



# Outstanding contribution of Professor József Szejtli to cyclodextrin applications in foods, cosmetics, drugs, chromatography and biotechnology: a review

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## Abstract

Cyclodextrins, natural oligosaccharides obtained from starch by enzymatic degradation, have been discovered 130 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 an eminent scientist and a visionary. Since the mid-1950s, he has devoted his life to cyclodextrins, publishing more than 500 publications, including 106 patent applications. Professor Szejtli is internationally recognized for his outstanding contribution to the cyclodextrin science and considered to be the “Godfather of Cyclodextrins.” This paper is a tribute to his scientific oeuvre. After a brief overview of his personal life, some important works published by Professor Szejtli in more than fifty years of career were highlighted. For example, he was the first to synthesize the <sup>14</sup>C labeled glucose-based  $\beta$ -cyclodextrin and published his oral metabolism. He was also the first to describe the acid hydrolysis of  $\beta$ -cyclodextrin and discovered that  $\beta$ -cyclodextrin formed inclusion complexes with hydrochloric acid. Professor Szejtli is the founder of International Cyclodextrin Symposia, the first of which was held in 1981 in Budapest.

**Keywords** Professor Szejtli · Tribute · Cyclodextrins · Applications

## Introduction

Cyclodextrins, natural oligosaccharides obtained from starch by enzymatic degradation, were discovered serendipitously in 1891 by the French pharmacist Villiers. However, expensive to produce, the three main native cyclodextrins, *i.e.*,  $\alpha$ -

$\beta$ - and  $\gamma$ -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

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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). Nowadays, cyclodextrins are used in practically all chemical and biological domains, both industrially and academically (Crini et al. 2018; Fourmentin et al. 2018a, 2018b; Arora et al. 2019; Fenyvesi et al. 2019; Morin-Crini et al. 2019).

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 Scharinger 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. 1), a Hungarian carbohydrate chemist. Indeed, 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, he published more than 500 publications on cyclodextrins and has given more than 200 invited lectures throughout his career. Professor Szejtli is internationally recognized and considered as an eminent scientist and a visionary, the “Godfather of Cyclodextrins” (D’Souza and Lipkowitz 1998; Loeve and Normand 2011; Crini 2014). Professor Tsuneji Nagai designated him as “Mr. Cyclodextrin.”

This paper is a tribute to his scientific oeuvre. First, it gives a general overview of his personal life and outstanding scientific career. Then, we highlight selected important works on starch and cyclodextrins published over five



Fig. 1 Professor József Szejtli; image credit: cycloLab

decades by Professor Szejtli. This article is an abridged version of the chapter published by Crini et al. (2020) in the series Environmental Chemistry for a Sustainable World.

## József Szejtli (1933–2004)

József Szejtli was born on December 28, 1933 in Nagykánizsa, 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 Ph.D. 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.

During 1963–1964, Dr. Szejtli was a Post-Doctorate 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, c, 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). 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 traveled extensively to convince everyone, from scientists and students to industrials, that cyclodextrins held great commercial promise. In the meantime, the first toxicological



**Fig. 2** Professor Szejtli when he received the permission from Chinoïn to establish the Biochemical Research Laboratory in 1972; source: CycloLab archives

studies had established that cyclodextrin administered orally was a harmless substance. In 1974, an important research project on cyclodextrins was launched at CHINOÏN 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, 1978c; 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 8th 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. His scientific oeuvre 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 (e.g., Szejtli 1977a, 1978c, 1982c, 1983a, 1985a, b, 1986a, 1987a, e, 1988b, 1990, 1992b, 1994, 1997, 1998, 2002, 2003, 2004a,b,c, 2005; Szejtli et al. 1978a, b, c, d; Szente et al. 1993; Szente and Szejtli 1998, 1999a, 2004; Redenti et al. 2000, 2001) and book chapters (e.g., Szejtli 1982a, b, c, b, 1984b, 1984c, 1987b, 1991a, 1991c, 1992a, 1996a, 1996b, 1996c, 1996d, 2004b, 2004c; Pitha et al. 1983; Szente et al. 1984c, 1999b; Szejtli et al. 1987; Szente and Szejtli 1988, 1999; Hinze et al. 1999; Morva et al. 1999), and 5 books (source: Cyclodextrin News Database).

Professor Szejtli has also 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, 20 Ph.D. dissertations, postdoctoral students and visiting scientists from various countries. Professor Szejtli was a member of various





**Fig. 3** With Professor Nagai celebrating the birthday of Professor Szejtli (70), a few months before his death; *source*: CycloLab archives



**Fig. 4** The József Szejtli medal; *source*: CycloLab

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 Brasilava (1988), the Moët-Hennessy Prize of Paris (1991) and the Széchenyi Prize (Budapest 2003).

