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Editors

Hydrophilic Matrix Tablets for Oral Controlled Release

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Contents

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Chapter 1
Hydrophilic Matrix Dosage Forms: Definitions, General Attributes, and the Evolution of Clinical Utilization

Peter Timmins, Samuel R. Pygall, and Colin D. Melia

1.1 Introduction

This chapter is intended to offer a brief introductory background around development, understanding of performance, behavior, and the clinical utilization of the hydrophilic matrix as a drug delivery platform. It is intended to indicate the nature of the materials described in greater detail in subsequent chapters and so enable and encourage readers to find their way to specific information of interest.

From the early patents first filed in the 1960s, we detail the hydrophilic matrix's early beginnings in extending the duration of drug release from tablet formulations, through the growth in fundamental academic studies throughout the 1980s and 1990s of the factors influencing drug release from such systems, through to the contemporaneous efforts with that work to model drug release and move towards developing predictive capability. The availability of improved analytical tools over the last couple of decades is considered and their transition to almost routine use to aid better understanding the processes that occur at a macroscopic, microscopic, and molecular level during drug release is detailed. The novel insights have helped define how a Quality by Design (QbD) approach to creating more robust hydrophilic matrix tablet products can be realized. Finally, we shift emphasis to detail the dosage forms' evolution and "coming of age" as a cornerstone drug development

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technology option to enable the successful commercialization of dosage forms of established medicines, demonstrating improved utility and tolerability and also enable the first time clinical use of some new chemical entities.

1.2 Some Guidance on Nomenclature Used in This Book

The term "controlled release" as used in the title of this volume conveys the broad utility of hydrophilic matrix tablets in creating formulations that provide a prolonged rather than an immediate release (IR) of drug. However, although still widely used, the term controlled release has been superseded by other terminologies in the official compendia. The United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the International Conference on Harmonization (ICH) each provide their own perspectives on nomenclature.

The USP describes oral dosage forms that do not provide immediate release of their drug content as "modified release" (MR) in which there are two subclasses, delayed release (DR) and extended release (ER, although XR is sometimes used) [1].

Delayed release products exhibit a lag time during which no drug is released, followed by the release of the entire drug content at a later time. Perhaps the most well-known examples of DR are gastro-resistant or "enteric coated" dosage forms. In these, the delay is achieved through film coating of an IR dosage form with a polymer that is essentially insoluble at gastric pH, but is soluble at intestinal pH. This delays drug release until the tablet has left the stomach. However, delayed release can also be achieved by compressing an erodible layer of material not necessarily possessing pH-dependent solubility around the core dosage form. The time taken for this material to erode in vivo then provides the delay to drug release. Hydrophilic matrix tablets can be designed for specialized applications, as delayed release dosage forms using this "compression coating" approach. For example, film coats and compression coats of microbially digestable polysaccharides such as pectins and dextran have been used for targeted colonic drug delivery [2–4].

However, the hydrophilic matrix is intrinsically an extended-release technology and this remains the single most common application of this type of dose form. Extended-release dosage forms are designed to liberate drug over an extended period of time and provide extended drug absorption. The USP recommends that alternate terms such as "prolonged-release," "repeat-action," "controlled-release," "sustained-release," and their acronyms should not be used to describe this category of dosage forms, and that for hybrid release profiles, the term "extended release" should also be used for:

(a) Combinations of immediate release with extended release.
(b) Combinations of immediate release with delayed release.
(c) Combinations of extended release with delayed release.

The EP recognizes the categories similarly, but refers to extended-release dosage forms as prolonged-release dosage forms [5]. To add to the variety of officially

preferred nomenclature, the WHO recognizes delayed release as is described above, but then uses the term "sustained release" in place of extended release [6]. ICH has attempted in its guidance ICH Q6A to manage nomenclature and uses the terms delayed release and extended release as defined in the USP [7]. Readers will forgive us therefore if, throughout the various chapters in this book, we do not adhere to a rigid nomenclature but use the terms extended release, controlled release, and sustained release interchangeably.

The focus of this book is hydrophilic matrix formulations because these provide a large number of extended-release oral medicines to the clinic. However there are several other types of matrix systems and it is worth at this stage defining how a hydrophilic matrix can be distinguished from these. A hydrophilic matrix is formulated using non-cross-linked, water swellable polymers that swell sufficiently rapidly to block pores at the tablet surface, provided a continuous layer of hydrated polymer surrounds a dry core dosage form. This surface "gel layer" is rarely a true gel, but is normally a concentrated entangled polymer solution, with sufficient viscosity and gel strength to provide longevity as a diffusion barrier to water penetration and drug release. The polymer can be both eroded mechanically at the surface, but also disentangle and dissolve. This is why these polymers are described as being capable of "unlimited swelling."

A hydrophilic matrix is not to be confused with a hydrogel. Hydrogel matrices comprise a cross-linked polymer in which is embedded a drug and they also release drug by hydration and swelling. However, because the polymer is cross-linked, the polymer remains insoluble, and the extent of swelling is limited, even when the matrix has been fully hydrated.

"Inert" or hydrophobic matrices use water-insoluble materials such as waxes, minerals, or plastics. They characteristically undergo very little swelling, and they tend to release drug by leaching processes such as percolation, although wax matrices can also undergo surface melting. The different materials used, and the lack of surface gel layer formation, often distinguish these types from a hydrophilic matrix. Amongst the other types, sugar matrices such as lozenges utilize soluble low molecular weight materials and release drug almost exclusively by surface dissolution, whereas matrices based on hydrolysable polymers such as poly(lactic acid) release drug through internal or surface chemical degradation after polymer hydration. In the hydrophilic matrix, polymer degradation does not play a significant role in the release process.

1.3 The Origin of the Hydrophilic Matrix Tablet

Hydrophilic matrix technology as an approach to the oral extended release of drugs has been used for over 50 years. Researchers in this area, including the contributors to this book, invariably cite the 1962 patent from the Richardson-Merrell company as the first ever description of this technology in the public domain [8]. Two of the inventors went on to describe the dosage form technology further in a research

paper a few years later [9], a brief note which is also widely cited as one of the earliest descriptions of hydrophilic matrix tablets in the pharmaceutical research literature. The patent describes work undertaken in the late 1950s which explores the utility of what the inventors call a "hydrophilic mucilaginous gum" which, when mixed with a drug and compressed into a tablet, yields a dosage form that does not "immediately dissolve or disintegrate on contact with gastric fluids," provided sufficient polymer is employed. These researchers appear to have been the first to describe how the tablet develops a surface layer of hydrated polymer on contact with aqueous media, and indicate it is a barrier to further water entry into the tablet. They recognized that the hydrated polymer layer was erodible, and they indicated that its erosion and consequent regeneration of the hydrated layer was a mechanism by which this type of tablet could provide sustained release of the active ingredient. Subsequently, over the last few decades (as described in this book) investigations of release mechanisms from hydrophilic matrix tablets have indicated that several mechanisms are likely involved, with their relative contributions to the overall drug release process depending on key factors such as the properties of the drug (e.g., solubility), the choice of polymer (e.g., viscosity grade) and the amount of polymer employed. The specific mechanisms and their relative contributions to the overall drug release profile can be assessed using a variety of methodologies which have evolved as the analytical tools have developed as described in many later chapters.

1.4 Characterizing and Modeling Drug Release from Hydrophilic Matrix Tablets: The Foundation of a Mechanistic Understanding

From early times, academic researchers have sought mathematical approaches which would allow the characterization of hydrophilic matrices and a better understanding of their behavior. Lapidus and Lordi [10] in the early 1970s were perhaps one of the first to explore the utility of the Higuchi equation [11, 12] to describe in vitro release of a water-soluble compound (chlorpheniramine maleate) from a hydroxypropyl methylcellulose matrix. They used an approach already applied to their predecessor hydrophobic (inert) matrices [13]. They noted that application of this equation to a dynamically evolving system such as a hydrating matrix required consideration of the changes that might occur in the matrix as dissolution proceeded. Others working at this early period of hydrophilic matrix tablet research pointed out that whilst the Higuchi equation can be used to describe the drug release kinetics of some tablets based on hydrophilic gums, they were by their nature not the matrix systems considered by Higuchi when deriving his equation [14]. With the recent 50 year anniversary of the publication that laid out the derivation and application of the equation, there has been a thorough discussion of the appropriateness or otherwise of using a simple square root of time model to describe the release of drugs from hydrophilic matrix

tablets [15]. However this early work suggested a model could be built that would describe release behavior in relation to formulation variables, and that predicting how to formulate to achieve a specific outcome might be realized. This encouraged further research into models that better described the mechanisms controlling drug release, and the influence of formulation factors that impacted on those mechanisms.

An empirical Power Law equation that allowed drug release data fitting to determine the exponent was first proposed at the beginning of the 1980s [16, 17]. It has been widely utilized [18] including a form that describes a lag time [19] and one which considers both diffusional and relaxation components of drug release [20]. Further more sophisticated modeling has emerged, notably from the work of Siepmann and coworkers [21].

Through to the late 1990s, research was focused on the development of insights into hydrophilic matrix systems as exemplified by the pioneering work from the Liverpool, Geneva, Parma, and Nottingham groups. The former two developing our knowledge of how drug and formulation variables might influence drug release [22–35], and the latter groups adding an understanding of matrix behavior and drug release mechanisms to this knowledge space [36–42] with the application of modern analytical tools to characterize dynamic events within hydrating dosage forms and so explain their behavior. The Colombo group studying hydration, swelling (including limiting that to beneficial effect) and erosion [43–52] provided the perspective around models based on fronts movements as useful models to characterize dosage form behavior [53].

This evolution of the understanding of drug release mechanisms in hydrophilic matrix tablets, combined with robust mathematical ways of describing them and with the appropriate analytical tools which can follow the processes of drug release at the macro, micro, and molecular level, offers the potential to design robust and also troubleshoot extended-release hydrophilic matrix tablet formulations non-empirically.

1.5 Evolution of Analytical Tools to Support the Mechanistic Understanding of Drug Release

In the early days of hydrophilic matrix research attempts to make analytical measurements beyond simple drug release profiles were made, in order to understand how formulation, processing variables, and the drug release environment (e.g., medium pH) modified drug release, and thereby rationalize formulation development. This often involved removing the dosage form from the test environment, and for example, measuring the wet swollen matrix to assess swelling rate, using a mechanical probe or sectioning the wet matrix to measure gel layer growth, or weighing the dried removed mass to calculate non-drug losses to assess erosion. These approaches did not allow real-time in situ examination during drug release.

Advances in the capability of imaging and spectroscopic instrumentation have allowed in situ examination of matrices and a dynamic real-time approach to

following the changes in the matrix as drug release occurs. The first pioneering studies applied magnetic resonance imaging (MRI) to hydrophilic matrix systems in the 1990s [54, 55]. These early studies utilized high field instruments with superconducting magnets, giving high resolution, but sample size restrictions did not allow a formulated dosage form to be examined within a compendial drug release test apparatus. The early work led to a number of subsequent investigations of MRI [56–63] and laid much groundwork for studies now using low field benchtop systems based on permanent magnets [64, 65]. These instruments offer the ability to observe the in situ evolution of the gel layer and characterize its development in parallel to studying drug release, without having to disturb the sample and also utilize a compendial drug release apparatus. It is possible to observe the different fronts developing in the matrix and follow these as drug release progress, and identify strongly versus weakly entangled polymer domains within the gel layer especially towards the interface with the bulk drug release medium where erosion may be occurring [66]. The technique has been used to explore the physical mechanisms of dosage form–food interactions investigating with a model system based on fat emulsions interacting with the hydrating gel layer [67].

The higher field systems are also now being adapted to look at formulated dosage forms and have the ability to look at drug and polymer simultaneously where different NMR active species (e.g., ^{19}F fluorine in fluorine substituted drugs) are involved. For example, investigation of the dissolution process of commercial quetiapine fumarate HPMC tablets in a USP 4 (flow-through cell) dissolution apparatus with simultaneous MRI imaging revealed the progressive change in overall tablet size, the gel layer, and glassy/non-glassy regions of the dry core with respect to hydration time [68]. In addition, the use of a quantitative ultrafast MRI technique together with ^{19}F NMR spectroscopy and ^{19}F one-dimensional imaging enabled the study of the hydration and drug release processes for a commercial hydrophilic matrix tablet (Lescol® XL) [69].

Infrared spectroscopy has also been utilized to explore the behavior of hydrophilic matrices. Fourier Transform Infrared (FTIR) imaging has the capability of providing maps of chemical composition, allowing the mixing homogeneity of active and excipient components at the matrix surface to be investigated [70, 71]. A focal plane array infrared detector provides the capability to measure thousands of IR spectra from different locations within the sample, thereby allowing collection of spatially resolved chemical information [72]. However, conventional FTIR microscopy may require lengthy measurement times, rendering it unsuitable for the study of dynamic processes, such as tablet dissolution and pseudo gel layer formation [72]. Attenuated total reflectance (ATR)-IR uses a diamond ATR accessory with high refractive index and has relatively short acquisition time, allowing a number of images to be compiled, and is therefore better suited to analyze drug release from tablets [70]. The technique has been applied in a number of studies to follow the processes involved in drug liberation from hydrophilic matrices [73]. These imaging techniques and other methods of physical characterization are detailed in Chap. 7.

1.6 Newer Approaches to Manufacturing Hydrophilic Matrix Tablets

Hydrophilic matrix tablets probably represent one of the least complicated and most elegant approaches to the manufacture of CR dosage forms; it involves simply the compression of blend of drug, the hydrophilic polymer retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. The drug and retardant blend may be granulated prior to compression to facilitate flow and reduce segregation risk. Given that there may be challenges with applying conventional pharmaceutical manufacturing approaches in producing hydrophilic matrix tablets at commercial scale, due to flow, compressibility of the polymers, and risks in wet granulation due to possible "runaway" of the process associated with difficulties in uniform addition and dispersion of granulating fluid, improved grades of polymers are being developed and alternate manufacturing approaches are being introduced to mitigate these challenges. For example, newer direct compression grades of HPMC have become available that can help avoid the challenges of wet granulation, and yet offer ready free-flowing, compressible blends for tableting.

The evolution of dosage form manufacturing approaches and their influences (or lack thereof) on dosage form performance have been explored as the interest in this type of dosage form has grown over the period since the first publications in the field in the early 1960s and as the tools to explore how the variables in manufacturing and formulation affect performance have become available and their utility has been demonstrated. Innovative approaches to manufacturing these dosage forms, such as hot melt extrusion, have been reported and have found application in commercially available medicines (for example Intac™ technology as used for Opana™ ER, Endo Pharmaceuticals). The application of melt extrusion to the manufacture of extended-release hydrophilic matrix formulations is included in a later chapter.

1.7 Commercial Considerations and Applications in the Evolution of Hydrophilic Matrix Tablets

There is a general perception that extended-release technologies are applied to medicines as a life cycle management approach for established medicines, thus enhancing the potential use of a product to seek to sustain market share for a mature product. However, these technologies offered more than the obvious dosing frequency improvements, enabling greater patient convenience, but also in many cases offered real clinical improvement. This included management of plasma peak concentration-associated adverse events, so physicians could now start to push doses higher and so improve exposure without pushing the peak concentration and so manage adverse event whilst optimizing efficacy.

An example of where an established drug can be effectively improved by the use of hydrophilic matrix technology is the extended-release formulation development of metformin. Although this was a drug generically in most markets, metformin was formulated as an extended-release formulation to successfully improve gastrointestinal adverse events associated with the immediate-release product as well as allow for once-daily dosing, convenient for patients as it is used with other anti-diabetics that are once daily, including now in fixed dose combinations [74–76]. It may be of value to that fraction of patients where metformin is valuable therapy and the immediate-release formulation is poorly tolerated by them.

Trospium chloride is a quaternary ammonium derivative of tropine with anticholinergic properties [77]. The development of a once-daily formulation of trospium chloride (Sanctura XR®, Allergan, Irvine, CA, USA) was a necessary step to maintain its place in the competitive antimuscarinic drug market; it was launched in the USA in 2008. In addition to convenience and improved compliance of once-daily dosing, the ER delivery system has been proposed to lower maximum plasma concentration levels of the drug compared with its twice-daily counterpart, thereby decreasing the incidence of side effects and increasing tolerability [78]. Trospium ER utilizes timed-release and pH-dependent-release technologies to achieve a relatively steady-state plasma concentration of drug. This is achieved through delivery of 60 mg of trospium to the entire length of the gastrointestinal (GI) tract.

Extended-release niacin has been developed recently as part of a combination product, where the release rate modification is intended to ameliorate flushing and risk of hepatotoxicity associated with immediate-release niacin administration at therapeutic doses [79]. It is worth noting that the pioneering work of Christenson and Dale from 50 years ago considered the value of extended release using a hydrophilic matrix as an approach to improving the tolerability of orally administered niacin.

