials is still a matter of debate, and many contradictions have been published in the literature. Some works suggest that the quantity of epichlorohydrin should be limited, while others advise that it should be increased	Morin-Crini and Crini (2013)
2014	There is a relationship between the chemical structure of the organic pollutant and the performance of the materials. Synthesis of bifunctionalized ECP materials containing ionic ligands and able to simultaneously remove organics, metals, and anions: the greater the number of grafted ligands, the higher the material's performance. A single material with both cationic and anionic charges is capable of removing multi-contaminants present at concentrations close to a few milligrams per liter but also at trace concentrations in synthetic solutions and in real discharge waters. The materials have amphoteric properties and can therefore be used over a wide range of pH values. The pre-treatment of a real effluent by an oxidation step significantly improves the efficiency of the subsequent adsorption	Crini (2014) and Charles et al. (2014)
2015	Amphoteric ECP materials are promising in wastewater treatment: they are able to decontaminate effluent with multiple contaminants present as traces in complex mixtures. Pilot-scale experiments demonstrate that ECP treatment alone or in combination with advanced oxidation pre-treatment can remove polycyclic aromatic hydrocarbons, volatile organic compounds, chlorophenols, and alkylphenols. In real effluents, competition effects appear, especially because of the presence of calcium at high concentrations, which can compete with other contaminants for the adsorption sires of the ECP materials	Crini (2015a, b) and Euvrard et al. (2015)
2015	The first book on cyclodextrins published by our group	Morin-Crini et al. (2015)
2016	Results confirm that the combined use of oxidation and adsorption on a bifunctionalized ECP material achieves high levels of pollutant removal. The complexing of contaminants with an ECP material is a possible decontamination process on an industrial scale for several reasons: efficiency in the elimination of contaminants even at trace levels, simple from a technological point of view, easily recyclable (regeneration) or disposable (incineration), interesting from an environmental point of view (to reduce the impact/toxicity of a effluent)	Charles et al. (2016) and Euvrard et al. (2016)
	Although host-guest inclusion, on the one hand, and surface adsorption and ion exchange on the other hand are the main phenomena interacting between modified ECP materials and contaminants, the interpretation of the results is difficult due to the wide diversity of polluting species present in real effluents, involving numerous other interactions in the adsorption process	

2017	Solid-state NMR and X-ray diffraction analysis are interesting techniques to characterize modified ECP materials	Crini et al. (2017), Euvrard et al. (2017), and Priac et al. (2017)
	The first study on the use of cyclodextrin-based materials to remove a mixture of five fungicides. Significant affinities are found with the mixture propiconazole + tebuconazole + epoxiconazole + bromuconazole + difenoconazole, five pesticides listed as priority substances in Europe. Multilayer adsorption due to π–π bonds and steric effects can be advanced to explain the differences of adsorption observed	
	ECP materials can also remove significantly endocrine disruptors such as alkylphenols and alkylphenol polyethoxylates	
2018	An updated review on the applications of ECP materials. Non-modified and modified ECP materials have proved to be efficient and more advantageous than conventional systems in water and wastewater treatment	Crini et al. (2018a)
2018	The first review on the adsorption mechanisms described during the complexation of contaminants by ECP materials. The mechanisms are still being debated because they involve various interactions that can occur simultaneously. There is nevertheless a consensus on the fundamental role of cyclodextrin units	Morin-Crini et al. (2018a)
2018	Two other books published on cyclodextrins	Fourmentin et al. (2018a, b)
2019	The last review on non-conventional sorbents for wastewater treatment	Crini et al. (2019b)

Table 8.2 The ten most cited papers in the ISI Web of Science and Scopus databases since 1998 with "cyclodextrin polymer" and "pollutant removal" in the topic of our works, July 02, 2020