In spring 2004, Professor Szejtli retired from his position in CycloLab but remained active in science (Fig. 3). He has devoted his life to cyclodextrins. József Szejtli tragically passed away on 26<sup>th</sup> November 2004.

At the 80th anniversary of his birth, in 2013, CycloLab established the Szejtli Prize (Fig. 4) to preserve his legacy, keep his memory alive and recognize his ground-breaking 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. With the ceremony at the International Cyclodextrin Symposia, the CycloLab's team hopes to keep Professor Szejtli in memory for long.

## Szejtli's scientific achievements

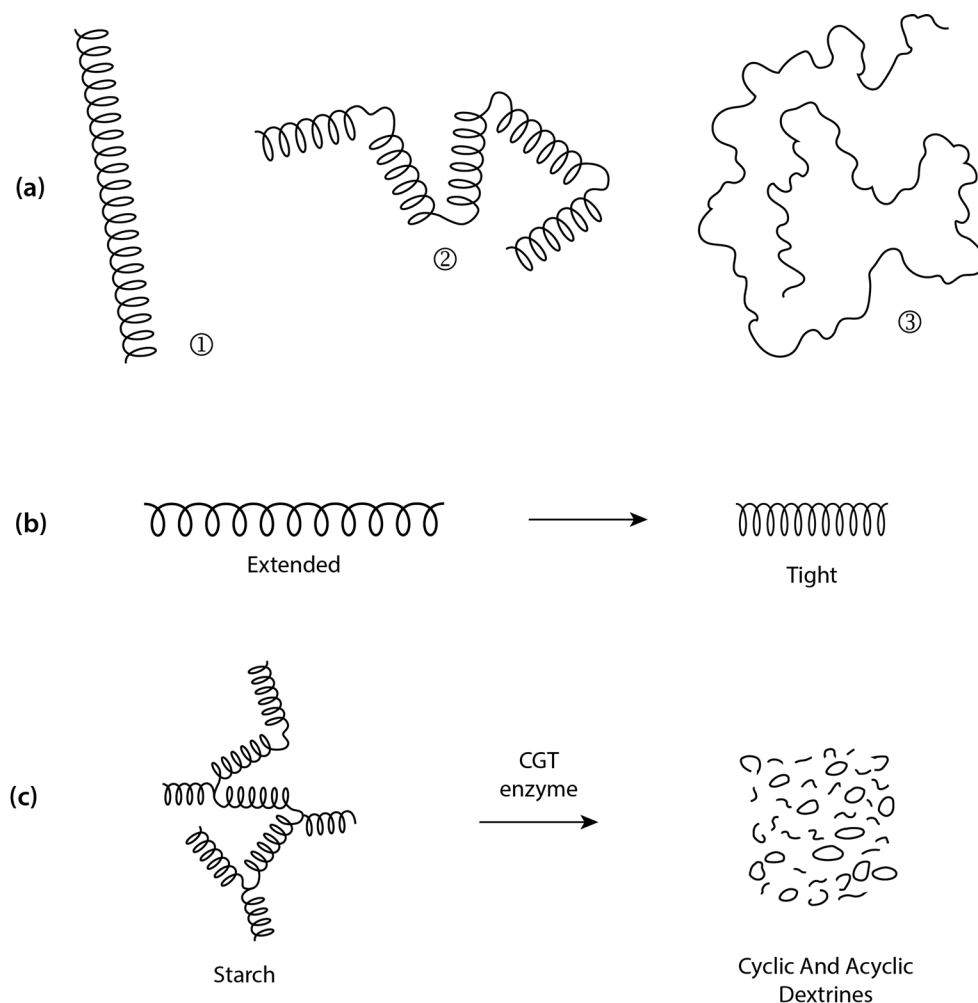
### Early work in starch

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  $\alpha$ -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. 5): 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).

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

**Fig. 5 a:** The rigid, rod-like helix (1), the segmented flexible coil-like helical structure (2), and 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 dextrans by cyclodextrin glycosyltransferase enzyme; *adapted from Szejtli (1971, 1975, 1982a)*



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. 5). 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 dextrans (Fig. 5) 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 glycosyltransferase 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, 1959b), 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 non-terminal bonds. The velocity of retrogradation decreased with increasing temperature and potato amylose containing 1–2 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, 1967b, 1968). Studying the amylose–iodine complex at low pH, 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 polyiodine chains, and this length 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.