1.8 Potential Hazards of Hydrophilic Matrices

Hydrophilic matrices when taken as a single dose have been rarely associated with issues of patient safety. However, some cases of gastrointestinal obstruction have been reported from products containing certain gums, most notably guar gum or konjac. As these polymers have been proposed for use in hydrophilic matrix tablets [80–82] a degree of caution in their use would seem prudent. A slimming product, Cal-Ban 3000®, was a hydrophilic matrix formulation which utilized guar gum as a swellable bulking agent. It was associated with several cases of esophageal and small bowel obstruction in adults, and was eventually embargoed by the FDA in 1990 [83]. A review of reported cases described how the “ability of guar to expand 10- to 20-fold may lead to luminal obstruction particularly in those with preexisting anatomical problems. The tenacious gel-like consistency of the material made it difficult to remove by endoscopy.” The use of Konjac (E425) in swellable foods and pharmaceuticals is a recognized choking hazard, particularly in children, and its use is restricted in many countries. Within Europe, it has been banned in jelly

confectionary because the high gel strength and poor solubility of the hydrated gum has resulted in pharyngeal sticking which has led to several child deaths worldwide [84]. This usually resulted from a chewable sweet of tablet size being inadvertantly swallowed. Esophageal obstruction by konjac tablets has been also reported in adults, the problem being that with every liquid swallow, the problem worsens [85, 86]. The choking and GI blockage hazards of these polymers appear to have arisen from the combination of size, swelling, and gum content of these products, and in particular the tenacious viscoelastic properties of guar gum and konjac when partially hydrated.

The GI obstruction could be made much worse when multiple hydrophilic matrix tablets are ingested, as happens in intentional overdose. This can result in the formation of large conglomerates (termed "pharmacobezoars") which can consist of a gelatinous, sticky mass of hydrated matrices, often with co-ingested tablets. It is reasonable to assume that this could occur with any hydrophilic matrix tablet in overdose, and with any polymer. Many cases have been described in the literature, including matrices containing HPMC [87, 88]. Emergency intervention by endoscopy or surgery is usually required to remove the obstructing mass, and prevent toxic levels of multiple drugs being released from the aggregate over a prolonged period of time [89].

1.9 The Role and Value of Hydrophilic Matrix Tablets in Twenty-First Century Medicine

Historically, extended-release oral drug delivery has been often regarded as a technology for improving the life cycle of marketed drugs. However in recent times there has been a shift towards adding clinical value by use of extended-release dosage forms, and the hydrophilic matrix in particular. It is now being considered as a viable formulation option earlier in the clinical development of drug candidates. It has become an enabling technology to assure the very best clinical performance in a real-world setting, with the technology and the drug being married in Phase 1 or early Phase 2 trials, rather than post-launch of an earlier drug product. The primary driver for this shift has been the recognition that extended-release formulations represent a time and cost-effective way to progress emerging clinical new drug candidates, rather than the alternative of eliminating any problematic pharmacokinetic deficiencies using discovery approaches. Using extended release to facilitate the rapid progress of drug candidates using the most appropriate formulation approach [from first-in-human (FIH) studies to clinical proof-of-concept (POC)] is particularly important when investigating a novel pharmacology, i.e., for first-in-class drugs.

There are some recently disclosed examples of drug candidates which have been advanced as extended-release dosage forms during their early development phase, allowing the dose to be optimized for better efficacy without the peak concentrations that would risk adverse events. The amelioration of serotonergic side effects for an experimental, potential antidepressant candidate by design of an appropriate

extended-release formulation to provide a product ready for Phase 3 clinical studies using complementary in vitro and in vivo assessments has been described [90]. Similarly the therapeutic use of an HIV attachment inhibitor required the early-stage exploration of extended-release feasibility and development. BMS-663068 was thus developed as extended release to get optimized C_{min} to assure antiviral activity whilst avoiding high C_{max} that was associated with gastric adverse events [91, 92].

The application of extended-release technology involving hydrophilic matrix tablets is moving to the earliest stages of the development of new medicines. Approaches have been described that enable the exploration of the feasibility of extended-release formulations of new drug candidates (unmarketed, novel compounds), with the extended-release development studies being conducted in the exploratory clinical phase (i.e., Phase 1/Phase 2) [93, 94]. The delivery of an appropriate extended-release formulation was deemed critical for the compounds in question, to allow the product to be able to advance to later stage (Phase 2/Phase 3) clinical studies. Brown et al. [95] have described in silico approaches to predicting feasibility of formulating extended-release formulations of established and novel compounds, thus avoiding multiple, iterative in vivo studies for optimization of the desired clinical formulation. Such techniques could be adaptable to a simple likely feasible/not feasible assessment on the basis of even limited though appropriate preclinical physicochemical and biopharmaceutical profiling of lead compounds.

The fundamental understanding of the dosage form technology that has occurred in the last 50 years, the ability to predict and model release rates, the ability to explore without having to set up clinical studies the effect of variation in drug release rates on pharmacokinetics in silico, and the rapid approaches to assessing formulation variables in vitro and in vivo described in this book have allowed for this very early development adoption with confidence.

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Chapter 2
Design and Evaluation of Hydroxypropyl Methylcellulose Matrix Tablets for Oral Controlled Release: A Historical Perspective

James L. Ford

2.1 Introduction

Hydrophilic matrix tablets (matrices) for oral use are designed to hydrate on swallowing, and form a 'gel' layer of hydrated polymer at the tablet surface to control the rate of drug release during passage of the matrix through the gastrointestinal tract. During gastrointestinal transit, the matrices are reduced in size through surface erosion and dissolution. This reduces the probability of expulsion of an exhausted 'ghost' matrix sometimes seen with earlier hydrophobic matrices, such as those based on fatty acids, waxes or ethylcellulose [1, 2]. Hydrophilic matrices release their drug content slowly, and their therapeutic effect is prolonged. However, in order to ensure a reproducible action on the body it is imperative that (1) the matrix remains intact and (2) the drug is released at a controlled rate. During gastrointestinal transit, hydrophilic matrices are subjected to a range of shear forces such as peristalsis, and they also encounter a variety of pH and chemical environments. In poorly formulated systems, these mechanical and chemical challenges can potentially cause the matrix to prematurely lose its integrity and break up [3].

The concept of using a water-swellable, non-cross-linked 'hydrophilic' polymer to control the release of drug from an oral matrix tablet was promoted in the 1960s. Thereafter, extensive studies have led to the development of a multitude of commercially marketed, oral drug delivery products which utilise the 'hydrophilic matrix' concept. Such products are generally matrices comprising a compressed powder, a mixture of drug and excipients with at least one hydrophilic polymer.

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A wide variety of natural, semi-synthetic and synthetic water-swellable polymers has been considered as release control candidates in hydrophilic matrices. Several of these materials are described in detail in Chaps. 4 and 5 of this book. However, by far the most widely used polymers are cellulose ethers, in particular hydroxypropyl methylcellulose (HPMC), which is also known as hypromellose. HPMC is a water-soluble, non-ionic cellulose ether that is enzyme resistant and chemically stable over the pH range 3.0–11.0 [4].

HPMC has now been used in hydrophilic matrices for over 50 years, and it is the aim of this chapter to review some of the earlier studies (up to the early twenty-first century) which laid the groundwork for our current understanding of HPMC in matrix formulations and has enabled their widespread use.

2.1.1 The Chemistry of Hydroxypropyl Methylcellulose

The structure of HPMC is a cellulose backbone with ether linked methoxyl and hydroxypropyl side group substituents attached through ether linkages to the cellulose chain hydroxyl groups (Fig. 2.1). During manufacture, pulp cellulose is treated with caustic soda and reacted with methyl chloride and propylene oxide to create the substituted polymer, and the grades of HPMC used in matrix tablets have substantial degrees of methoxyl but rather less hydroxypropyl substitution. It should be noted that the latter introduces a secondary hydroxyl group, although in HPMC, unlike some other cellulose ethers, there is little evidence for additive substitution of these groups.

Polymer properties are strongly influenced by the ratio of methoxyl and hydroxypropyl substitution, and this is reflected in the United States Pharmacopeia

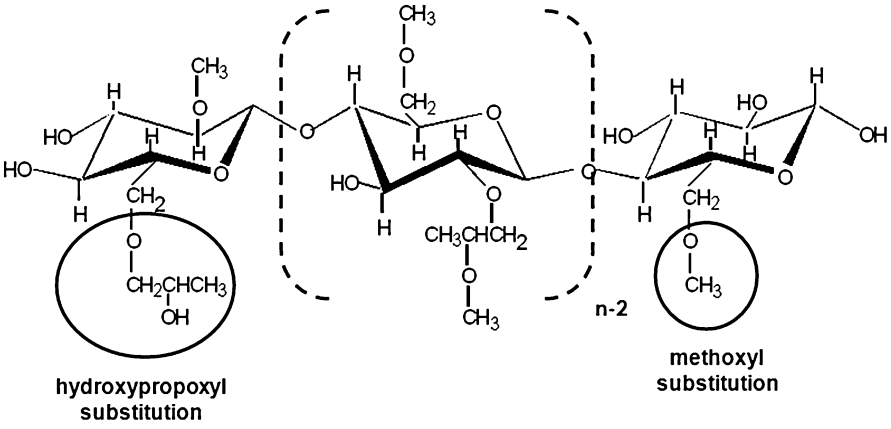

Fig. 2.1 The chemical structure of HPMC (hypromellose). This is an illustrative diagram. The degree of substitution and position of the methoxyl and hydroxypropoxyl groups are not the same on each anhydroglucose unit. (Reproduced with permission of Colorcon Inc.)

(USP) designation of different HPMC types (HPMC 2208, HPMC 2906 and HPMC 2910) in which the first two numbers designate the average methoxyl (22<u>08</u>) and the last two numbers, the average percent hydroxypropoxyl (22<u>08</u>) substitution. Commercial designations vary but HPMC grades obtained from the Dow Chemical Company were widely used in the early literature. Dow designated the USP types above as Methocel® K, F and E, respectively, and added a suffix to indicate the dilute solution viscosity, as an indicator of polymer molecular weight [4]. In hydrophilic matrices, the most commonly used grades of HPMC are 2208 (Methocel K) and 2910 (Methocel E), with viscosities ranging from 100 cP to 100,000 cP [5]. The Dow nomenclature is widely used in this chapter, and to facilitate the subsequent discussions, we will illustrate this system using Methocel K100LV and K15M as examples. The letter K indicates that both grades are USP type HPMC2208. 100LV indicates a dilute solution viscosity of 100 cP, and therefore a 'low viscosity' HPMC, whilst 15M indicates a dilute solution viscosity of 15,000, which is a 'high viscosity' grade of HPMC. Further details of HPMC polymer chemistry, characteristics and details of commercial grades are provided in Chap. 3.

2.1.2 Early Considerations and the Drive for an Increased Understanding of HPMC Matrices

With the benefit of hindsight, four separate groups of publications in the decades 1960–1990 can be regarded as having pioneered the utilisation of HPMC in matrix tablets. An early description of the hydrophilic matrix concept appears in the patent of Christenson and Dale [6], and the initial work by Lapidus and Lordi [7, 8] was followed by studies by Salomon and co-workers [9–11]. This was followed by patents filed in the United States by Schor et al. [12, 13], and a review article by Alderman [14]. The publications emanating from these four centres of research became impetus for a massive widening of research into HPMC, and its use in hydrophilic matrices.

The review article from Alderman [14] outlined some incontrovertible advantages of cellulose ethers in hydrophilic matrices, which include:

- The ability to provide a wide range of desired drug release profiles.
- pH-independent performance.
- Manufacture of reproducible dosage forms by conventional production methods.
- Wide acceptance and GRAS status.
- Cost effectiveness.

Other fundamental characteristics that made HPMC an ideal candidate for hydrophilic matrix tablets included the ability to hydrate rapidly on exposure to aqueous fluids, and the simplicity of tablet formulation.

2.1.2.1 The Work of Lapidus and Lordi

The early work of Lapidus and Lordi [7, 8] described many characteristics of HPMC matrices that have held true ever since. They explained, for example, how matrices incorporating low viscosity HPMC grades were more susceptible to attrition and exhibited poorer control of drug release than matrices containing high viscosity HPMC. They were perceptive in recognising that differences in matrix performance could be attributed to the presence of different drugs. They plotted drug release (root time) against W_0 (the dose of the drug) for soluble drugs, and noted that deviations from linearity were observed at an earlier stage in matrices containing sodium salicylate than those containing chlorpheniramine maleate. This difference, they explained, resulted from sodium ions having a greater ability to dehydrate HPMC than chlorpheniramine maleate [8]. They showed that drug release could be influenced by the ionic content of the dissolution medium, and suggested that inorganic ions with a high affinity for water could dehydrate and result in a 'salting out' of the polymer. As a result, in low ionic strength environments, the gel layer remained unaffected but at high ionic strengths there could be loss of gel integrity and disintegration of the matrix [8]. In this way they anticipated much of the later work on HPMC matrix behaviour in the presence of drugs and ions. They also showed how compression coating an HPMC coat around a matrix containing a soluble drug (chlorpheniramine maleate) resulted in a zero-order release, and they anticipated that drug release would remain linear with time until the drug was depleted from the core [8].

2.1.2.2 The Work of Salomon and Co-workers

Salomon et al. [9–11] also reported zero-order release from potassium chloride cores coated with an HPMC barrier. The release rate was unaffected by the coating, although the time taken to reach a quasi-stationary diffusion state increased with increasing thickness of the coat [9–11].

2.1.2.3 The United States Patents of Forest Laboratories

In 1983 Schor et al. [12, 13], on behalf of Forest Laboratories, authored two patents which for a period restricted the content and types of cellulose ether that could be used in commercial HPMC matrices. A multitude of drugs was covered by these patents and their claims also included mixtures of HPMC containing up to 30 % ethyl cellulose or sodium carboxymethylcellulose. US4369172 [12] specified HPMC with a hydroxypropoxyl content of 9–12 %, a methoxyl content of 27–30 % and an average molecular weight of <50,000. This covered the use of low viscosity HPMC 2910 grades. US4389393 [12] specified an HPMC with a hydroxypropoxyl content of 4–32 %, a methoxyl content of 16–24 % and an average molecular weight of at least 50,000 in matrices having less than 1/3 of the solid weight as HPMC.

This latter patent covers some of the most commonly used formulations of HPMC matrix: those which utilise up to 30 % of a high viscosity HPMC2208. Both patents have now expired.

2.1.2.4 The Work of Alderman

Alderman [14] proposed a number of broad hypotheses which, on closer examination, are sometimes but not always universally applicable. These included:

- HPMC 2906, HPMC 2910 and methylcellulose may not hydrate sufficiently quickly to prevent matrix disintegration.
- Particle size and particle size distribution can affect hydration rate.
- Increasing the polymer viscosity grade (polymer molecular weight) decreases the diffusion rate of incorporated drugs and renders the matrix less susceptible to erosion.
- Increasing the polymer concentration will slow down drug release.
- Strongly ionic salts may prevent hydration of HPMC,
- HPMC solutions are stable in the pH range of 3–11 but strongly acidic drug salts may produce stability issues.
- An increase in tablet size will decrease drug release rate,
- Low levels of calcium phosphate, a non-swelling insoluble excipient, can destroy the extended release properties of the matrix due to non-uniformity in the gel layer.
- Soluble excipients increase drug release rate.

Many of these suggestions deserve further explanation since drug release from an HPMC matrix is a complex process, and it depends on a multitude of factors and variables. Understanding the factors that control drug release should start with simple studies with HPMC and water, and then the release of individual drugs in water in order to eliminate the influence of other factors. Only after this basic understanding is developed can factors such as drug solubility, ionic strength and matrix formulation be investigated and fully understood. However, before we can consider the factors that control drug release, it is important to identify how drug release can be presented, and to summarise the early work which attempted to understand the mechanisms by which drugs are released. Therefore, in this chapter, the mathematical presentation of drug release and early ideas on drug release mechanisms are described prior to a discussion of the factors that influence drug release from HPMC matrices.

2.2 Mathematical Models of Drug Release

The early work of Lapidus and Lordi [8] utilised equations developed by Higuchi [15, 16]. The aqueous solubility of a drug is a key factor influencing the mechanism of release and this permits different mathematical interpretations of drug dissolution rates in HPMC matrices to be undertaken [8, 15, 16].

If the drug has a low aqueous solubility, such that it has not completely dissolved when the polymer is hydrated, then diffusion will occur from a saturated solution. Equation (2.1) describes drug release from a single face of a tablet in these circumstances [16]

$$W_r/t^{1/2} = S\left[D'\varepsilon C_s(2W_0/V - \varepsilon C_s) \right]^{1/2} \tag{2.1}$$

W_r is the amount of drug dissolved in time t, W_0 is the dose of the drug, S is the effective diffusional area, V is the effective volume of the hydrated matrix, C_s is the solubility of the drug in the release medium, ε is the porosity of the hydrated matrix and D' is the apparent diffusion of the drug in the hydrated matrix.