Journal	Article title	ISI Web of Science Times cited	Scopus Times cited	References
Bioresource Technology	Non-conventional low-cost adsorbents for dye removal: a review	2777	2872	Crini (2006)
Progress in Polymer Science	Recent developments in polysaccharide-based materials used as adsorbents in wastewater treatment	1382	1396	Crini (2005a)
Separation and Purification Technology	Removal of C.I. Basic Green 4 (Malachite Green) from aqueous solutions by adsorption using cyclodextrin-based adsorbent: kinetic and equilibrium studies	674	688	Crini et al. (2007)
Chemical Reviews	Review: a history of cyclodextrins	599	604	Crini (2014)
Dyes and Pigments	Kinetic and equilibrium studies on the removal of cationic dyes from aqueous solution by adsorption onto a cyclodextrin polymer	307	317	Crini (2008)
Journal of Separation Science	Synthesis, characterization, and applications of adsorbents containing cyclodextrins	238	247	Crini and Morcellet (2002)
Progress in Polymer Science	Environmental applications of water-insoluble beta-cyclodextrin-epichlorohydrin polymers	216	212	Morin-Crini and Crini (2013)
Bioresource Technology	Studies on adsorption of dyes on beta-cyclodextrin polymers	175	190	Crini (2003)
Journal of Applied Polymer Science	Sorption of aromatic compounds in water using insoluble cyclodextrin polymers	137	132	Crini et al. (1998b)
Journal of Hazardous Materials	Adsorption of C.I. Basic Blue 9 on cyclodextrin-based material containing carboxylic groups	120	127	Crini and Peindy (2006)

treatment step for the detoxification of municipal effluents. Their results clearly indicated that ECP materials are efficient as non-conventional adsorbents to treat complex mixtures. Bioassays also confirmed the environmental benefits obtained after ECP polymer treatment: the decrease in pollutant concentrations in effluents resulted in a significant reduction of toxicity water. The authors also showed that both inclusion complex formation of pollutants with cyclodextrin and physisorption due to the polymer network played a role in the adsorption mechanism. These chemical and biological results are very encouraging. Now, the industry should be convinced to use these materials in their wastewater treatment plants as we mentioned in our last review (Morin-Crini et al. 2018a).

Table 8.3 Authors of recent research on pollutant removal by insoluble cyclodextrin-epichlorohydrin materials (selected papers)

Corresponding author	Country	Pollutants(s)	Experimental protocol	Effluents[a,b]	Mechanism(s)	References
Wilson L.D.	Canada	P-nitrophenol, trinitrophenol	Batch	SS	Inclusion complexation, interstitial binding sites, hydrogen bonds	Danquah et al. (2018)
Hao X.K.	China	Nitrophenols	Batch	SS	Inclusion complexation	Li and Hao (2019)
Ji H.	China	2,4,6-Trichlorophenyl, bisphenol A	Batch	SS	π-π interactions, host-guest interactions	Huang et al. (2020)
Li X.	China	Erochrome black T	Batch	SS	Electrostratic interactions, inclusion complexation, π-π interactions, intraparticle diffusion	Li et al. (2019)
Lü Q.	China	Bisphenol S	Batch	SS	Inclusion complexation, hydrogen bonds, hydrophobic interactions	Lü et al. (2018)
Luo J	China	Phenol	Batch	SS	Inclusion complexation	Cai et al. (2017)
Tsai F.C.	China	Acid orange 7	Batch	SS	Intraparticle diffusion, inclusion complexation, hydrophobic interactions	Zhang et al. (2017)
Xie X.C.	China	Bisphenol A, 3-phenylphenol, ethinyl estradiol	Batch	SS	Inclusion complexation, hydrogen bonds, hydrophobic interactions, association complexes due to the polymer network	Xu et al. (2019)
Zhao H.	China	Lead, cadmium	Batch	SS	Chemisorption	Zheng et al. (2019)
Zhang Y.	China	Methylene blue, methyl purple, Congo red	Batch	SS	Inclusion complexation, hydrogen bonds, hydrophobic interactions	Zhang et al. (2019)
Zhu L.P.	China	Bisphenol A, 2-naphthol, 2,4-dichlorophenol, propranolol hydrochloride	Batch	SS	Inclusion complexation, specific interactions	Wang et al. (2017)