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 *Commandante* Fidel Castro (Fig. 6). Professor Szejtli then turned exclusively to the cyclodextrins from the 1970s onwards. Indeed, after his return in Hungary, he initiated a comprehensive cyclodextrin research and development.

### 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. His works were spread across different disciplines: Chemistry, Biochemistry, Biology, Health Science, Agriculture, Environmental Sciences, etc. With his



**Fig. 6** Professor Szejtli referring to the *Commandante* Fidel Castro, University of Havana, Cuba, 1970; source: CycloLab archives

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 detail 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. 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 was 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).

Professor Szejtli was also a visionary. Since the mid-1980s, he suggested new potential markets for cyclodextrins, *e.g.*, in biotechnology (Szejtli 1985a, 1986a, 1990, 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 cosmeo-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 1990, 2003).

## Highlights in Szejtli’s fundamentals works

### 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

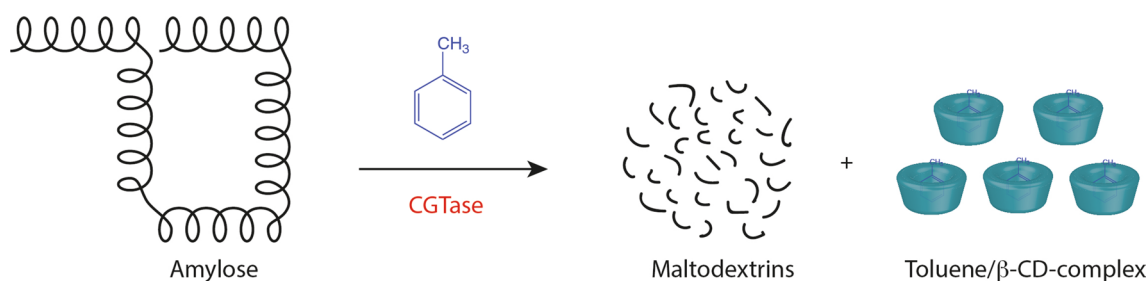
by Professor Szejtli. In this paper, Professor Szejtli pursued the history of cyclodextrins written by Professor French, which was also updated 9 and 16 years later by Loftsson and Duchêne (2007), and Crini (2014), respectively. The history as written by Professor Szejtli was divided into three major periods (Szejtli 1998): discovery 1891–1935, exploration 1935–1970 and utilization 1970 to the present day. 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, wrote: “Cyclodextrins can be consumed by humans as ingredients of drugs, foods, or cosmetics.”

### 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 laboratory curiosities and were extremely expensive. The method of preparation of  $\beta$ -cyclodextrin, illustrated in Fig. 7, 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 glucosyltransferase enzyme was added. The purification of the enzyme was made by affinity chromatography. In the solvent technology (Fig. 12), an appropriate complex-forming agent was added to the conversion mixture. If toluene was added to this system, the toluene/ $\beta$ -cyclodextrin complex formed was separated immediately, and the conversion was shifted toward  $\beta$ -cyclodextrin formation. If *n*-decanol was added to the conversion mixture,  $\alpha$ -cyclodextrin was mainly produced, whereas with cyclohexadecanol,  $\gamma$ -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