If the drug dissolves completely when the matrix is hydrated then Eq. (2.2) applies.

$$W_r/t^{1/2} = 2W_0\left(S/V \right)\left(D'/\pi \right)^{1/2} \tag{2.2}$$

Although Eqs. (2.1) and (2.2) predict a zero intercept, a lag time will inevitably exist prior to the commencement of drug release. Equations (2.1) and (2.2) predict a dependence of release on the square root of time, but changes in the structure of the matrix for example in its tortuosity (τ) will alter the release rate since τ is related to the actual diffusion coefficient D by Eq. (2.3)

$$D' = D/\tau \tag{2.3}$$

Because drug release is assumed to be generally driven by diffusion it has become customary to present drug release data as a function of root time ($t^{1/2}$). However tablet attrition (erosion) especially at lower HPMC contents can contribute significantly to the release of drug and this causes a positive deviation in the $t^{1/2}$ profile. Negative deviations, due to depletion of the drug in the matrix, may also occur once a proportion of the drug has been released. Estimates of when these deviations from root time release occur include 70 % [17] or 30 % [15, 16] of drug release, respectively.

Drug release data can be additionally interpreted using the simple empirical relationship (often referred to as Power Law) shown in Eq. (2.4) [18]:

$$M_t/M_\infty = kt^n \tag{2.4}$$

$M_t/M\infty$ is the fractional release of the drug, t is the release time, k is a constant incorporating the structural and geometrical characteristics of the release device and n is a release exponent indicative of the release mechanism. In the case of swellable tablets such as HPMC matrices, n is 0.45 for diffusional (Fickian) release and 0.89 for erosional zero-order release [19]. These equations are less than the theoretical 0.5 and 1 because of shape changes in the matrix. Equation (2.4) has been further

modified to Eq. (2.5) to account for a lag period (l) or initial burst at the beginning of matrix hydration [20, 21]:

$$M_t/M_\infty = k\left(t-l\right)^n \tag{2.5}$$

Following adoption of this correction factor, values of $n=0.71$, 0.65, 0.67 and 0.64 have been obtained for the water-soluble drugs promethazine hydrochloride, aminophylline, propranolol hydrochloride and theophylline, respectively [22]. Less soluble drugs such as indomethacin and diazepam gave values of $n=0.9$ and 0.82 whilst tetracycline hydrochloride showed a value of 0.45, possibly due to loss of hydrochloride leading to the precipitation of tetracycline base [22].

Numerous other models have been developed subsequently, for example, Rinaki et al. [23] who have developed a modified 'Power' law which models the entire drug release curve, but it is not the aim of this chapter to describe more recent models. For further information on additional mathematical modelling approaches the interested reader is directed to the work of Siepmann and colleagues [24–27].

2.3 Mechanisms of Drug Liberation

Hydrophilic matrices rapidly form a surface 'gel' layer on exposure to aqueous media. Hydration is accompanied by a progressive plasticisation of HPMC leading to swelling and, as the chains uncoil and extend, more locations become available for hydrogen bonding and further molecular entanglements [28–30]. The overall result is an increase in the thickness of the gel layer surrounding the matrix, which retards disintegration and prevents further rapid water penetration into the matrix [31]. The thickness of the gel depends on the rate of water penetration, the movement of water within the matrix, the degree of polymer swelling, the dissolution of drugs and excipients and the rate of gel removal by matrix erosion [32, 33]. The outermost layer of gel becomes fully hydrated, the polymer dissolves, and this contributes to the erosion of the matrix surface. As time progresses, water continues to penetrate slowly into the core until the whole matrix has undergone hydration and it eventually erodes completely.

In the initial stages of hydration, a rapid burst of soluble drug may be released but, thereafter, drug release is controlled by diffusion of the drugs through the gel and/or the gradual erosion of the gel which exposes fresh surfaces containing drug. It is often said that the diffusion of dissolved drug controls the release of water-soluble drugs, whereas erosion of the matrix controls the release of poorly soluble drugs. In most cases, however, both diffusion and erosion occur simultaneously [28, 30, 34]. Three phases of swelling have been described from images obtained by the non-invasive technique of magnetic resonance imaging: (a) the growth of the gel layer with time, (b) a reduction in the size of the dry core of the polymer as more of the polymer becomes hydrated and finally (c) a decrease in matrix diameter with time, before the matrix finally dissolves completely, leaving no core or 'ghost' [35].

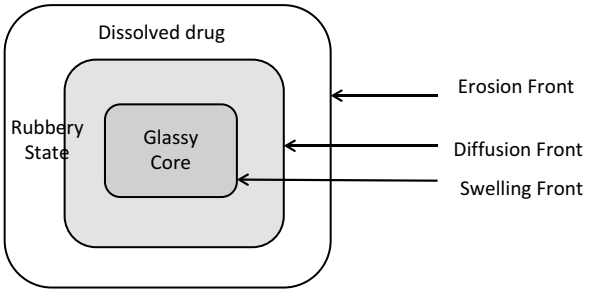

Fig. 2.2 Schematic cross section through an HPMC matrix following exposure to an aqueous fluid and partial release of drug. The three moving fronts are clearly delineated. The rubbery state will contain both dissolved drug and undissolved drug particles

An alternative approach describes cellulose ethers as glassy polymers which under ambient conditions are below their glass transition temperature. The T_g of HPMC has been reported to be 157–180 °C [36]. When exposed to aqueous fluids, the polymer at the matrix surface imbibes water and hydrates, resulting in a lowering of T_g to a temperature below ambient, and a polymer which is now in the rubbery state. This process results in swelling, and it sets up two moving fronts within the matrix (Fig. 2.2). These are (1) the interface between the glassy polymer and the rubbery state, which represents the approximate position of the solvent front and (2) an outer interface between the fully hydrated polymer and the surrounding solvent where erosion, chain disentanglement and polymer dissolution are occurring. The distance between these fronts can be regarded as the gel layer thickness. The water content at the outer periphery will be close to 100 %, and at the inner interface, near the equilibrium moisture content of the polymer. However, some authors consider that the main driver for drug release is the thickness between the diffusion and the erosion front, and not the distance between the swelling and erosion fronts [32].

When the rate of erosion is equal to the rate of solvent penetration, the gel layer thickness is kept constant and it is alleged that under these conditions, zero-order release of water-soluble drugs can occur [37]. However, this assumption does not take into account the reduction in matrix surface area as a result of erosion.

The structure of the hydrated 'gel' layer is not homogeneous [38]. Freeze fracture SEM shows that after 1 h hydration, the outermost regions of the 'gel' appear uniform (ice crystals prevented any more detailed interpretation of gel microstructure) but within the central and inner regions of the gel there was an extensive pattern of less hydrated polymer domains, surrounded by more extensively hydrated regions. The solvent front was clearly visible as a layer of partially hydrated HPMC fibres which were morphologically different to the hydrated gel and the dry polymer particles in the core. This boundary layer became more extensive and diffuse with time [38]. Bajwa et al. [39] have used confocal fluorescence imaging to describe the microstructural development of the gel layer during early gel layer formation, up to 15 min after immersion. Images showed there was an initial uptake of liquid into the tablet pore network followed by individual swelling of surface polymer particles and the creation of the gel layer by outward columnar swelling and lateral coalescence of the swelling HPMC particles [39].

Gel layer microstructure is further complicated by air bubbles entrapped within the gel layer. These may cause changes in the kinetics of drug release [40]. The bubbles arise from air in the voids of the dry tablet core, trapped during compression, being surrounded by swelling polymer particles at the solvent front [41].

2.4 Fundamental Characteristics of HPMC Pertinent to Its Inclusion in Matrix Tablets

There are many potential factors that could contribute to drug release in HPMC matrices, and an understanding of these is required before the processes of drug release can be rationalised. It should be already apparent to the reader that drugs and dissolution media are implicated as modifiers of drug release, but it is important to attempt to understand the inter-relationship between water and HPMC before incorporating complicating factors such as the drug into this relationship. By necessity, many of the studies described here have examined static systems, such as preformed gels or matrices swelling in unstirred environments, with the inference rightly or wrongly that the study conclusions can be applied to matrices in a dynamic environment. Despite these limitations, such studies have been fundamental to our understanding of HPMC matrix performance.

2.4.1 The Interaction of HPMC with Water

In common with other hydrophilic polymers, HPMC can absorb water vapour in the dry state and retain water molecules in its amorphous regions [42]. As a consequence, there can be important changes in polymer physical properties [43]. Water sorption by HPMC is dependent on particle surface area, and as particle size increases, the internal absorption of water reduces, and external adsorption increases [44]. Many workers also consider that when hydrated in water, more than one state of water exists in the surface gel layer of a HPMC matrix. They postulate that water may exist as (a) tightly bound water that interacts with polymer chains and is non-freezable, (b) free water which is freezable and (c) water that exists in bound states between these two extremes [45–49]. Nokhodchi et al. [44] have predicted that HPMC 2208 could contain as much as ~31 % w/w moisture before free water can be detected, and this value remains unaffected by particle size or viscosity grade [44]. Other studies have suggested that once HPMC has imbibed water, it is distributed in at least three states. These have been described as (1) bulk water which melts at 0 °C and has the characteristics of normal water (2) loosely bound water which interacts weakly with the polymer and (3) bound water which is incapable of freezing at 0 °C because of interaction with the polymer [50]. In one study, the water interactions of a low viscosity HPMC 2910 (Methocel E5) have been characterised

by differential scanning calorimetry (DSC). Bulk and loosely bound water melted in the endotherm front with a peak around 0 °C, and with 6.2 ± 1.3 mol of water being associated with each polymer repeating unit [51].

The dissolution of HPMC is considered to be a multi-stage process, with each state of water showing an initial endotherm due to the uptake of water followed by a dissolution process which is exothermic. The net heat of solution has been estimated at −32.8 cal/g which confirms the exothermic nature of the HPMC dissolution process [51].

DSC studies of preformed gels prepared from high viscosity HPMC 2208 (Methocel K15M) showed straight line relationships between the melting energy of the unbound water and the percentage of HPMC present in the gel [45]. It has been estimated that an HPMC:water ratio of ~5:4 allows HPMC to become fully hydrated without the presence of free water. This corresponds to 8.5 mol of water being associated with each polymer repeating unit of HPMC 2208 [45].

Rajabi-Siahboomi et al. [52] have used NMR microscopy to examine the self-diffusion coefficient (SDC) of water and to map the mobility of water within the gels formed around a hydrating HPMC matrix. The results showed a gradient of mobility across the gel layer, with lower SDC values in the axial direction than in the radial direction of the tablet. This suggested that the properties of the gel layer might be different in axial and radial directions.

Incorporated drugs can also influence polymer hydration. For example, inclusion of propranolol hydrochloride into preformed gels reduces the water required to hydrate HPMC 2208 (Methocel K15M) and it is probable that there is a redistribution of water in these gels when soluble drugs are present [45]. Salsa et al. [53] have also suggested that the presence of hydrophobic or poorly water-soluble drugs can affect polymer hydration, though disruption of the hydrogen bond network and a diminishing of the amount of water bound by the polymer.

2.4.2 Thermal Gelation and Cloud Point

Aqueous HPMC solutions and gels exhibit reversible thermal gelation on heating, usually with the appearance of a cloud point. This is a result of polymer dehydration and hydrophobic interactions in the methoxyl-rich regions of chain substitution [54, 55]. At low temperatures HPMC molecules are fully hydrated and polymer:polymer interactions are thought to be largely limited to entanglements. As the temperature rises, solution viscosity at first decreases, before rising sharply as a result of the formation of a three-dimensional insoluble gel network through hydrophobic associations [56]. The temperature at which this occurs is called the thermal gelation temperature, and it is dependent on the degree of substitution, and the presence of ionic species which may ‘salt out’ the polymer [14].

Another effect of increasing the temperature is visual precipitation, often called cloud point behaviour. An incipient precipitation temperature can be recorded at 97.5 % light transmittance which corresponds with the commencement of visual

precipitation of the polymer. A cloud point is reached when the transmittance is reduced to 50 % [57] and this is dependent on the concentration of HPMC [57]. The cloud point and thermal gelation temperatures do not always coincide because, in some circumstances, a turbid solution can be achieved before reaching a cloud point. This can make the determination of cloud point subjective [56, 58]. High concentrations of polymer can also lead to a thermal gel being formed before turbidity occurs, whilst at low polymer concentrations a turbid solution can be observed before gelation [56].

In many pharmaceutical studies, the cloud point has been used to assess drug–polymer interactions and the effects of ionic materials which cause 'salting in' or 'salting out' of the polymer [56]. Pharmaceutical alkyl celluloses of the HPMC family (methylcellulose, HPMC 2910, HPMC 2906 and HPMC 2208) exhibit cloud points of approximately 47 °C, 56 °C, 58 °C and 71 °C, respectively, as aqueous 2 % w/w gels [59].These values decrease with polymer concentration, and over the range 0.5–2.0 % w/w, the changes in cloud point have been reported to be 10 °C/% for methylcellulose and about 2 °C/% for HPMC 2910, HPMC 2906 and HPMC 2208. This reflects the high sensitivity of methylcellulose solubility to temperature changes. Cloud point temperature is influenced only slightly by viscosity grade and by the substituent variation that occurs within the different USP types of HPMC.

Dissolved drugs are capable of increasing or decreasing the cloud points of HPMC solutions. Thus aminophylline, tetracycline hydrochloride, promethazine hydrochloride and propranolol hydrochloride 'salted in' the polymer, raising the cloud point of HPMC 2208 (Methocel K4M), whereas cloud point was unaffected by the presence of quinine sulphate and theophylline [56]. Drugs can also lower the cloud point of HPMC by interfering with polymer hydration and 'salting out' the polymer. An investigation of diclofenac sodium, by examining chemicals representative of constituent portions of the drug molecule, identified 2,6-dichloroaniline hydrochloride as the chemical moiety within this drug which might lower the cloud point [60]. Various electrolytes may also increase or decrease the cloud point and thermal gelation temperature in relation to their position within the lyotrophic series [56]. In parallel with their effects on polymer hydration and water uptake, changes in cloud point temperature may indicate that a drug or excipient has the potential to modify polymer behaviour, and cloud point measurements have been therefore used as an indirect screen for substances that might modify drug release from HPMC matrices.

2.4.3 Gel Layer Thickness and Matrix Swelling

A thermal mechanical analysis comparison of HPMC mini-matrices containing 4,000 cP viscosity grades of HPMC 2910 (Methocel E4M), HPMC 2906 (Methocel F4M) and Methocel HPMC 2208 (Methocel K4M) could not identify differences in the thickness of the surface gel layer between different USP grades [59]. The experimental geometry is shown in Figs. 2.3, and 2.4 shows typical swelling data for

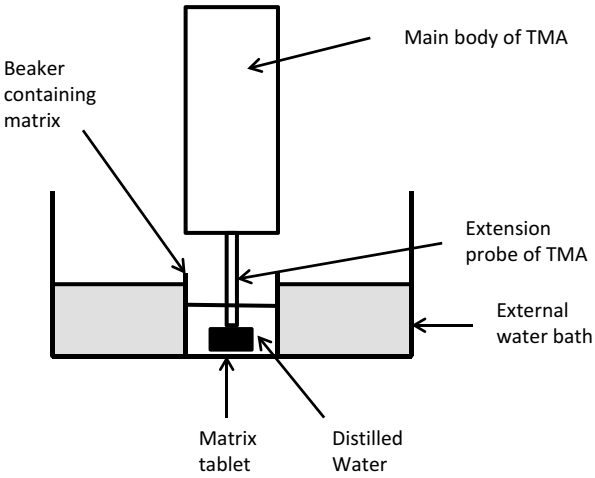

Fig. 2.3 The thermal mechanical analyser geometry used to measure the rate and extent of swelling in cellulose ether matrix tablets. (Reproduced from [59].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/ textbook via Copyright Clearance Center

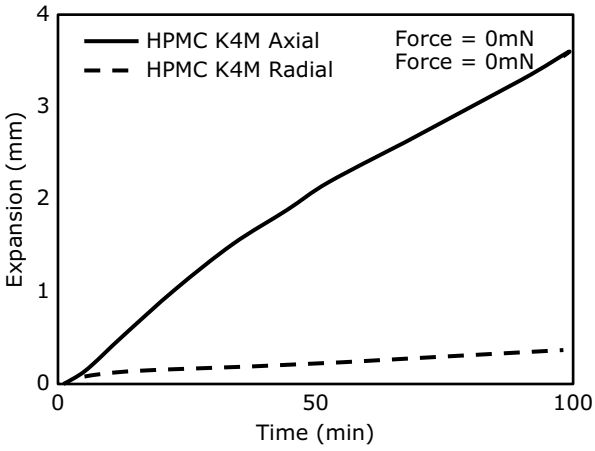

Fig. 2.4 Axial and radial expansion of a compact containing HPMC 2209 (Methocel K4M) at 37 °C measured by thermal mechanical analysis. (Reproduced from [59].) International journal of pharmaceutics by Elseviers BV. Reproduced with permission of Elsevier BV in the format reuse in a book/ textbook via Copyright Clearance Center

matrices manufactured from these materials. The expansion rate was ranked methylcellulose > HPMC 2910 > HPMC 2906 > HPMC 2208 in the radial direction. Methylcellulose swelled so rapidly at 37 and 45 °C that the matrix disintegrated [59]. Swelling in the axial direction was in the rank order HPMC2906 > methylcellulose > HPMC 2910 = HPMC 2208 at 24 °C, but changed to methylcellulose > HPMC 2906 > HPMC 2208 > HPMC 2910 at 37 °C or 45 °C [59]. Using a laser beam to measure volume, the rate of volume increase was ranked as HPMC 2208 > HPMC 2910 > HPMC 2906 [59] and the respective increases in volume were 424, 280 and 230 %. It is recognised that these increases, which were observed under static conditions, would not be sustained in dissolution testing or in vivo conditions and perhaps this emphasises the need for dynamic conditions so that the matrix can undergo erosion. Release of drugs from HPMC matrices can never be solely diffusion controlled.