(continued)

Table 8.3 (continued)

Corresponding author	Country	Pollutants(s)	Experimental protocol	Effluents[a,b]	Mechanism(s)	References
Fenyvesi É.	Hungary	Estradiol, ethinyl estradiol, estriol, diclofenac, ibuprofen, bisphenol A	Column, batch	RE, SS	Inclusion complexation, hydrogen bonds, hydrophobic interactions, association complexes due to the polymer network	Fenyvesi et al. (2020)
Nagy Z.M.	Hungary	Bisphenol A, hormones, ibuprofen, ketoprofen, naproxen, diclofenac	Column, batch	SS, RE	Inclusion complexation	Nagy et al. (2014)
Vyas A.	India	Drugs	Batch	SS	Inclusion complexation, specific interactions	Gidwani and Vyas (2014)
Doostan F.	Iran	Cobalt, zinc, copper	Batch	SS, RE	Chemisorption, electrostatic interactions	Heydari et al. (2017)
Nojavan S.	Iran	Benzene, toluene, ethylbenzene, xylenes	Solid-phase extraction	SS	Inclusion complexation	Nojavan and Yazdanpanah (2017)
Sheibani H.	Iran	Methylene blue, phenol, 1-naphthol, 2-naphthol	Batch	SS	Inclusion complexation, adsorption surface, specific interactions	Heydari et al. (2018)
Mishael Y.G.	Israel	Bisphenol A	Batch, column	SS, RE	Hydrophobic size inclusion, electrostatic interactions	Shabtai and Mishael (2018)
Cosma P.	Italy	Atrazine	Batch	SS	Inclusion complexation, complex surface adsorption, association complexes	Romita et al. (2019)
Kurasaki M.	Japan	Metals, phenols, aromatics	Batch	SS	Inclusion complexation, surface adsorption, association complexes, electrostatic interactions	Sikder et al. (2019)
Ogawa K.	Japan	Bisphenol A, 4-nonylphenol, methyl orange	Batch	SS	Inclusion complexation	Ogawa and Hiromi (2015)
Sikder M.T.	Japan	Cadmium	Batch	SS	Chemisorption	Sikder et al. (2017)

Kwak S.Y.	Korea	Bisphenol A	Batch	SS	Inclusion complexation	Lee and Kwak (2020)
Valente A.J.M.	Portugal	Metals, phenols, aromatics, dyes, pharmaceuticals	Batch, column	SS, RE	Inclusion complexation, surface adsorption, association complexes, specific interactions	Cova et al. (2018)
Isasi J.R.	Spain	1-Naphthol, 2-acetanaphthalene, tannic acid	Batch	SS	Inclusion complexation, specific interactions	Fujiyoshi et al. (2019)
Gabaldón J.A.	Spain	Direct blue 78	Batch	SS	Inclusion complexation, hydrogen bonds, hydrophobic interactions	Murcia-Salvador et al. (2019)
Uyar T.	Turkey	Phenolphthalein, phenanthrene	Filtration, batch	SS	Inclusion complexation	Celebioglu et al. (2019)
Dichtel W.R.	USA	Perfluorooctanoic acid	Batch	SS	Inclusion complexation, hydrophobic interactions	Xiao et al. (2019)
Suri R.P.S.	USA	Steroid hormones, perfluorooctanoic acid, bisphenol A	Batch	SS	Inclusion complexation	Bhattarai et al. (2014)

[a]*SS* synthetic solutions
[b]*RE* real effluents

Finally, from a fundamental point of view, cross-linking cyclodextrin polymers continue to be of interest to the scientific community, as evidenced by the many publications on the subject that are published each year (Table 8.3), and I am sure it will last for years.