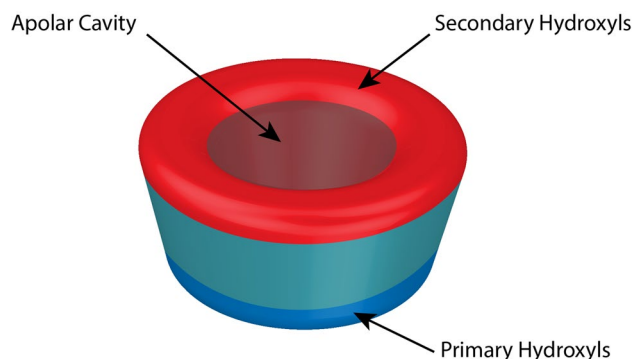




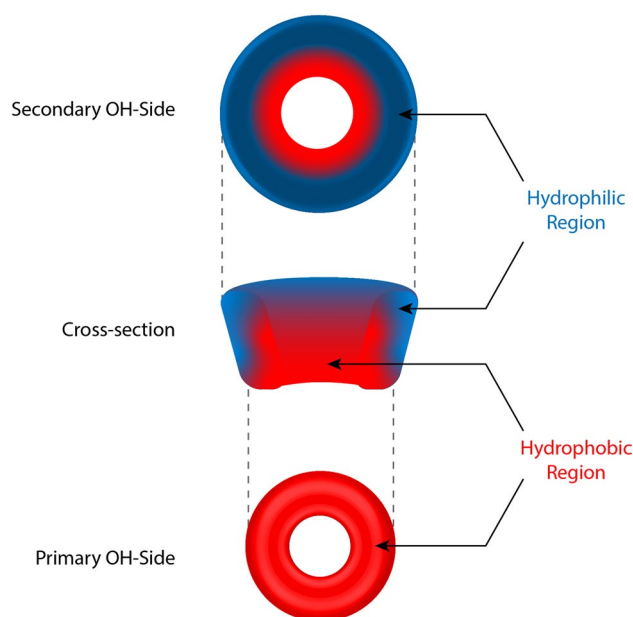
**Fig. 7** Production of  $\beta$ -cyclodextrin; adapted from Szejtli (1988a)

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).

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  $\alpha$ -1, 4-type glycosidic linkages, in agreement with the conclusions described by Professor Casu (Crini 2014). The same structural units were found in starch. 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 non-bonding 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 representation of a “cyclodextrin capsule” is reported in Fig. 8. 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 9 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 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 intra-molecular hydrogen bonds in  $\beta$ -cyclodextrin counteracted its hydration and reduced its solubility as compared to other native cyclodextrins (Szejtli 1978, c, 1982a, 1995).



**Fig. 8** 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; the lining of the internal cavity is formed by hydrogen atoms and glycosidic oxygen bridge atoms; therefore, this surface is slightly apolar; adapted from Szejtli (1978)



**Fig. 9** Hydrophilic and hydrophobic regions of cyclodextrins; adapted from Szejtli (2004a)



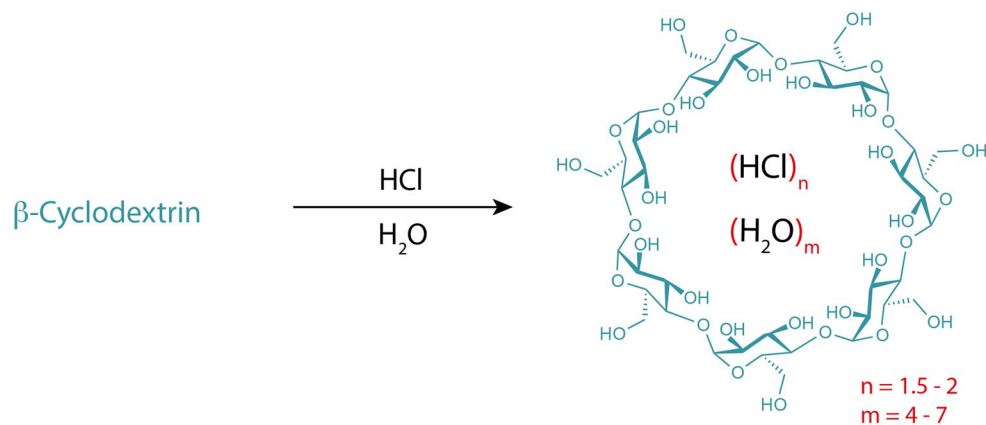
## Types, formation and structures of inclusion complexes

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  $\beta$ -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  $\beta$ -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  $\beta$ -cyclodextrin increased during the reaction because the  $\alpha$ -1,4-bonds present in the macrocycle and in linear dextrans, *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. 10). This complex contained 1.8 molecules of hydrochloric acid per cyclodextrin unit. After storage at room

temperature for one year, it still retained 1 mol of hydrochloric acid, and storing the product in sealed vials for one 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, c).

In the 1980s, Professor Szejtli pointed out the fact the preparation of cyclodextrin inclusion complexes was simple. Their preparation and characterization was 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 were 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, c), powder X-ray diffraction (Szejtli 1977b, 1978c), polarography (Daruhazi et al. 1982, Szejtli 1982a), thin-layer chromatography (Szejtli 1978, c, 1982b), gas chromatography (Szejtli 1982c), UV–visible spectroscopy (Szejtli et al. 1978b), nuclear magnetic resonance spectroscopy (Szejtli 1983b), infrared spectroscopy (Szejtli et al. 1978b), thermo-analysis (Szejtli 1978, c), mass spectrometry (Szejtli et al. 1977a, 1997b) and differential scanning calorimetry (Novák et al. 1993). For instance, mass spectrometric investigations proved that from a mixture of (*O,O*-dimethyl

**Fig. 10** Structure of the  $\beta$ -cyclodextrin–HCl complex proposed by Professor Szejtli; adapted from Szejtli (1977b)



*O*-(2,2-dichlorovinyl)-phosphate with  $\beta$ -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  $\beta$ -cyclodextrin, demonstrating that the insecticide was bound in the complex.