In the presence of drugs, matrix gel layers became thinner. The swelling order of HPMC 2208 (Methocel K4M) matrices containing 50 % drug were 'no drug' > tetracycline hydrochloride > propranolol hydrochloride > indomethacin [59]. It was clear that drug could influence polymer hydration and swelling, because both the rate of swelling and the rank order were changed. Matrices containing propranolol hydrochloride were ranked methylcellulose > HPMC 2208 = HPMC 2906 > HPMC 2910, and for matrices containing tetracycline they were methylcellulose > HPMC 2906 > HPMC 2910 > HPMC 2208, but for matrices containing the poorly soluble drug indomethacin, the rank order was methylcellulose (collapsed) > HPMC 2208 > HPMC 2906 > HPMC 2910. In the presence of soluble drugs, methylcellulose matrices remained intact and thus the drug must contribute in some way to the structure of the gel and the integrity of the matrix [59].

Wan et al. [61] have shown how the swelling of ibuprofen HPMC matrices follows root time kinetics. In the absence of drug the swelling rates were 0.44, 0.42, 0.49 and 0.53 % s^{-1}, respectively, for HPMC 2208 grades which were viscosity equivalents of Methocel K4M, K15M, K30M and K50M. It was also found that as the drug:polymer ratio within the matrix was varied a direct relationship existed between the release rate of ibuprofen and the reciprocal of the swelling rate. This was the case in all four viscosity grades.

The dimensional changes involved in matrix swelling can be complex. Early NMR microscopy (magnetic resonance imaging) studies of pure HPMC matrices showed that the rate and extent of gel layer growth were similar in both axial and radial directions (Fig. 2.5) [62]. The HPMC matrix swelled in the axial direction, but this was a result of changes in the unwetted core which shrank in the radial direction but swelled in the axial. In some cases, 50 % of axial swelling was due to expansion of the core. Matrix swelling also produced dumbbell-shaped matrices. This was brought about partially by the expansion of the core, and partially because ingress of water occurs through both the face and the wall at the corners of the tablets [62, 63].

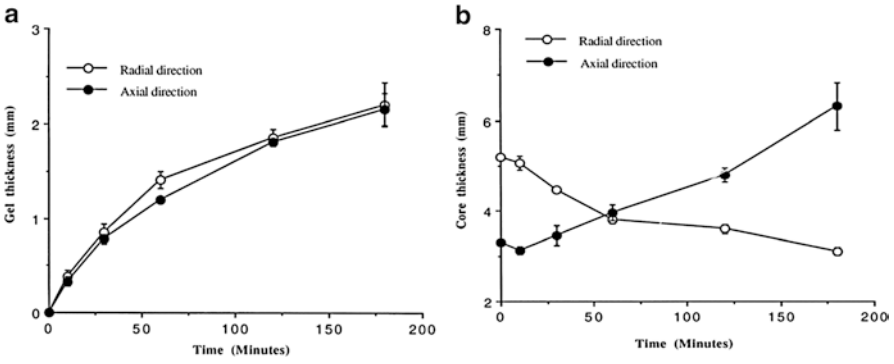

Fig. 2.5 Gel layer growth (**a**) and dimensional changes in the dry core (**b**) in HPMC2208 (Methocel K4M) matrix tablets during hydration, measured from MRI images. (Reproduced from [62].) Journal of controlled release: official journal of the Controlled Release Society by controlled release society. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

Axial expansion of the core in isolation to the development of the gel layer is not well documented, but uniaxial relaxation of the elastic energy stored during compaction would be an obvious cause [45, 64]. Swelling differences have also been attributed to the relative differences in surface area between the faces and edges of the matrices. The axial surface area is so much greater that water is able to imbibe more extensively in this direction [24, 59, 62].

2.4.4 Water Uptake by HPMC Matrices

It has been suggested that different USP grades of HPMC may differ in their rate of hydration, as a consequence of their different ratios of methoxyl to hydroxypropoxyl substitution. The proposed order was HPMC 2208 > HPMC 2910 > HPMC 2906 > methylcellulose, and it was claimed that these differences would allow drug release rates to be modified by choosing a different grade [14]. Mitchell et al. [59] have used the disappearance of free water as an assessment of hydration rates, and concluded that hydration rates in methylcellulose, HPMC 2208, HPMC 2906 and HPMC 2910 were not significantly different (Fig. 2.6). They proposed that

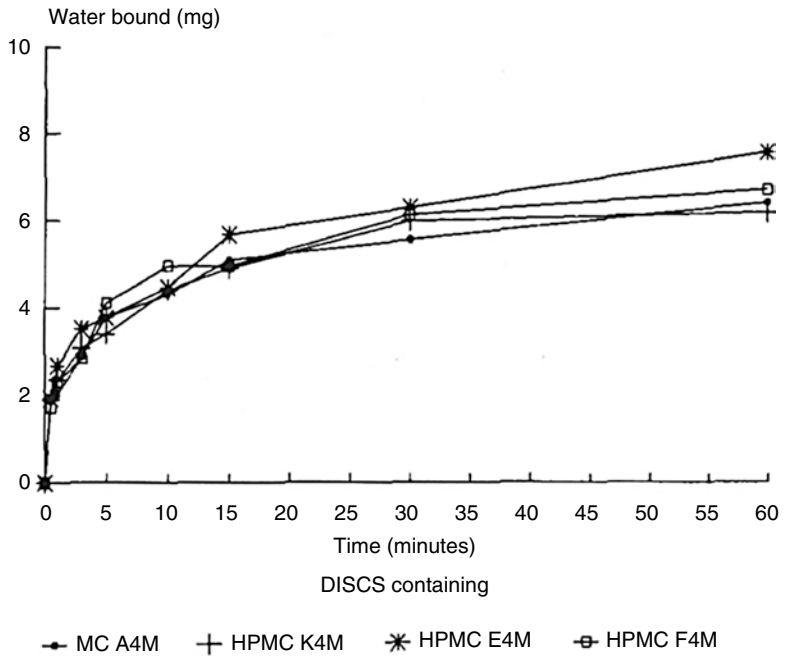

Fig. 2.6 The water bound by discs of different HPMC types over a period of 60 min hydration. (Reproduced from [59].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

other factors such as gel strength would play a significant role in the observed differences in drug release rates [59]. Gel strength, when measured on 6 % gels, was ranked methylcellulose > HPMC 2208 (K4M) > HPMC 2910 (E4M) > HPMC 2906 (F4M) [59].

2.5 Fundamental Factors That Affect Drug Release in HPMC Matrices

One of the major problems in establishing any clear trends and defining the principles of drug release from formulated HPMC matrices is the conflicting evidence in the published literature. The work of Dahl et al. [65] illustrates the difficulties in establishing even the basic principles. These authors examined seven batches of HPMC, all marketed as Methocel K15M HPMC 2208, and all of equivalent particle size range. They measured the release rate of a moderately soluble drug, naproxen, and found this to be 25–27 % h^{-1} in the case of five HPMC batches, but only 12–14 % h^{-1} for the two remaining products. Such data suggests that so-called similar HPMC products could behave in highly disparate ways. The one significant correlation was with hydroxypropyl content, which was 8.7–11.1 % in the five similar batches and 5.3 and 7.2 % in the two outlying batches. Notwithstanding this, some positive trends have been identified and the following sections emphasise those which might be considered to be the most important for the performance of HPMC matrices.

2.5.1 Ratio of Drug to HPMC

In general, the greater the content of HPMC within a matrix, the slower is the drug release rate [14, 17, 20, 32] and it has been demonstrated that the HPMC:drug ratio is often the major factor controlling release in HPMC matrices as shown in Fig. 2.7 [17, 21, 22]. Lower HPMC:drug ratios (<1:1) can lead to attrition, a positive deviation from root time release profiles and burst release if tablet disintegration occurs[17–21]. The polymer:drug ratio also affects the tortuosity of the gel, and it is likely that formation of a strong gel layer occurs in matrices with high polymer contents. At lower HPMC contents, the gel layer may not form as rapidly and gel strength may be lower. Xu and Sunada [66] have postulated that the diffusion layer becomes stronger and more resistant to diffusion and erosion as the HPMC content is increased. There is also an expectation that once a threshold HPMC content is exceeded, the effects due to viscosity and particle size will become less evident. This polymer content may lie within the range of 30–40 % since this appears to be the range at which similar drug release profiles are obtained from HPMC grades of different substitution types of HPMC (HPMC 2208, 2906, 2910) [21].

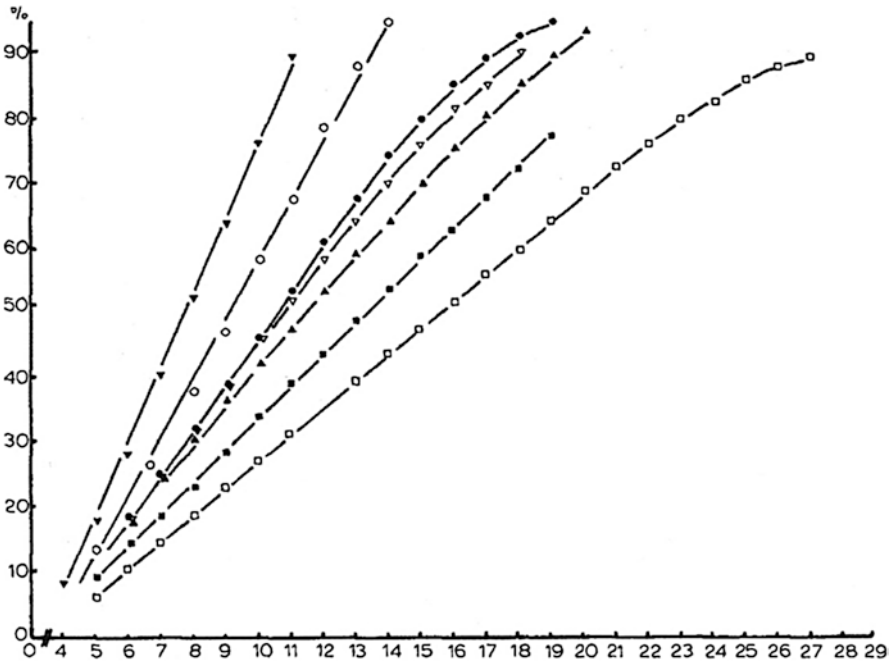

Fig. 2.7 The effect of promethazine hydrochloride: HPMC 2208 (Methocel K15M) variation on the promethazine release of 25 mg promethazine into water at 37 °C from tablets containing (mg of HPMC) *filled inverted triangle*, 20; *open circle* 25; *filled circle*, 40; *open triangle*, 50; *filled triangle*, 80; *filled square*, 120; *open square*, 160. Ordinate % Promethazine hydrochloride dissolved. Abscissa $\sqrt{}$time ($min^{-1/2}$). (Reproduced from [17].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

2.5.2 HPMC Substitution Type

Rapid polymer hydration is required to form the gel layer. This protects the matrix from excessive water penetration into the matrix, and prevents the rapid dissolution of soluble components. Alderman [14] has proposed that HPMC K2208 grades can hydrate more rapidly than HPMC 2906, HPMC 2910 or methylcellulose, and as a result, HPMC substitution type can significantly modulate drug release. However, the studies of hydration rates described above have found they were not significantly different and that other factors should be sought to account for the differences in drug release rate [59]. Substitution type can be important in the case of poorly soluble drugs in which erosion is the predominant control mechanism. One study has shown how the release of a soluble drug (propranolol hydrochloride) occurred at similar rates in HPMC 2910, HPMC 2208 and HPMC 2906 matrices [59]. However, in the case of a poorly soluble drug (acetazolamide) there were clear

differences between the grades, with the rank order of drug release decreasing (HPMC 2910 > HPMC 2208 > HPMC 2906) reflecting the rank order of matrix erosion in the absence of drug [67]. The same rank order has been found in the release of diclofenac sodium from HPMC matrices [60].

Bonferoni et al. [67] have measured the erosion resistance of isolated gels and hydrated matrices using creep recovery and oscillatory rheometry. Determinations of the residual viscosity, storage (G′) and loss (G″) moduli on 5 % or 7 % w/w HPMC gels gave rankings of HPMC 2208 > HPMC 2906 > HPMC 2910, indicating that HPMC2208 was the most elastic. This ranking correlated with the release of the polymer by erosion from 5 % gels. However the relevance of isolated gel studies to hydrated matrices is doubtful, as erosion from (drug free) matrices has been ranked HPMC 2910 > HPMC 2208 > HPMC 2906 [67]. This study also perhaps highlights how inclusion of a drug adds further complications, potentially changing the gel strength, and erosion rates.

As with many of the factors that control drug release from HPMC matrix tablets, even the commercial source of an apparently similar grade of HPMC may cause differences in release. Shah et al. [68] have compared a number of HPMC 2208 batches produced by different manufacturers. Those produced by Shin-Etsu Ltd gave bimodal release profiles whereas a similar Dow product displayed a non-bimodal drug release when incorporated in matrices.

In the case of soluble drugs, substitution type may only exert an effect when low levels of drug are present. When propranolol hydrochloride was included in matrices containing >50 % polymer HPMC 2208, 2906 and 2910 (Methocels K4M, E4M and F4M grades) all performed similarly. In the same polymers, the diffusion rates of propranolol through 10 % w/w gels varied only from 3.1 to 3.8×10^6 cm^2 s^{-1}, which suggests that HPMC substitution grade did not affect diffusion in uniform gels [69]. However, NMR imaging maps of water self-diffusion coefficient have suggested that different substitution types may give rise to different water diffusional mobilities in the matrix gel layer [62]. The diffusion of water in gels has been estimated at around 10^{-6} cm^2 s^{-1} [70] but appears to depend on the molecular weight of the polymer. In HPMC 2208 gels it was faster in a low molecular weight HPMC (Methocel K100) than in a higher molecular weight grade (Methocel K4M) [70].

Despite these studies, it is clear that substitution type can have significant effects in matrix dissolution tests, as a result of the polymer response to different dissolution media. Velasco et al. [71] have investigated the effects of dissolution media on the drug release properties of matrices containing 160 mg propranolol hydrochloride and either 50 mg or 150 mg HPMC. They compared water, 0.1 M HCl and phosphate buffer pH 7.4 as dissolution media. HPMC 2906 (Methocel F4M) and HPMC 2208 (Methocel K4M) achieved control of drug release, but 50 mg HPMC 2910 (Methocel E4M) failed to control drug release in all three media used. Matrices containing 50 mg methylcellulose (Methocel A4M) showed burst release in 0.1 M hydrochloric acid, whereas matrices containing both 50 and 150 mg methylcellulose (Methocel A4M) exhibited burst release in phosphate buffer. This highlighted the sensitivity of methylcellulose to media containing phosphate ions [71].

2.5.3 HPMC Viscosity Grade

Alderman [14] suggested that different viscosity grades of HPMC can be used to modify the release rates of drugs. The rationale was that higher viscosity grades have a higher gel viscosity, which will both slow drug diffusion in the gel layer and also render it more resistant to erosion. These conclusions have been supported by Lapidus and Lordi [8] and Daly et al. [72]. However, other studies have indicated that it is not universally true [17, 21, 73]. In one study, it was found that the release of promethazine hydrochloride from matrices containing several high viscosity grades of HPMC 2208 (Methocels K4M, K15M and K100M) were virtually identical at all polymer:drug ratios. Drug release rates were slower than drug release from similar matrices containing a low viscosity HPMC 2208 (Methocel K100) [17]. Similar findings have been reported for propranolol hydrochloride and aminophylline [21]. One explanation may be that the low viscosity Methocel K100 also possesses low gel strength, whereas all the higher molecular weight HPMCs possess similar gel strengths [59]. We also find that the release of soluble drugs is independent of molecular weight amongst the high viscosity HPMCs and this is perhaps not surprising since (1) diffusion rate is a function of the molecular size of the drug [74] and (2) gel tortuosity is independent of both the grade of HPMC and of the drug [75]. Given that the hydration of HPMC within the gel layer is also modified by the presence of different drugs this is probably not universally true. Water penetration into HPMC compacts is slow, around 40 μm h^{-1}, but this can be changed by incorporated drugs and surface active agents [70].