Acknowledgments The solid-state NMR spectroscopy of cyclodextrins was my entrance to the world of oligosaccharides and polysaccharides, and a lot of what I know I owe to my two scientific mentors Professor Michel Morcellet (*Laboratoire de Chimie Macromoléculaire*, Lille, France) and Research Director Giangiacomo Torri (*Istituto di Chimica e Biochimica G. Ronzoni*, Milan, Italy), to whom I would like to express my immense gratitude. This chapter is dedicated to them in recognition of their constant inspiration and for their excellent spirit of cooperation, unlimited enthusiasm, and great friendship.

I am also particularly grateful to all those who have contributed to this work through several friendly and fruitful national, European, and international collaborations, with particular attention to Dr. Nadia Morin-Crini (Besançon, France), Pr. Benito Casu (Milan, Italy), Pr. Yahya Lekchiri (Oudja, Morocco), Pr. Bernard Martel (Lille, France), Mr. Cesare Cosentino (Milan, Italy), Dr. Carmen Vecchi (Milan, Italy), Dr. Marco Guerrini (Milan, Italy), Dr. Anna-Maria Naggi (Milan, Italy), Pr. Edwin Yates (Liverpool, UK), Dr. Marcella Chiari (Milan, Italy), Dr. Peter Winterton (Toulouse, France), Dr. Corina Bradu (Bucharest, Romania), Dr. Bruno Perly (Gif-sur-Yvette, France), Pr. Joëlle Morcellet (Lille, France), Dr. Ludovic Janus (Lille, France), Pr. Joël Vebrel (Besançon, France), Pr. Pierre-Marie Badot (Besançon, France), Dr. Sophie Gavoille (Besançon, France), Mr. Xavier Hutinet (Champlitte, France), Mr. Jean-François Minary (Devecey, France), Dr. Danielle Bonenfant (Montréal, Canada), Pr. Elena Vismara (Milan, Italy), Dr. Giuseppe Trunfio (Messina, Italy), Pr. Robert Haussler (Montréal, Canada), Pr. Sophie Fourmentin (Dunkerque, France), Dr. Marc Fourmentin (Dunkerque, France), Pr. Eric Lichtfouse (Aix-Marseille, France), Pr. Lee D. Wilson (Saskatchewan, Canada), Dr. Éva Fenyvesi (Budapest, Hungary), Dr. Vincent Placet (Besançon, France), and Pr. Andrei Sarbu (Bucharest, Romania).

I would also like to thank all the PhD students (Sabrina Bertini, Davide Sforzini, Angelo Cambiaghi, Yvan Lunghi, Angelo Ficaro, Roberta Suardi, Alessandro Ficarra, Nadia Morin, Mustapha Quendouchen, Frank Delval, Olivier Adam, François Renault, Bertrand Sancey, Jérémie Charles, Anne Priac, Elise Euvrard) and postdoctoral fellows (Harmel N. Peindy, Capucine Robert, Trann Phan, Giuseppe Trunfio, Lucian Staicu, Sonia Loiacono, Chiara Mongiovi) who have worked on this topic.

Finally, I would like to sincerely thank the industrialists (*SILAC Industrie*, *Papeterie du Doubs*, *GEMDOUBS*, *Minoterie Pont*, *Altadis-Seita*, *Papeterie de Mandeure*, *Incotex Textile*, *Electrolyse Abbaye d'Acey*, *VMC Pêche*, *Zindel, Galvanoplast*, *Roquette*, CycloLab) and the various financial contributors to our projects (*Agence de l'eau Rhône Méditerranée Corse*, *FEDER*, *Europe*, *INRA Transfert*, *Région Franche-Comté*, *Ville de Besançon*, *OSEO/ANVAR*, *Incubateur de Franche-Comté*, *Agence de l'Environnement et de la Maîtrise de l'Energie*, *Université de Franche-Comté*).

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