### 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. 1998; 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 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. 11), 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).

### 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 as follows: (1) the modification of the physicochemical properties of the guest molecule; (2) the modification of the chemical activity of the guest; (3) the stabilization of substances sensitive to light or to oxygen; (4) the uptake of volatile substances; (5) the complexation and transport of substances; and (6) technical advantages. 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 (Szejtli 1987b, 1988a; Szejtli et al. 1987), biotechnological (Szejtli 1990, 1991a) or medical (Szejtli 1994) applications.

### Cyclodextrins derivatives

Besides being “molecular capsules,” cyclodextrins were “basic materials” for the production of derivatives and polymers, biologically active substances and reagents in

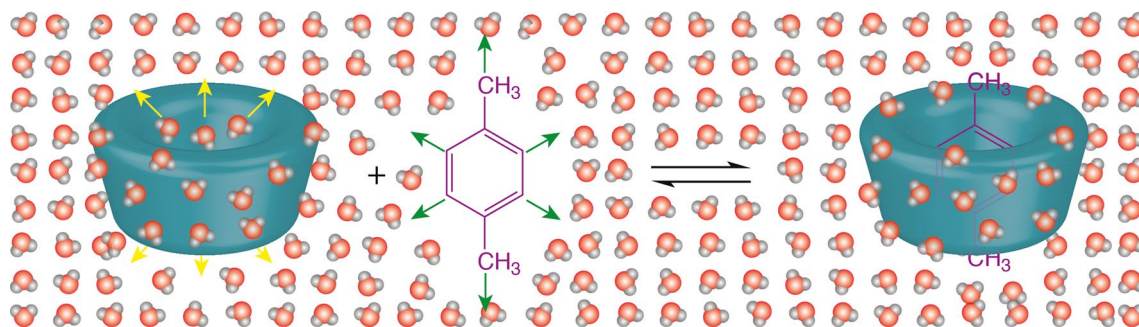
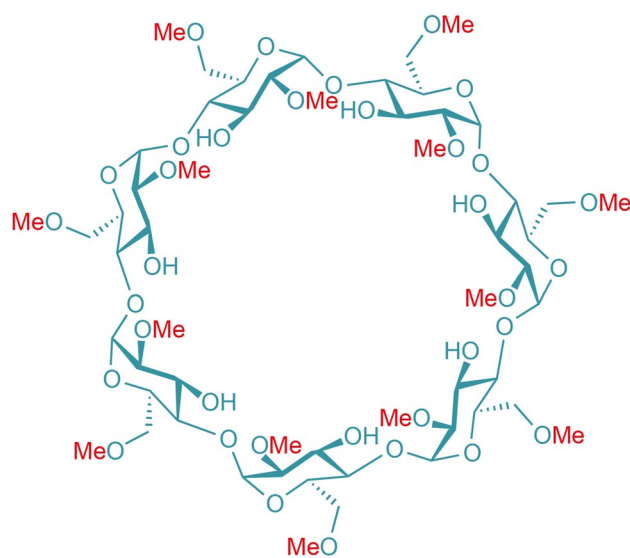


Fig. 11 Formation of an inclusion complex between *p*-xylene, the guest and a cyclodextrin molecule; adapted from Szejtli (1978)

analytical chemistry and diagnostics. Professor Szejtli prepared various cyclodextrin derivatives and polymers (Szejtli 1982a, 1984a, 1988a, 1998; Szente and Szejtli 1999). 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 amino-cyclodextrins, by eliminating the hydrogen atom of the C5-CH<sub>2</sub>OH 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 (1) to improve the solubility of the native cyclodextrins, (2) to improve the association between the cyclodextrin and its guest, (3) to reduce its reactivity, (4) to bind specific functional groups and/or (5) to create new molecular or macromolecular structures, *e.g.*, for chromatographic purposes.

Among the numerous cyclodextrin derivatives, heptakis-(2,6-di-*O*-methyl)- $\beta$ -cyclodextrin or dimethyl- $\beta$ -cyclodextrin, abbreviated DIMEB, has been particularly studied by Professor Szejtli (Szejtli et al. 1980f, 1982a; Szejtli 1983b, 1984a). Its structure is reported in Fig. 12. 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  $\beta$ -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 dimethylsulfate, 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  $\beta$ -cyclodextrins containing 60–70% of DIMEB, 10–15% of heptakis-(2,3,6-tri-*O*-methyl)- $\beta$ -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



**Fig. 12** Structure of heptakis-(2,6-di-*O*-methyl)- $\beta$ -cyclodextrin or dimethyl- $\beta$ -cyclodextrin, abbreviated DIMEB

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 degree 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.