2.5.4 HPMC Particle Size

HPMC particle size can have a considerable effect on matrix drug release. Typical drug release data in Table 2.1 shows how the release rate of propanolol hydrochloride decreased as the polymer particle size was reduced from >355 μm to 150–210 μm. Further reductions in particle size caused no further reduction in release rate.

Table 2.1 The effect of polymer particle size on matrix drug release rates

	Particle size of HPMC (μm)					
Content of HPMC (mg)	Unsieved	>355	210–355	150–210	75–150	<75
57	8.07	44.72	10.91	7.77	7.69	8.49
95	6.86	56.70	6.47	6.74	6.56	6.57
140	6.02	35,2	5.66	6.04	5.76	5.67
285	4.44	3.90	4.19	4.16	4.05	4.09

Matrices contained 160 mg propranolol hydrochloride with 57, 95, 140 or 285 mg of hydroxypropyl methylcellulose HPMC 2208 (Methocel K15M) on the dissolution rates (% $min^{-1/2}$). Reproduced from [76]. International journal of pharmaceutics by ELSEVIER BV. Reproduced with permission of ELSEVIER BV in the format reuse in a book/textbook via Copyright Clearance Center

Coarse particle size fractions of HPMC are thought to hydrate too slowly to allow sustained release and they can result in burst release. Campas-Aldrete and Villafuerte-Robles [77] have observed that under these conditions swelling HPMC particles were unable to bind effectively to adjacent particles, resulting in disintegration of the matrix. Coarse particle sizes of HPMC may also allow water penetration and disintegration to occur before the formation of the gel layer which protects the internal drug from dissolution. One study has suggested that the use of larger sized particles (>355 μm) of HPMC 2208 (Methocel K15M) creates larger pore sizes that decrease the stability of the gel structure (Mitchell et al. [78]). In contrast, smaller fractions of HPMC allow rapid hydration and uniform gel layer formation [14]. Heng et al. [79] have identified a threshold size of 113 μm for HPMC 2208, above which the use of larger particle sizes results in faster drug release rates.

Some authors believe that particle size effects are observed only at polymer levels of less than 10 % [77], although there is later evidence to suggest otherwise. As with any factor controlling drug release in HPMC matrices, these effects are confounded by the polymer content of the hydrating matrix. In general, the higher the content of HPMC, the slower is the drug release rate [9, 14, 17, 21]. In addition, low polymer levels tend to produce matrices with burst release. Bonferoni et al. [78] have further posited that HPMC particle shape may alter drug release. They suggested that fibrous-shaped HPMC particles can provide decreased drug release rates and a reduced initial burst. In the case of low-dose drugs, a fine particle size of the polymer may also be preferred in order to control drug release rates [76].

2.5.5 Drug Factors

The influence of drugs per se is difficult to rationalise. As noted previously in this chapter, the drug itself may affect the hydrated gel structure by ‘salting in’ or ‘salting out’ the HPMC, and any potential weakening or strengthening of the gel structure has obvious implications for drug diffusion and gel strength [75, 80].

Drug particle size may also affect release rates, but this depends on drug solubility and the polymer:drug ratio. In the case of freely water-soluble drugs, it has been claimed that drug particle size has a minimal effect on drug release rate, except at low levels of HPMC, and with large particle size fractions of the actives (Table 2.2) [17, 21]. This is presumably because, under these circumstances, the matrix is loose, tends to disintegrate and demonstrates greater channel formation [21, 29, 81]. However, for drugs with low aqueous solubility, drug particle size influences drug release rate because, being poorly soluble, their rate of dissolution depends on particle surface area [69] (Table 2.3). Dissolution profiles when presented on a root time basis are sigmoidal and they often exhibit an initial non-linear region from 2 to 4 h which is probably due to poor wetting [22, 69]. In addition, because erosion is the dominant mechanism, the many factors described above that influence gel strength can also affect the drug release. HPMC viscosity grade also becomes an important factor because higher viscosity grades have higher gel strengths [69].

Table 2.2 The influence of drug particle size on matrix drug release rates

Propranolol hydrochloride particle size (μm)	Weight of HPMC 2208	
	57 mg HPMC	285 mg HPMC
	Drug release rates (% $min^{-1/2}$)	
63–90	7.83	3.63
90–125	7.52	3.77
125–180	6.49	3.64
180–250	7.98	3.80
250–500	28.30	3.98

Matrices contained 160 mg propranolol hydrochloride with 57 or 285 mg HPMC 2208 (Methocel K15M). Reproduced from [21]. International journal of pharmaceutics by ELSEVIER BV. Reproduced with permission of ELSEVIER BV in the format reuse in a book/textbook via Copyright Clearance Center

Table 2.3 Effect of HPMC content and indomethacin particle size on the dissolution rate of indomethacin from hydroxypropyl methylcellulose HPMC2208 (Methocel K15M) matrices

Content of HPMC (mg)	Dissolution rates[a] (% $min^{-1/2}$)		
	Particle size of indomethacin (μm)		
	63–90	90–125	125–180
36	2.02	1.74	1.19
200	2.00	1.21	0.84

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[a]Mean of three determinations

Dissolution rates tend to decrease with increasing HPMC:drug ratio, and at a constant ratio they decrease with increasing drug particle size (Table 2.3).

The influence of drug solubility on the performance of HPMC matrices needs further deliberation. The reader should by now have understood that the performance of any particular drug in an HPMC matrix must be considered on a case-by-case basis. As early as 1968, Lapidus and Lordi [8] recognised that differences in the release of sodium salicylate and chlorpheniramine maleate could be differentiated on the greater ability of the sodium ions of the salicylate salt to dehydrate HPMC, and that different drug characteristics, such as high or low solubility, can give rise to different gel characteristics and drug release [34, 82, 83]. In very simple terms, highly soluble drugs are thought to be released principally but not exclusively, by diffusion whilst poorly soluble drugs are released primarily by erosion. In addition, highly soluble drugs may act as pore formers (as will freely soluble excipients), which may make the pathways within gel structures less tortuous [84]. Estimates of the erosion contribution to drug release have been made by quantifying polymer release in addition to drug release. In matrices containing the soluble drug adinazolam mesylate, only 35 % of the matrix polymer had eroded at the point when the drug had been fully released [85]. In comparison, for the less soluble drug alprazolam, around 65 % of the polymer had dissolved. In the case of flurbiprofen, a drug of even lower

solubility, the profiles for drug and polymer dissolution were superimposable [85]. Drugs such as diclofenac sodium may cause disruption in the gel layer that leads to matrix failure as a result of salting out effects [86] and it has been proposed that some drugs increase the diffusion of water by altering water binding to the polymer [70]. Indirect evidence of these effects arises from cloud point studies and it has been claimed that charged drugs, or those that possess long side chains, are less mobile due to their potential interaction with the gel. This alone may increase the time taken for such drugs to diffuse through the gel structure [87, 88].

2.5.6 Dissolution Media

Lapidus and Lordi [8] postulated that inorganic ions in the dissolution media can modify drug release through their effect on HPMC gel structure. Their effects would reflect the affinity of different ions for the water of hydration in the polymer. In some dissolution media, this would result in slower drug release rates whereas in others such as 0.2 M sodium sulphate and 0.2 M magnesium sulphate, a sharp increase in release rate was observed. This was attributed to the prevention of uniform gel hydration causing a discontinuity in the gel layer structure [7]. The ability of individual ions to alter HPMC hydration is reflected by their effect on cloud point which follows their order in the lyotropic series. Anions are generally more potent than cations [56].

Using HPMC matrices prepared without drug, Mitchell et al. [56] showed that matrix disintegration time can vary with the ionic strength of the medium, and that this mirrored the hydration of HPMC. With a soluble drug (propranolol hydrochloride) included in the matrix, they showed how progressive increases in the ionic strength of the dissolution media slowed drug release until a minimum was reached, beyond which further increases in ionic strength led to 'burst' release of the drug. Knowledge of the cloud point of HPMC in solutions of the given ions, they proposed, could be used to predict when a matrix would exhibit burst release [56].

Sheu et al. [89] showed how the release of diclofenac sodium is retarded in the presence of sodium chloride and attributed this to 'common ion effects' altering the drug solubility. Bajwa et al. [39] have shown how salts can affect gel layer growth during the earliest stages in the formation of the gel layer. Using confocal fluorescence imaging, they identified disintegration mechanisms which might underlie the acceleration of drug release in high ionic strength media. They found that gel layer growth was progressively suppressed over the range 0.1–0.5 M NaCl, but above 0.6 M HPMC particles swelled but could not coalesce to a gel layer. This disruption of gel barrier formation resulted in enhanced liquid penetration of the core and surface disintegration of the matrix due to the inhibited coalescence. These studies should not be read in isolation of the fact that the saline concentrations used far exceed those found in the human gastrointestinal tract, although subsequently it has been shown that other ions such as multivalent citrates exhibit the same effects at much lower concentrations.

Because the pH of dissolution media is commonly controlled by inorganic solutes, it should be obvious that buffering agents in the dissolution medium may influence matrix drug release through ionic effects. Although Alderman [14] claimed that HPMC matrices were relatively free from problems induced by pH, it was already understood that pH can influence drug release for drugs with a marked pH-dependent solubility. As early as 1966, Lapidus and Lordi [7] had suggested that that using a dissolution media below pH 3 modified the release of chlorpheniramine maleate consistent with the reduced viscosity of cellulose ether solutions at pH values below 3. Specifically, this was attributed to a change in polymer hydration as a result of protonation of ether linkages and a reduction in the tortuosity of the hydrated gel [7].

Not only can pH modify drug release by modifying the structure of the hydrating gel, but the solubility and dissolution rate of weak acid and weak base drugs can be reduced when the media pH approaches the drug pKa, because significant amounts of drug become unionised and less soluble. The slower release of chlorpheniramine at pH 7.5 has been attributed to such a decrease in drug solubility [7] and Ford et al. [90] have demonstrated that release of promethazine hydrochloride, which was maximal at pH 1 or 3, decreased as the medium pH was raised from 5 to 7 and then to pH 9. The drug pKa was 9.1 and these effects were attributed to decreased drug solubility at the higher pH.

Changes in media composition can be used to highlight the potential hazards of HPMC matrix formulations. Roberts et al. [91] have studied aspirin HPMC matrices in hydro-ethanolic media and found that drug release is accelerated in proportion to the drug solubility in the medium (Fig. 2.8). There was an initial rapid burst of drug release in media comprising 40 % ethanol. Drug release was erosion and diffusion

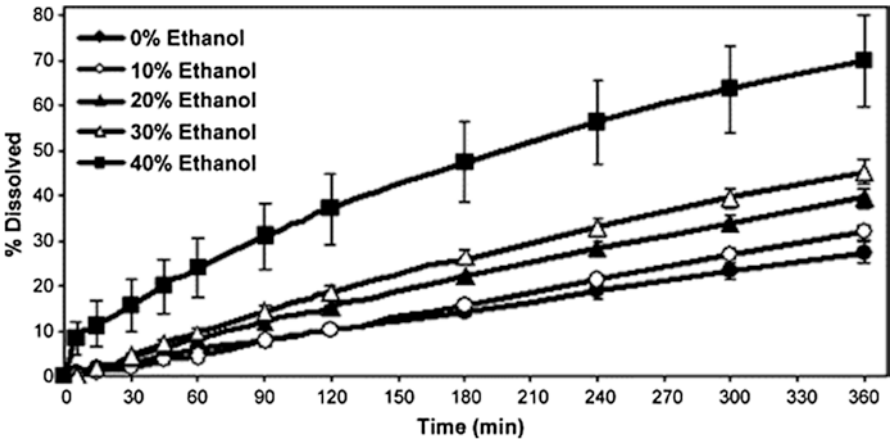

Fig. 2.8 The effect of ethanol concentration on the release of aspirin from HPMC matrices in hydro-alcoholic media. (Reproduced from [91].) International journal of pharmaceutics. Online by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

mediated in 40 % ethanol, whereas in media containing 0, 10, 20 and 30 % ethanol, erosion-controlled release predominated. Cloud point studies showed that ethanol altered the hydration of HPMC [91].

2.6 The Inclusion of Excipients in HPMC Matrices

Excipients are included in HPMC matrices to improve their physical characteristics and to modify the drug release profile. When an excipient is included as a diluent or filler it will dilute the amount of HPMC in the matrix, and as a result, often increase the drug release rate. Misinterpretations can arise when an excipient apparently changes the drug release rate, but is in fact merely changing the HPMC to excipient ratio. HPMC matrices usually contain a tablet lubricant, but their effect appears to be insignificant. One study has shown how 0.75 % magnesium stearate did not affect drug release from HPMC 2208 (K15M) matrices of promethazine hydrochloride [17].

In some cases, however, an added excipient may interact with the HPMC to modify gel strength or polymer hydration. The excipient may also interact with the drug, for example, to change its solubility, and in these ways excipients can significantly alter drug release rates.

Matrices containing cellulose ethers as a sole rate controlling polymer do not provide zero-order release. In the case of soluble drugs the release exponent (Eqs. 2.4 and 2.5 above) has values in the order of $n = 0.6–0.75$. This indicates that erosion of the polymer and dissolution of the drug both contribute to drug release [22]. Highly soluble drugs pose a particular problem as they exhibit a highly curved root time release profile, and can also suffer initial bursts of drug release at the beginning of the dissolution test. However, Baveja et al. [37] have shown how combining HPMC with sodium carboxymethylcellulose can markedly change the shape of the drug release profile, to produce near zero-order in vitro release of soluble drugs and obviate the burst release effects [37].

2.6.1 Lactose and Calcium Phosphate

Lapidus and Lordi [8] showed that whilst adding a soluble diluent such as lactose increased the drug release rate of chlorpheniramine more than an insoluble diluent such as calcium phosphate, this happened only at high diluent levels (>50 %). Both diluents effectively reduce the concentration of HPMC. Lactose was thought to decrease the tortuosity of the diffusion path of the drug and many other studies have shown how replacing HPMC with lactose results in higher drug release rates [88, 92]. Alderman [14] has suggested that non-swelling, insoluble fillers can actually prevent slow release. As little as 10 % dicalcium phosphate could destroy sustained release because the gel layer would be unable to swell evenly. Another study has shown how replacement of HPMC by up to 75 % lactose or calcium phosphate

increases drug release rates (of 25 mg promethazine hydrochloride) whilst maintaining linear root time dissolution profiles [22]. Only in tablets containing 10 mg HPMC and 30 mg lactose or calcium phosphate were differences apparent between these two excipients, despite their greatly differing solubilities. Drug release rates were little changed by the particle size of lactose or calcium phosphate [22].

2.6.2 Sodium Carboxymethylcellulose

Matrices which combine HPMC with sodium carboxymethylcellulose (NaCMC) can provide zero-order in vitro release profiles for several highly soluble drugs. This suggests that this polymer combination allows the erosion front to move at the same rate equating as the swelling front [37]. In dilute solution these two polymers exhibit a synergistic increase in solution viscosity either as a result of direct interaction between the polymer chains [93] or coil expansion of the anionic polymer in the mixed environment [94]. However, there is also the possibility of drug:NaCMC complex formation [95]. An illustrative example of the complexity of these systems is provided by an HPMC/NaCMC matrix formulation developed for zero-order release of chlorpheniramine maleate [96]. Extended release could have arisen as a result of rheological synergism, but as chlorpheniramine can complex with the anionic carboxyl residues of the polymer, zero-order kinetics could have arisen from poorer drug solubility and an increased role for erosion. However, mixed HPMC:NaCMC matrices can be also successful in providing extended release of drugs with low aqueous solubility [97]. In highly acidic media such as simulated gastric fluid (pH 1.2) the NaCMC becomes insoluble. It does not contribute to the surface gel and may even promote disintegration of matrix especially at low levels of HPMC. Mixed HPMC:NaCMC matrices therefore can be pH sensitive [95, 98]. Sodium carboxymethylcellulose has been combined with other cellulose ethers for the same purpose. One study has demonstrated that whilst matrices containing a single polymer (hydroxypropylcellulose, sodium carboxymethylcellulose or methylcellulose) exhibited root time release profiles, matrices containing mixtures of hydroxypropylcellulose or methylcellulose with sodium carboxymethylcellulose allowed zero-order in vitro release to be achieved once the polymer:drug ratio was optimised [99].

Other anionic polysaccharides of natural origin such as alginates can fulfil a similar role to NaCMC in HPMC polymer mixtures. These are discussed in detail in Chap. 4.

2.6.3 Ionic Exchange Resins

Ion-exchange resins are cross-linked, water-insoluble polymers. They possess ionisable functional groups which form drug–resin complexes with oppositely charged drugs. Several studies have shown how the release of ionised drugs from HPMC

matrices can be delayed by incorporating ion-exchange resins [96, 100]. It has been proposed that, as the drug dissolves in the gel layer, a drug–resin complex will form in situ and drug can only then be released when sufficient counter-ions are available to displace the drug from its binding sites.

Although they may be susceptible to changes in the ionic strength of the dissolution environment, embedding ion-exchange resins in an HPMC matrix offers several advantages over a simple matrix containing an ion-exchange polymer alone. Prior soaking of the resin in a solution of drug is not required, and the combination may provide a buffering capacity which can render the system pH independent. A wide range of drug release profiles can be obtained by changing the HPMC:resin ratio [96].

The type of resin used is important. It has been found, for example, that Dowex 2X-8 provided a greater reduction in the release rate of penicillin V than Amberlite IRA 410, and that the weakly basic ionic exchange resin Amberlite IRA 47 was more effective at retarding sodium salicylate than the strongly basic anionic exchanger Dowex 2X-8, because of its greater exchange capacity [96]. The counter-ions associated with the resins are also important. In the case of Amberlite CG 50, a weak acid exchanger, hydrogen ions were found to retard the release of chlorpheniramine maleate effectively whereas sodium ions caused disintegration of the matrix [96].

2.6.4 Carbomer

A polymer interaction can occur between the hydroxyl group of HPMC and the carboxyl group of Carbopol 940 which, it has been claimed, has the potential for decreasing the size and weight of matrix tablets [101]. Perez-Marcos et al. [102] have utilised Carbopol 974 with HPMC to provide controlled release of propranolol hydrochloride. Matrices containing different polymer ratios exhibited similar dissolution rates at 5–35 % drug release, but burst release was observed in formulations containing more than a 3:1 ratio of Carbopol to HPMC. This was attributed to the formation of a propranolol Carbopol complex.

2.6.5 Surface Active Agents

In situ interactions between drugs and excipients have been used to enhance the extended release properties of hydrophilic matrices. It has been shown that inclusion of anionic surface active agents such as sodium alkyl sulphates can retard the release of drugs such as chlorpheniramine maleate from an HPMC matrix [72]. These surfactants form poorly soluble complexes with drug, and the hydrocarbon chain length of the surfactant appears not to be a major factor in drug release rates [73]. Another study has shown how sodium dodecyl sulphate can retard the release

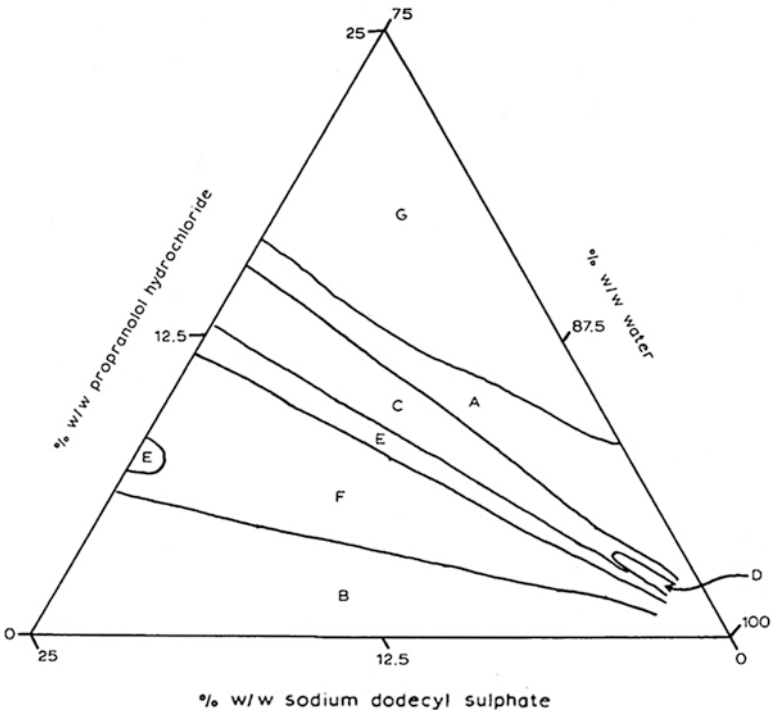

Fig. 2.9 Ternary phase diagram of the propranolol hydrochloride—sodium dodecyl sulphate—water system containing >75 % water. Key (A) isotropic liquid, (B) isotropic liquid, (C) two immiscible liquid phases, (D) anisotropic liquid (liquid crystal), (E) liquid + propranolol dodecyl sulphate (precipitate), (F) emulsion and (G) liquid + excess propranolol hydrochloride. (Reproduced from [103].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

of propranolol hydrochloride through in situ formation of propranolol dodecyl sulphate [103]. The estimated solubility product of this compound was 4×10^{-8} M^2 [103] which compares with a value of 1.83×10^{-7} M^2 obtained for chlorpheniramine dodecyl sulphate. When the surfactant content of the matrix was increased, the root-time dissolution rates of these tablets were proportional to the remaining un-reacted propranolol hydrochloride [103]. However, it should be noted that any drug/polymer/surfactant/water system is intrinsically complex because there can be interaction between each component and/or phase separation. Just how complicated can be judged by the simple three-component phase diagram shown in Fig. 2.9.

The effects of a drug interaction can be demonstrated by studies of cetrimide, which being cationic is, however, too toxic to include in tablets. Cetrimide does not yield a poorly soluble salt and when included in chlorpheniramine HPMC matrices it marginally increases, rather than retards, drug release [103]. This effect occurs despite the ability of cetrimide to increase the solution viscosity of HPMC. Other authors have noted how surfactants can increase the diffusion rate of water in HPMC gels by altering its binding with the polymer [70].

2.6.6 Buffers

Buffers are added to matrix formulations to maintain gel layer pH in a range which will stabilise the release kinetics of drugs which have pH-dependent solubility [104]. A number of examples are detailed in Chap. 11.

As we have seen, the inclusion of ionic materials in HPMC matrices can affect the ability of the polymer to hydrate and swell. This applies to ions in both the external medium and the microenvironment of the gel layer [105]. In a manner analogous to the concentration gradient of a soluble drug, and indeed HPMC across the gel matrix (Katzhendler et al. [106]), it is likely that there is also a pH gradient across the gel layer in buffered matrices, with the periphery of the gel having a pH closer to the medium than layers closer to the tablet core. Pillay and Fassihi [107] have shown how inclusion of sodium bicarbonate in the tablet results in a gel pH > 8, whereas in the absence of buffer, the pH of the internal matrix is similar to that of the dissolution media. Indirectly this latter result provides evidence that solutes in the dissolution media can also moderate the pH of the gel layer, and that they can follow the solvent front into the hydrating matrix.

The use of buffers to modify pH is not without concern. If at any stage the pH change is reversed so that the drug precipitates, different polymorphic forms of drug with changed physicochemical characteristics might be formed. This would lead to unpredictable changes in drug release rate. Indeed, the use of inappropriate or unintended buffering may change an ionised soluble form of a drug to its insoluble free base or acid with similar consequences.

2.6.7 Microcrystalline Cellulose and Other Excipients

In addition to using diluents such as calcium phosphate or lactose to improve the formulation of HPMC matrices, other commercial excipients have also found favour. Microcrystalline cellulose (Avicel®) has been compared with calcium phosphate (Emcompress®) by Vargas and Ghaly [108] and the effects of these two diluents could not be differentiated in matrices containing 30 % or 40 % HPMC. However, below an HPMC content of 30 %, the use of microcrystalline cellulose increased drug release rates whilst matrices containing calcium phosphate were slower. Levina and Rajabi-Siahboomi [109] have compared several different fillers, including spray-dried lactose, microcrystalline cellulose and partially pregelatinised maize starch (Starch 1500®). Model formulations containing 30 % w/w drug, 20 % w/w HPMC, 0.5 % w/w fumed silica, 0.25 % w/w magnesium stearate and 49.25 % w/w filler were used to control the release of chlorpheniramine maleate and theophylline. The incorporation of Starch 1500 in the matrices was found to give a significant reduction in drug release rates compared with the other fillers. The authors suggested that Starch 1500 enhanced the retardation of drug release through a synergistic interaction with HPMC which contributed to gel layer viscoelastic properties.

The inclusion of other swelling materials, such as guar gum, gum arabic, carrageenan or corn starch into HPMC matrices, can cause partial disintegration of the dosage form and it was considered that the slower swelling of these polymers may result in a partial failure of the forming gel layer (Streubel et al. [110]). The use of superdisintegrants such as Explotab® and Ac-Di-Sol® should clearly be avoided as they can lead to rapid water uptake, swelling and wicking, leaving a highly porous and weak matrix (Lee et al. [111]). Other potential disintegrants such as microcrystalline cellulose, however, have been shown to decrease drug release rates, presumably by swelling little and physically obstructing drug release [66, 108, 111].

2.7 Manufacture of HPMC Matrices

2.7.1 Tablet Size

A number of simple factors need to be considered when formulating HPMC matrix tablets. Although the ratio of the ingredients may be similar, drug release rates are dependent on the geometry and shape of the tablets, and their surface to volume ratio. In many cases the relationship between release rate and surface area is linear [22, 83, 112] and diffusion pathways are shorter in smaller tablets which is why faster drug release occurs [24, 113]. If small tablets are required, then the higher surface to volume ratio means that the content of HPMC should be increased.

2.7.2 Compaction of HPMC

HPMC grades are generally suitable for the manufacture of tablets by nearly all unit processes commonly used by the pharmaceutical industry to manufacture tablets. The performance of HPMC in granulation processes is described in Chap. 3.

The tensile strength of HPMC matrices is dependent on the substitution type of HPMC because it is believed the hydrophobic methoxyl-substituted regions decrease inter- and intra-particulate hydrogen bonding and reduce matrix strength [5, 43, 114]. The compression and compaction properties of HPMC also depend on particle size, moisture content, compression force, compression speed and viscosity grade, with particle size being considered the most important factor in controlling the tensile strength of HPMC matrices [115]. Increased compression speed usually decreases the tensile strength of low molecular weight HPMC tablets, with low viscosity HPMC 2208 (Methocel K100LV) being more sensitive to changes in compression speed than other HPMC grades [116]. Powder moisture content is also a variable. HPMC grades probably contain about 6 % moisture as supplied, which will be tightly bound to the polymer. If this value is exceeded then inter-particulate bonding can be reduced, reducing the tensile strength of tablets [117].

Although increasing compaction force will increase the density of HPMC tablets this has little effect on the drug release profiles [17, 118, 119]. Increasing the compaction pressure from 93 to 1,395 MN m^{-2} did not modify the release of promethazine from HPMC 2208 (K15M) matrices and all values were within ±8.2 % of the mean [45]. There are claimed differences in relation to HPMC molecular weight. Tablet hardness did not affect the release rate of matrices containing Methocel K100 or K4M grades of HPMC 2208, but some changes were observed in matrices containing HPMC 2208 (Methocel K15M) when compressed at higher compaction pressures [118]. Salomon et al. [9–11] confirmed that changes in compression force (and it was claimed, particle size and tablet thickness) had little effect on the release rate of potassium chloride. It did however alter the lag period that preceded drug release.

Sheskey and Cabelka [120] have examined the re-workability of HPMC. The type of milling procedure had minimal influence, and reworked tablets exhibited good physical characteristics. HPMC 2208 formulations demonstrated higher tablet hardness values overall than tablets from HPMC 2910. Dissolution of three model drugs form reworked tablets were not significantly affected by variables such as compression force, the type of rework procedure, the presence of additional lubricant or the level of reworked material incorporated in the tablet [120].

2.8 Conclusions

This chapter has outlined some of the fundamental studies of HPMC hydrophilic matrix systems that were published in the twentieth century. More recent developments are described in other chapters in this book. HPMC as a polymer provides a variety of chemistries and viscosities which can be used to moderate drug release. Adding other excipients and adjuncts provides further versatility for this platform, enabling pharmaceutical formulators to obtain the required drug release characteristics for their drug of choice.

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Chapter 3
An Industrial Perspective on Hydrophilic Matrix Tablets Based on Hyproxypropyl Methylcellulose (Hypromellose)

Marina Levina and Ali R. Rajabi-Siahboomi

3.1 Introduction and Background

Hydrophilic matrices are a popular and widely used technology for achieving extended oral drug release. Hydroxypropyl methylcellulose (HPMC, hypromellose USP) is the most common polymer of choice as the rate-controlling excipient in hydrophilic matrix systems. The popularity of HPMC arises from its physicochemical characteristics but also its safety, global compliance and availability [1–4]. HPMC displays good compression properties and matrices can accommodate high doses of drugs. It can provide highly reproducible release profiles. As a non-ionic polymer, it exhibits pH-independent drug release provided that this is also a characteristic of the drug. It has a very broad regulatory acceptance (for example, in the FDA's Inactive Ingredient Database—IID, 2014 [5]). There are many HPMC-based hydrophilic matrix extended release products on the market. The formulation development of these matrices follows simple principles, and this chapter considers the most critical formulation and processing parameters.

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Table 3.1 Polymer characteristics of different USP types of Dow METHOCEL™ grades of HPMC

HPMC Grade (METHOCEL™)	HPMC Substitution Type (USP)	Methoxyl (%)	Hydroxypropoxyl (%)	Viscosity grade (cP)
K	2208	19–24	7–12	3, 100, 4000, 15000, 100000
E	2910	28–30	7–12	3, 5, 6, 15, 50, 4000, 10000, 15000
F	2906	27–30	4–7	50, 4000

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3.2 The Chemistry of HPMC

As a result of its crystalline nature, native cellulose is not soluble in water but when substituents are introduced, this structure breaks down and cellulose derivatives such as HPMC become water soluble (Fig. 2.1). The substitution pattern along the chain is not regular, and in particular it is believed there are methoxyl-rich and unsubstituted native cellulose regions on the molecule [6]. HPMC is commercially available from Dow Pharma & Food Solutions (USA), Ashland (USA), Shin-Etsu (Japan) and other suppliers based in the Asia Pacific region. The majority of the data described in this chapter, and the experience of the authors, are based on the use of HPMC manufactured by the Dow Pharma & Food Solutions under the trade name Methocel™. This and other HPMC brands are available in a range of chemical grades which differ both in their degree of hydroxypropoxyl and methoxyl group substitution and in their dilute solution viscosity (Table 3.1). The USP distinguishes different HPMC (hypromellose) grades by their methoxyl and hydroxypropoxyl group substitution. The two USP types most commonly used in matrices are 2910 and 2208, with high viscosity grades of 2208 (Methocel K) being the most widely used in the formulation of hydrophilic matrices.

3.3 Mechanisms of Drug Release from HPMC Matrices

On contact with aqueous fluids, the HPMC in a hydrophilic matrix hydrates rapidly to form a gelatinous layer (the gel layer) around the surface of the tablet [1, 7]. The formation, structure and characteristics of the gel layer have been studied using many techniques, including cryogenic scanning electron microscopy, video optical microscopy, ultrasound, NMR microscopy and confocal laser scanning microscopy [8–15]. These studies have shown how drug release from HPMC matrices occurs as a consequence of a number of key processes. These include polymer wetting, hydration and swelling, gel layer formation, drug dissolution and diffusion of drug in solution through the gel layer. An additional factor is the dissolution and erosion

of the polymer at the edge of the gel layer, a process which both reduces the size of the matrix and releases undissolved drug particles. In reality, the underlying mechanism of drug release from HPMC matrices is more complex because it involves many dynamic processes resulting in the moving boundaries known as the swelling, diffusion and erosion fronts [16–18]. It is considered that soluble drugs are released primarily by diffusion through the gel layer, whereas drugs with lower solubility are mainly released through gel erosion [19, 20]. In the case of most drugs, however, a combination of both processes is involved [19, 21]. Various mathematical models have been used to describe the processes and kinetics of drug release from HPMC matrices [22–26]. However, from the perspective of the pharmaceutical formulator, the principal factors that can be adjusted in order to influence the drug release profile are the polymer type and content, the drug, the various excipients and the manufacturing processing parameters. The influence of these factors is the focus of this chapter.

3.4 Critical Polymer Attributes

Rapid polymer hydration and uniform formation of the gel layer are critical to the subsequent integrity and performance of HPMC matrices. The polymer variables that most significantly affect matrix performance are the polymer substitution type, viscosity grade (molecular weight), particle size and amount of polymer in the matrix [16, 27, 28].