## Highlights in the fields of applications studied by Professor Szejtli

### Cyclodextrins in foods

The applications of cyclodextrins as multifunctional food ingredients in various domains have been studied in detail (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). 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). 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. 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  $\beta$ -cyclodextrin as reported by Szente and Szejtli (1986). In contact with water, the complex bound flavor substances were released immediately. In a previous work (Lindner et al. 1981), flavor- $\beta$ -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.

### 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 33<sup>rd</sup> Starch Convention of the Arbeitsgemeinschaft Getreideforschung 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 in 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).

### 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 Frömring, 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  $\beta$ -cyclodextrin in pharmaceutical industries, pointed out the enhancement of drug bioavailability by  $\beta$ -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, b; Szente et al. 1984a). Two years later, in 1979, Professor Szejtli unambiguously proved that orally applied  $\beta$ -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,  $^{14}\text{C}$ - $\beta$ -cyclodextrin or  $^{14}\text{C}$ -glucose were given orally to rats, and the radioactivity was measured in blood by liquid scintillation method. The results showed that the peak of radioactivity appeared in blood within 10 min in the case of labeled glucose, while a rather protracted and low maximum was found between 2 and 10 h in the case of labeled  $\beta$ -cyclodextrin. The values of respiration of  $^{14}\text{C}$  proved that  $\beta$ -cyclodextrin was metabolized in rat. Eight hours after oral administration of 313 mg/kg  $^{14}\text{C}$ - $\beta$ -cyclodextrin, a very small amount (3  $\mu\text{g}$ ) was detected in 1000  $\mu\text{g}$  of blood. On the basis of investigations of radioactivity distribution, it was claimed that  $\beta$ -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.”

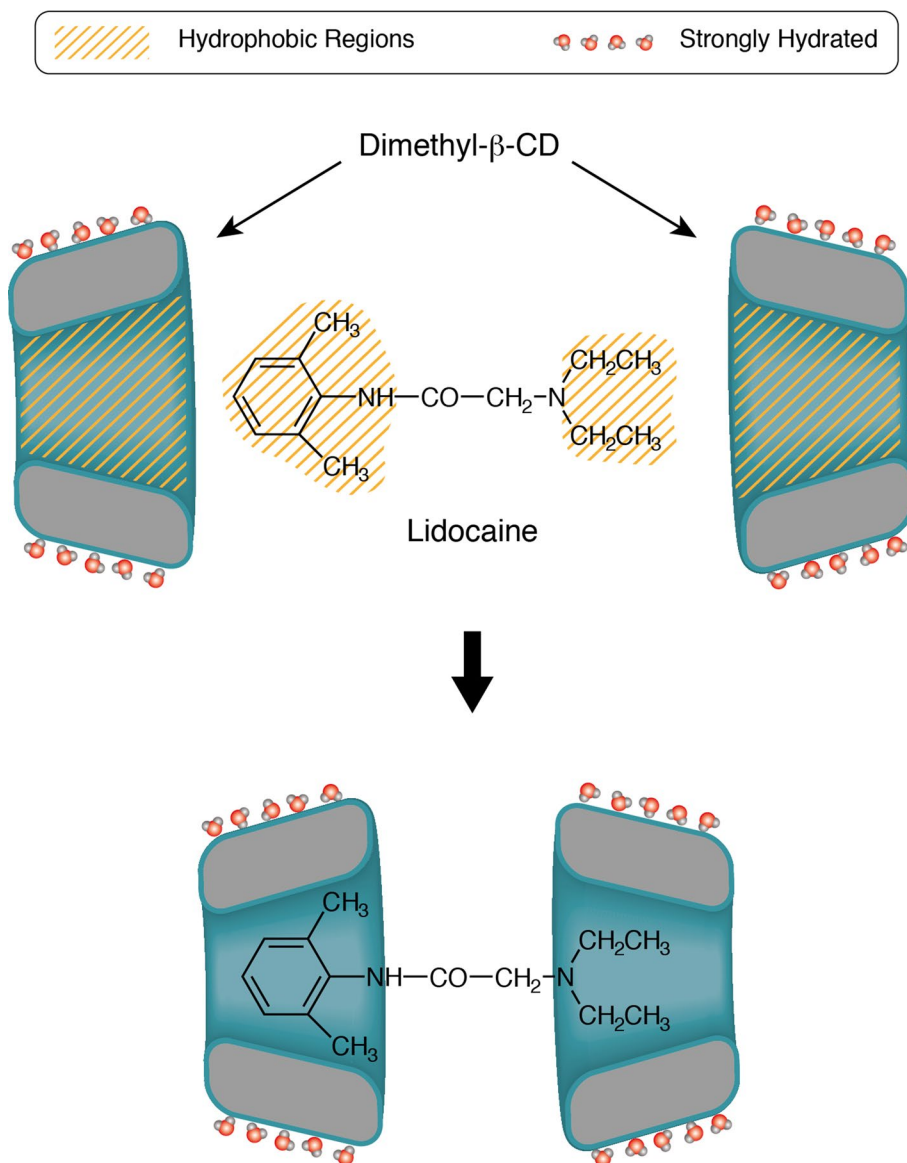
At the beginning of the 1980s, several patents on highly soluble cyclodextrin derivatives including DIMEB and polymers were patented by Professor Szejtli and his collaborators (Szejtli et al. 1980d, e, g, h, 1981b, b). The DIMEB was an interesting substance in drug formulation due to the fact that it 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. 13. 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  $\beta$ -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 Frömring and Szejtli wrote a famous