3.4.1 Substitution

The type of substituent and the degree of substitution control the hydrophilicity of alkoxy cellulose ethers such as HPMC. In general, increasing the average number of substituents on the cellulose chain will reduce polymer hydrophilicity because each substituent replaces a hydroxyl group. It has been shown that substituent type can influence polymer hydration, swelling and water transport [29]. Methoxyl groups are more hydrophobic and reduce polymer swelling to a greater extent than hydroxypropyl groups [6, 30]. Dahl et al. [30] have investigated how the physicochemical properties of HPMC influenced the release of naproxen, and concluded that the degree of hydroxypropyl substitution was an important factor in controlling drug release. More recent studies [31] have provided evidence that the degree of hydroxypropyl substitution is a key parameter that affects drug release, especially in formulations containing low solubility drugs in which erosion is the main mechanism of drug release. An example (Fig. 3.1) illustrates the significant changes in the release that can occur with changing polymer hydroxypropyl content. Therefore, it may be appropriate to evaluate the sensitivity of a chosen formulation to the degree of hydroxypropyl substitution, and if necessary to develop tighter control of this parameter with the polymer suppliers.

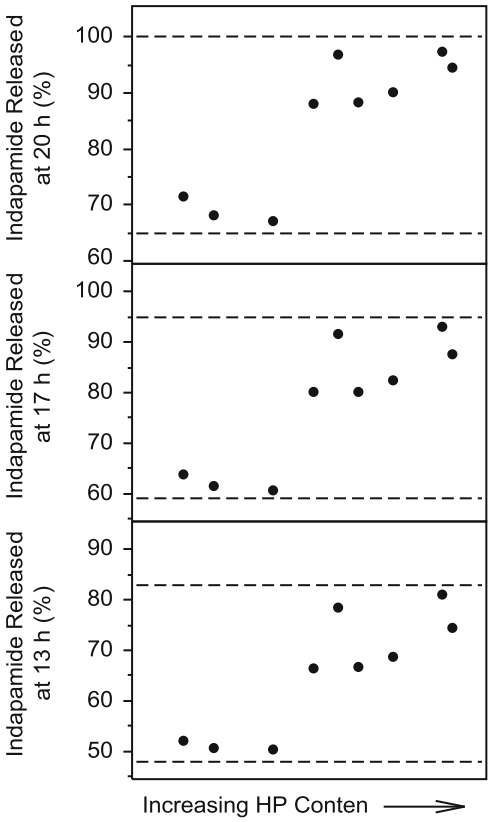

Fig. 3.1 The influence of hydroxypropoxyl substitution on indapamide release from HPMC matrices. The figure shows drug release with respect to hydroxypropoxyl (HP) content for different batches of low viscosity USP2208 (METHOCEL™ K100LV CR). *Formulation*: Indapamide (2.5 %), METHOCEL™ K100LV CR (40 %), lactose (40 %), MCC (16.5 %) and 1 % mag stearate and talc (tablet weight 200 mg). Reproduced with permission from the Dow Chemical Company®, ™ Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

3.4.2 Viscosity Grade

In the case of linear polymers, the polymer chain length and polydispersity define the average molecular weight. However, HPMC manufacturers do not describe commercially available HPMC polymers according to molecular weight, or give an indication of polydispersity [32]. Instead, commercial literature indirectly specifies acceptable molecular weight ranges for their products through dilute solution viscosity values. In the case of HPMC, this is measured as the apparent viscosity of a 2 % aqueous solution at 20 °C.

In general, matrix drug release becomes slower as the average molecular weight of HPMC is increased. Higher viscosity grades of HPMC are often used for highly soluble drugs, whereas low viscosity grades of HPMC can be used in formulations for low solubility drugs. Mechanistically speaking, when an HPMC matrix is hydrated in aqueous media, the polymer is transformed from a solid glassy state to the rubbery state of the gel layer. As the aqueous media continues to penetrate the tablet, there is swelling of the polymer on and below the surface which, along with stress relaxation in the core, results in swelling of the whole matrix [33]. A polymer

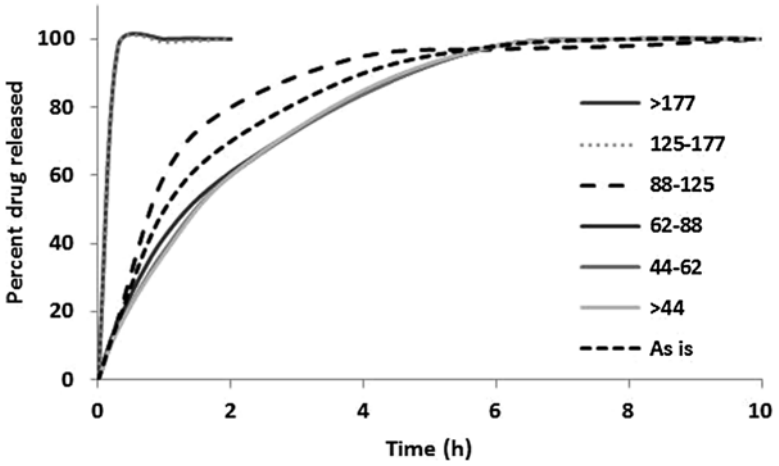

Fig. 3.2 Influence of HPMC particle size on drug release. The legend shows the particle size fraction in microns of the polymer. *Formulation*: METHOCEL™ K4M (20 %), theophylline (5 %), lactose (74.5 %) and magnesium stearate (0.5 %). *Conditions*: USP apparatus 2, 50 rpm, 900 mL DI water. Reproduced with permission from the Dow Chemical Company®, ™ Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

concentration gradient is formed across the gel layer, with the highest concentration of polymer at the gel: dry core interface (the swelling front) and the lowest at the outer edge of the gel surface (the erosion front) [16]. At this outer boundary, the polymer chains dissolve and detach from the matrix, and this process, in combination accelerated by shear forces in the dissolution or gastrointestinal environment, results in matrix erosion. Matrix formulations which utilise low viscosity grades of HPMC exhibit high erosion rates, and have thinner gel layers, leading to more rapid drug release [28, 34–36].

3.4.3 Polymer Particle Size

HPMC particle size can significantly influence the drug release performance of the matrix (Fig. 3.2). Small particles allow rapid and uniform polymer hydration and reliable gel layer formation. Conversely, if very coarse HPMC particles are used in a matrix, drug release can become uncontrolled. Mitchell et al. [37] have examined the dissolution rate of propranolol hydrochloride from matrices containing different sized fractions of HPMC (Methocel K15M). Drug release rate decreased as the particle size of HPMC was reduced from >355 μm to 150–210 μm, but further reductions in polymer particle size caused no further changes. Burst release of propranolol HCl occurred at the extremes of large particle size and low HPMC concentration.

Polymer particle size can also have a significant effect on drug release when the formation of the gel layer is compromised. For example, when polymer content is too low, it can result in an incomplete gel layer and partial or complete tablet disintegration [38–40]. Miranda et al. [41, 42] have found a linear relationship between HPMC matrix percolation thresholds and polymer particle size. In essence, the formation of a coherent gel layer occurs most readily when the polymer particles are close to each other, as is the case for relatively small particles in a tablet that contains a sufficient amount of HPMC. However, Kabanda et al. [43] have demonstrated that even with 30 % w/w HPMC in the formulation, a polymer sieve fraction above 125 μm did not provide extended release: in their example 100 % drug was released in 1 h. Mitchell and Balwinski [44] have generated experimental HPMC samples by sieving, producing "coarse, fine, narrow and bimodal fractions" with differing particle size distributions. They found that drug release was significantly faster in formulations where 50 % of polymer particles were greater than 63 μm.

3.4.4 Polymer Batch-to-Batch Consistency

The pharmacopoeial specifications for HPMC provide a range of values with respect to substitution and solution viscosity. Since many attributes of HPMC play a significant role in product functionality [30, 45–51], controlling the impact of batch-to-batch variation is critical for its use in hydrophilic matrices. In addition, although HPMCs from different suppliers have similar pharmacopoeial specifications, their physicochemical differences can cause significant variability in drug release profiles [6, 29, 52–54].

HPMC is typically produced by a batch process in which discrete quantities of polymer are manufactured from wood or cotton pulp cellulose. Batch differences, in both substitution and polydispersity, can arise from the manufacturing process, in addition to the natural variability of molar mass in the original source cellulose [55]. In addition to the major manufacturers of HPMC, there are other, smaller industrial suppliers who may use different manufacturing procedures and raw materials. Their HPMC may comply with pharmacopoeial monographs, but may perform differently to those from the major suppliers [53, 56].

Batch-to-batch variations in the physical properties of HPMCs are typically small and should not significantly influence the performance of a properly formulated, extended release hydrophilic matrix tablet. However, if a formulation is not robust and batch variation is large or combined with other adverse variables, this can potentially result in a final pharmaceutical dosage form that does not meet the specified performance. Mitchell and Balwinski [57] have provided a framework with which to systematically investigate the drug release variability that might be expected for typical extended release matrix formulations within the monographed viscosity ranges of HPMC. Using pentoxifylline, theophylline and hydrochlorothiazide as model drugs, they found that drug release variability over the USP viscosity ranges was greatest for low viscosity grades of HPMC, such as Methocel E50 and

K100 LV. Drug release variability due to differences in HPMC viscosity was found to be greater in formulations which had a substantial contribution from erosional drug release, but smaller in the case of formulations which had a predominantly diffusion-based drug release mechanism.

It has been demonstrated that HPMC polymer of a similar pharmacopoeial HPMC grade but obtained from different suppliers can differ in formulation performance [53, 58–60]. Dahl et al. [30] have also reported that tablets formulated from different batches of the same pharmaceutical grade of HPMC can exhibit different drug release profiles. Since the dissolution performance of the product appeared to be dependent on the chemical composition of HPMC 2208, the results indicated that pharmaceutical manufacturers must be aware of the potential consequences of polymer lot-to-lot variability and of changing suppliers, without proper characterisation of their HPMC excipients.

3.5 Formulation Considerations

In the literature, numerous relationships have been reported between formulation parameters and drug release profiles. Typically the following assumptions can be held to be generally true [61, 62]:

- Drug solubility and drug/polymer ratio are important factors.
- Drug release is more rapid for soluble drugs than for poorly soluble drugs.
- Drug release is more rapid with a soluble filler than with an insoluble filler in the matrix.

3.5.1 Physicochemical Characteristics of the Drug

Many drug characteristics can affect release profiles from HPMC matrices; and drug solubility is probably the most important factor. Figure 3.3 shows how, in the same formulation, slower release rates are obtained with drugs of lower aqueous solubility (theophylline, diclofenac Na) than with the freely soluble drug, chlorpheniramine maleate. As a result, some formulators may combine different viscosity grades of HPMC in order to achieve the desired drug release kinetics for specific drugs [63, 64].

However, Baveja et al. [65] have shown how, despite almost identical aqueous solubilities, the drugs ephedrine HCl, phenylpropanolamine HCl, salbutamol sulphate, terbutaline sulphate, reproterol HCl and aminophylline exhibited different release rates from HPMC matrices. This was attributed to differences in drug molecular shape and size. On the other hand, it has been reported that for soluble drugs, the drug particle size had no significant influence on matrix release kinetics [66, 67]. Only in the extreme of very large drug particles, in formulations that contained relatively low levels of HPMC, was there a noticeably faster drug release rate as these formulations had high matrix porosity and low tortuosity. With poorly

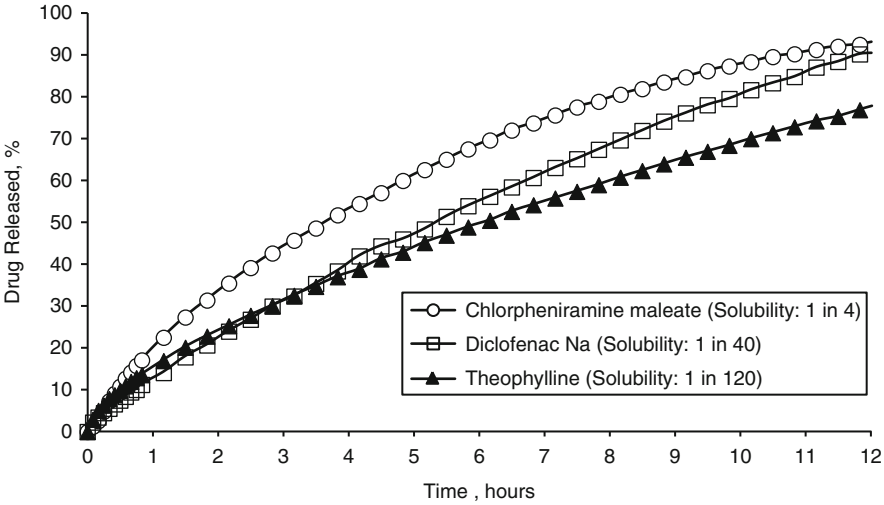

Fig. 3.3 The influence of drug solubility on drug release from HPMC matrices. *Formulation*: METHOCEL K4M (20 %), drug (30 %), MCC (49.5 %) and magnesium stearate (0.5 %). Tablet weight 333 mg. *Conditions*: USP apparatus 2, 100 rpm, 1,000 ml water Reproduced with permission from Colorcon Inc

soluble drugs, however, there are particle size effects, as their dissolution rates are surface area dependent.

Although as a non-ionic polymer, HPMC itself is not significantly affected by pH, the release profiles of drugs having pH-dependent solubility can be significantly influenced by changes in media pH [68]. Weakly basic drugs often show pH-dependent solubility. This can cause problems with drug bioavailability when an extended release matrix enters the small intestine [69] because penetration of intestinal fluid may cause conversion of ionised drug salts to their less soluble base form. These effects are dependent on the drug p*K*a in relation to the pH of the intestinal fluids, but this conversion, total or partial, reduces the amount of the drug that diffuses through the gel layer [70].

3.5.2 HPMC Type and Grade Selection

A variety of HPMC grades can be used in hydrophilic matrix formulations. The two most common substitution types are HPMC 2208 and HPMC 2910 (Table 3.1). HPMC 2208 is perhaps the most popular, and has been reported to produce slower drug release profiles than other HPMC types of similar molecular weight. The availability of different viscosity grades enables formulators to design matrices with predominantly diffusion, erosion or mixed diffusion/erosion mechanisms. Figure 3.4 shows how drug release is retarded as the viscosity grade of the HPMC is increased,

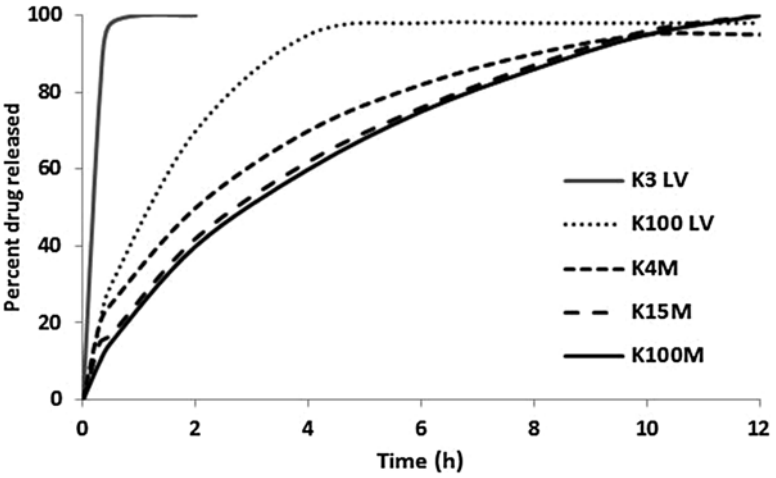

Fig. 3.4 Influence of polymer viscosity (molecular weight) on drug release from HPMC matrices. The figure legend shows the viscosity grade of USP2208 HPMC used in the formulation. Viscosity values of 2 % polymer in water at 20 °C, for the studied METHOCEL™ grades: 3 mPa s (K3 LV), 100 mPa s (K100 LV), 4,000 mPa s (K4M), 15,000 mPa s (K15M) and 100,000 mPa s (K100M). *Formulation*: METHOCEL™ (20 %), theophylline (5 %), lactose (74.5 %) and magnesium stearate (0.5 %) *Conditions*: USP apparatus 2, 50 rpm, 900 mL deionised water. Reproduced with permission from the Dow Chemical Company®, ™ Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

an effect ascribed to an increased viscosity of the gel layer [68]. Water uptake, drug diffusion and polymer erosion all exhibit a considerable dependence on polymer molecular weight [71], and it has been claimed that the use of a higher viscosity grade of HPMC can produce more robust matrices that are less prone to erosion during their passage through the gastrointestinal tract [72, 73]. High viscosity HPMCs when hydrated also form a more viscous and entangled gel layer less affected by agitation conditions during in vitro testing. Matrices containing higher viscosity grades of HPMC are also less likely to be affected by the ionic strength of the dissolution media [74, 75].

3.5.3 HPMC Content

The rate of drug release in HPMC matrices is controlled principally by the HPMC content in relation to the content of drug [71, 76, 77]. Figure 3.5 shows how drug release slows as the polymer content in the formulation is increased. When polymer content is relatively low (less than 20–30 %), the hydrated matrix may be more porous and have low gel layer strength. This leads to more rapid drug diffusion and matrix erosion [78].