**Fig. 13** Schematic illustration of the interaction between lidocaine and dimethyl- $\beta$ -cyclodextrin DIMEB; adapted from Szejtli (1983b)



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

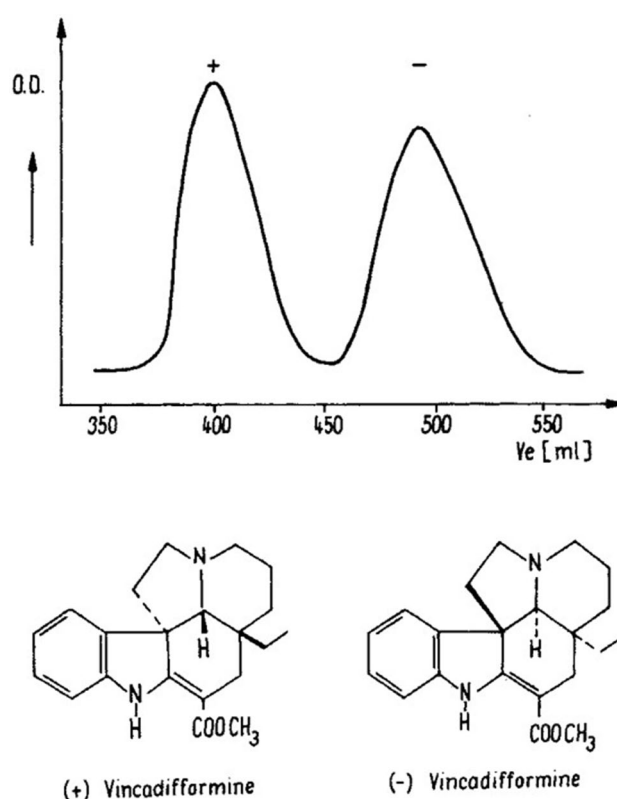
### Applications of cyclodextrins in chromatography

Inclusion complexation of lipophilic guest molecules by soluble  $\alpha$ - and  $\beta$ -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, c, 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  $\beta$ -cyclodextrin polymers (Zsádon et al. 1979b; Szejtli 1980), also prepared by cross-linking cyclodextrins using epichlorohydrin, was in gel inclusion chromatography for amino acids (Zsádon et al. 1979a), alkaloids (Zsádon 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 14 shows the resolution of 500 mg racemic mixture of (+) and (–) enantiomers of vincadifformine on a  $\beta$ -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). Insoluble  $\beta$ -cyclodextrin polymer was also 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 1 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). 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.

### 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



**Fig. 14** Separation of the enantiomers of racemic vincadifformine by passing its aqueous solution through a  $\beta$ -cyclodextrin polymer column; source: CycloLab archives

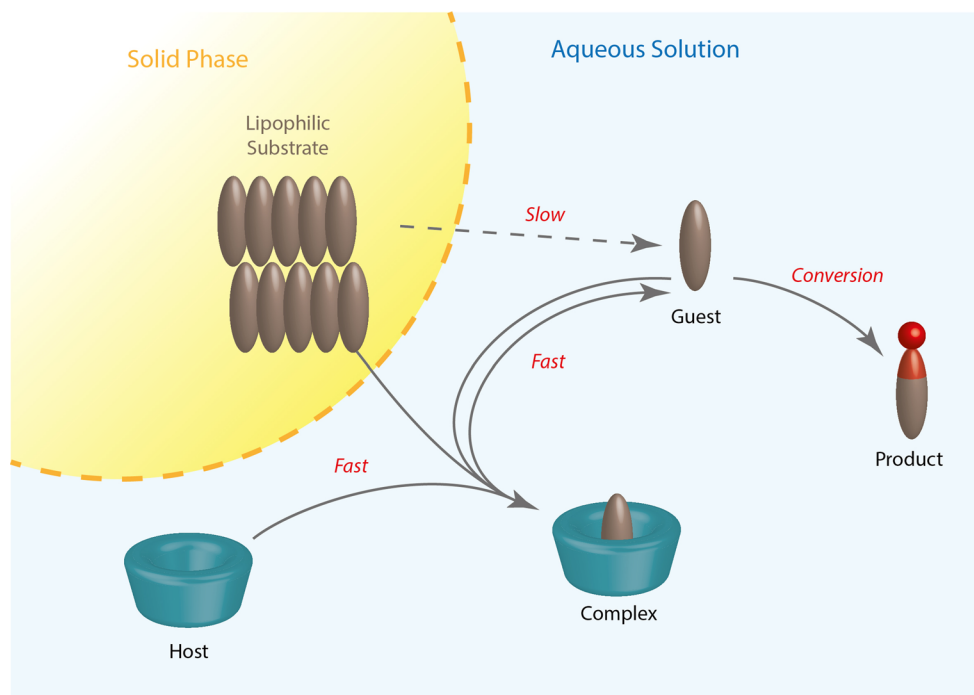
did not damage the microbial cells or the enzymes. The majority of processes involved an enzyme-catalyzed transformation of a substrate in aqueous solution. In enzymic and microbiological transformations of various substrates, *e.g.*, microbiological substrate conversion, fermentation, enhancement of 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 1990). 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. 15 (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 1990). In many cases, the reaction was accelerated through continuous removal of the inhibiting products by

**Table 1** 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	

**Fig. 15** 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 (1990)



cyclodextrin molecular encapsulation (Szejtli 1990, 1991a, 1996; Szejtli and Osa 1996).

### 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; Zsador 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  $\beta$ -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 cosmeo-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 non-volatile, long-lasting formulations, prevention of the phytotoxic effect of certain fungicides, etc. (Szejtli 1983a, 1984a, 1985a, b). The interaction of some non-ionic tensides with native cyclodextrins (Szejtli 1987c, d; Bujtas et al. 1987; Szogyi et al. 1987) and insoluble  $\beta$ -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  $\alpha$ -cyclodextrin and  $\alpha$ -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  $\beta$ -cyclodextrin was the best solubilizing agent of UVA and UVB filters (Fenyvesi

et al. 2004). The solubility of  $\beta$ -cyclodextrin was also 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  $\beta$ -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  $\alpha$ - and  $\beta$ -cyclodextrins and hydroxypropyl- $\beta$ -cyclodextrin, under laboratory-controlled composting conditions was investigated (Verstichel et al. 2004). Fully acetylated cyclodextrins were found to be non-biodegradable 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. 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 (Szejtli 2005).

## Conclusions

This review 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 has published numerous results on these molecules in more than fifty years of career. For example, Professor Szejtli was the first to synthesize the  $^{14}\text{C}$  labeled glucose-based  $\beta$ -cyclodextrin and published his oral metabolism. He was also the first to describe the acid hydrolysis of  $\beta$ -cyclodextrin and discovered that  $\beta$ -cyclodextrin formed inclusion complexes with hydrochloric acid. Professor Szejtli is the founder of International Cyclodextrin Symposia, the first of which was held in 1981 in Budapest. 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.



**Table 2** What cyclodextrin for what purpose?

	Drugs/Parenteral	Drugs/Per os	Drugs/Topical	Cosmetics	Foods	Biotechnology	Analytical chemistry	Chemical industry
$\alpha$ CD	+	+++	+++	+++	+	+	+	+
$\beta$ CD	–	+++	+	+	++	++		+++
$\gamma$ CD	+	+++	+++	+++	+++	–		+++
HP $\beta$ CD	++	++	+++	+++	–	++	++	++
SBE	+++	+	–	–	–	–	++	–
MeCD	+	+	+	–	–	+++	++	+++

CD cyclodextrin, SBE sulfobutyl- $\beta$ -cyclodextrin, MeCD methylated cyclodextrin

–: 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

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 laboratory, 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 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 the young co-workers that Professor Szejtli attracted in the early 1980s are now world-renowned cyclodextrin experts and members of the 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.

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