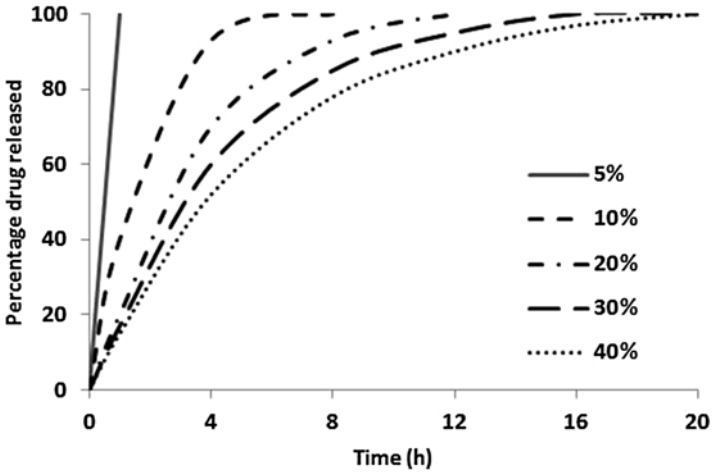

Fig. 3.5 Influence of HPMC matrix content on drug release. The figure legend shows the percentage by weight of HPMC used in the formulation. *Formulation*: METHOCEL™ K4M (q.s), propranolol HCl (10 %), lactose (q.s) and magnesium stearate (0.5 %) *Conditions*: USP apparatus 2, 50 rpm, 900 mL deionised water. Reproduced with permission from the Dow Chemical Company®, ™ Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

One of the key factors in the popularity of HPMC matrices is their ability to achieve reliable and consistent drug release profiles, and including a sufficient quantity of polymer in the formulation can minimise or even eliminate any effects arising from variability in raw materials or manufacturing processes. It has been suggested that an HPMC content of around 30 % w/w improves the robustness and in vivo performance of hydrophilic matrices [79]. Gonçalves-Araújo et al. [80] have claimed that the optimum content of HPMC polymer, based on percolation theory, is 20 % v/v of the matrix. Above 20 % v/v, an infinite cluster of polymer will be formed, ensuring uniform hydration and maintaining the integrity of the system in controlling the drug release. In another study, Tajarobi et al. [81] have identified a critical point (percolation threshold) of around 30 % w/w HPMC which they claim is crucial for the reliable control of drug release rates. Drug solubility has a significant effect on the polymer percolation threshold. Fuertes et al. [82] have estimated HPMC percolation thresholds to be 14.7–18.4 % (v/v) for ranitidine HCl, 24.8–25.8 % (v/v) for theophylline and around 31.2 % (v/v) in matrices containing acetaminophen. Using gamma scintigraphy, Ghimire et al. [83] have investigated HPMC at concentrations below (20 % w/w) and above (40 % w/w), the reported values for polymer percolation threshold. They found that erosion was faster in tablets containing 20 % w/w polymer than for matrices with 40 % w/w HPMC. The latter exhibited more robust in vivo performance and a stronger correlation with in vitro erosion profiles. These findings are in

agreement with earlier in vivo studies that demonstrated a sufficient level of HPMC (40 and 42.5 % w/w) would guarantee optimum peak drug responses and duration of action [84]. In reality, the need to produce a robust formulation by including a relatively high concentration of HPMC is typically challenged by limitations in the geometry of matrix tablet, especially the ability to swallow tablets containing high dose drugs. This is why typical matrix formulations often contain between 30 and 40 % w/w HPMC.

3.5.4 Excipient Selection

In its simplest form, a hydrophilic matrix is a compressed powder mixture of drug and a water-swelling viscous polymer. However, other excipients are included in the formulation to aid processing by improving powder flow, compressibility, lubricity and sometimes drug solubility. Excipients typically utilised in hydrophilic matrices are fillers, binders, lubricants and glidants. In some cases, the matrix may also contain buffering agents, stabilisers, surfactants and other polymers to improve or optimise drug release and/or the stability of the formulation. All excipients can modulate the drug release rate.

Fillers act as bulking agents and improve flow, compressibility and other bulk manufacturing characteristics. They can have a significant impact on drug release, and their effect will depend on the filler type, content, polymer and drug substance. Melia [7] has suggested that there is considerable potential for interaction between the polymer network and added excipients, and this may influence the formation and properties of the gel layer. Jamzad et al. [85] has pointed out that the inclusion of excipients in hydrophilic matrices containing water-soluble drugs can have significant implications for swelling dynamics, front movement, drug release kinetics and the in vivo performance of HPMC matrices.

A number of studies have demonstrated how commonly used fillers can influence drug release from HPMC matrices. These include lactose, microcrystalline cellulose (MCC), dicalcium phosphate (DCP), mannitol and partially pregelatinised starch [28, 36, 86–91]. Typically, formulations containing water soluble fillers such as lactose or mannitol produce the fastest release profiles, while the inclusion of insoluble fillers, such as microcrystalline cellulose or dicalcium phosphate, lead to slower drug release. These differences can be attributed to the higher rate of water transport due to an increased osmotic pressure gradient in tablets containing soluble fillers [81–85]. Soluble fillers also leach out of the matrix and potentially dilute the gel layer, resulting in faster drug diffusion and gel erosion. Figure 3.6 shows how formulations containing similar concentrations of HPMC, drug and fillers exhibit the slowest drug release when a partially pregelatinised starch (PPS) (Starch 1500®) is used in the matrix [87]. The effect observed is not just a difference in tortuosity due to particles of partially soluble filler, but also the excipient actively

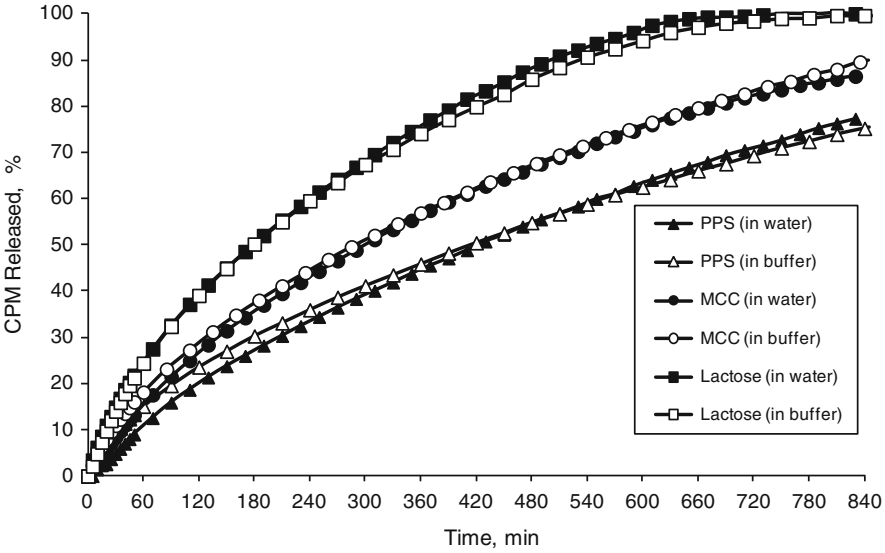

Fig. 3.6 Effect of different fillers on drug release from HPMC extended release matrices (The fillers used were partially pregelatinised starch (PPS), microcrystalline cellulose (MCC) and lactose) *Formulation*: chlorpheniramine maleate—CPM (30 %), METHOCEL K4M (20 %), fillers (49.25 %), colloidal silicon dioxide (0.5 %) and magnesium stearate (0.25 %) *Conditions*: USP apparatus 2, 100 rpm, 1,000 ml, in water and in pH 7.4 phosphate buffer. Reproduced from [87] with permission through the copyright clearance centre

contributes to drug release kinetics through a physical interaction between PPS and HPMC. The filler forms an integral structure within the HPMC gel layer. Michailova et al. [92] have characterised HPMC/pregelatinised starch hydrogels as "filled" composite systems, where starch filler functions as a supporting frame, while HPMC forms the continuous disperse medium. In comparison with cellulose derivatives, pregelatinised starch hydrates to a considerably lower degree due to the formation of intra-molecular hydrogen bonds in the highly branched amylopectin [93]. It has been proposed that these bonds suppress the mobility of polymer segments and diminish the overall degree of HPMC/pregelatinised starch hydration, resulting in lower gel layer diffusivity and decreased drug release rates. In a different study, Jans and Vandecruys [94] have investigated the influence of pregelatinised starch on the robustness of HPMC matrix performance in a human clinical trial. It was shown that a pregelatinised starch filler helped to prevent dose dumping. Therefore, within the context of HPMC matrix tablets, fillers cannot be regarded as neutral additives as they can significantly alter water penetration, tablet erosion and therefore the mechanism and rate of drug release.

Williams et al. [95] have investigated the potential for fillers to modulate the sensitivity of HPMC matrix formulations to dissolved sucrose. They proposed that more resistant formulations could be designed by using appropriate fillers. In a model matrix containing 30 % HPMC in a lactose: MCC mixture, the further addition of soluble diluents (dextrose and D-xylose) produced swollen, highly erodible matrices in 0.7 M sucrose solution, which collapsed and rapidly released drug after 1–4 h. In contrast, matrices containing microcrystalline cellulose provided extended release for up to 10 h. Therefore, by selecting the most appropriate excipients for a specific HPMC tablet formulation, the tolerance of matrices to challenging in vitro and in vivo environments may be significantly improved.

The influence of other additives has been investigated with respect to gel layer formation and drug release. Examples have included surfactants [96, 97] and alkalising buffers [98, 99]. As a latter example, a formulation containing 10 % felbinac, 39 % HPMC, dextrose and varying amounts of sodium citrate exhibited biphasic release. Increasing the citrate content increased the immediate release phase and reduced the extended release phase. Studies of early gel layer formation suggested gel barrier disruption and enhanced liquid penetration in the presence of buffer. However, release of sodium citrate into the medium meant that pH modification of the gel layer was transitory (<2 h) and corresponded with the early phase of immediate release. This provides further evidence that the hydrated polymer barrier was a less efficient diffusion barrier when trisodium citrate was present in the gel layer [99]. The disruption of the gel layer was attributed to Hofmeister effects from this multivalent ion. When a monovalent buffer with higher p*K*a was used, it provided more effective pH control and less disruption to the gel layer [100].

3.5.5 The Inclusion of Other Polymers

Matrices containing a highly water-soluble drug with a single polymer will usually exhibit root time release kinetics, due to the time-dependent changes in diffusional path-length and matrix surface area [91, 101, 102]. They can also exhibit a significant "initial burst" of drug when matrices are first hydrated [103, 104]. To reduce these effects, and as a means of optimising drug release profile, a range of polymer combinations have been studied. HPMC matrices containing mixtures of low and high viscosity grades of HPMC can be advantageous [28, 35, 36, 63, 64, 105, 106], and even in formulations where different polymers are added, HPMC is typically used as the primary polymer. In others there is potential to lower the total polymer content required in the matrix. These are not covered in detail here, but are summarised in Table 3.2.

Table 3.2 Examples of polymers added to HPMC matrix formulations to modulate drug release

Polymer	Nature	References
Methylcellulose, hydroxypropyl cellulose	Hydrophilic, non-ionic	Ebube et al. [107], Ebube and Jones [108], Vueba et al. [89]
Polyethylene oxide	Hydrophilic, non-ionic	Gusler et al. [109], Liu and Fassihi [110], Lalloo et al. [111]
Sodium carboxymethylcellulose	Hydrophilic, anionic	Baveja et al. [101], Ranga Rao et al. [112], Devi et al. [113], Bonferoni et al. [114], Wan et al. [115], Dabbagh [116], Lotfipour et al. [88], Conti et al. [20], Nokhodchi et al. [117], Contreras et al. [118]
Sodium alginate	Hydrophilic, anionic	Timmins et al. [119], Howard and Timmins [120], Huang et al. [121]
Guar and xanthan gums	Hydrophilic, neutral or anionic	Varshosaz et al. [122, 123], Gohel et al. [124], Mughal et al. [125]
Carrageenan	Hydrophilic, some are anionic	Bonferoni et al. [49]
Carbomers	Hydrophilic anionic	Abrahamsson et al. [126], Li et al. [127], Samani et al. [128], Bravo et al. [129, 130], Tiwari and Rajabi-Siahboomi [131]
Ethylcellulose	Water-insoluble, non-ionic	Abrahamsson et al. [132], Nokhodchi et al. [133], Maghsoodi and Barghi [134]
Methacrylic acid copolymers	Anionic cationic or neutral	Takka et al. [135], Nokhodchi et al. [97], Al-Taani and Tashtoush [136], Lotfipour et al. [88], Tatavarti et al. [137, 138]
Polyvinyl acetate phthalate	Enteric anionic	Tiwari and Rajabi-Siahboomi [139, 140]
HPMC acetate succinate (HPMCAS)	Enteric anionic	Streubel et al. [141]

3.6 Manufacturing Considerations

A principal reason for the popularity of HPMC matrix systems is undoubtedly that they can be manufactured easily on existing tablet production equipment, and using conventional pharmaceutical processes.

3.6.1 Granulation and Compression

Direct compression is a preferred method of tablet manufacture because it is simple and low cost. However, in formulations with high content of HPMC, direct compression can be challenging because poor powder flow can lead to variations in tablet weight, especially on high speed tablet presses [142–144]. However, direct compression is more feasible when drugs with good flow and compressibility are

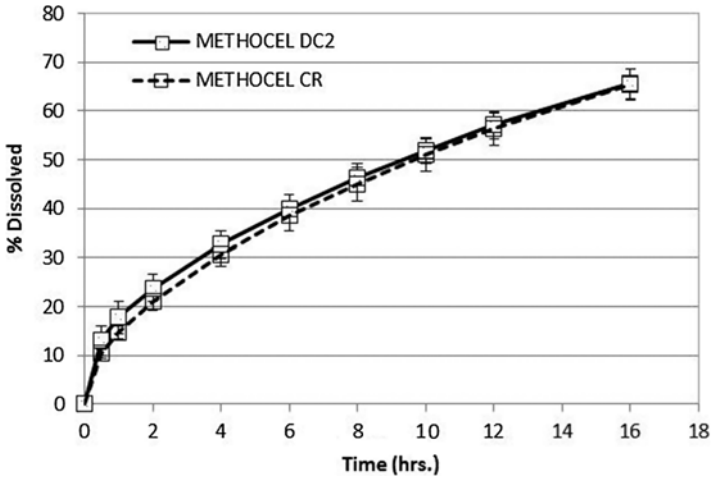

Fig. 3.7 Drug release from METHOCEL K4M CR and the directly compressible grade METHOCEL™ DC2 *Formulation*: METHOCEL K4M CR & DC2 30 %, naproxen 20 %, lactose 30 %, Starch 1500 10 %, mag stearate and silicon dioxide 1 % (tablet weight 400 mg) *Conditions*: USP apparatus 2, 100 rpm, pH 7.4 phosphate buffer. Reproduced with permission from Colorcon Inc

combined with excipients designed for direct compression. Recently, a direct compression grade of HPMC (Methocel DC2) has been developed in which a patented "design particle morphology" (DPM) reduces the fibrous component of the polymer. This has improved powder flow without significantly changing the drug release profile (Fig. 3.7).

Wet granulation methods are sometimes employed in the manufacture of HPMC matrices, but these are more difficult. Methods include dry, low/high-shear and fluid-bed processing. High-shear granulation is often the preferred commercial route for granulating matrix formulations due to the shorter processing times, the contained ("one-pot") environment and the availability of large-scale production facilities. However, the use of water as the granulating liquid in formulations containing large quantities of HPMC can result in undesirable gelling, lumpy granule formation and subsequent effects on drug release rates. The use of various organic solvents such ethanol, isopropyl alcohol (IPA), dichloromethane and acetone has been explored to overcome this. The ability of HPMC to form lumps is directly related to its viscosity in a specific solvent system. Darunkaisorn et al. [145] have ranked HPMC viscosity in different solvents as water > ethanol: dichloromethane > IPA-water > IPA > dichloromethane > ethanol. Clearly the use of organic solvents for HPMC granulations is costly and has obvious safety issues, and so hydro-alcoholic solvents are often used. A number of studies have demonstrated how these can reduce granule over-densification, segregation during compaction, low tablet mechanical strength and variations in release profiles [143, 144]. Roe et al. [144]

have shown that poor tablet breaking force obtained from water granulations was due to over-densification of the granules as a result of HPMC hydration. Granulation with ethanol resulted in significantly higher tablet mechanical strength.

During wet granulation of HPMC matrix formulations, the quantity of granulating liquid and the wet massing time both have significant effects on granule properties. An increase in either can result in increased granule size and density, and a potential loss of tablet mechanical strength [145–147]. To avoid lump formation, the granulating solution is typically added using a spray system, and it has been found that smaller sized nozzles provide a narrow granule size distribution [63, 146]. Alternative approaches have included the use of foam [147, 148] or moist granulation [149], both of which use very little water to initiate agglomeration. HPMC powder also can be added extra-granularly to minimise lump formation [150]. Whilst the incorporation of HPMC either intra- or extra-granularly does not influence the drug release, it can provide significant improvements in formulation flow and the matrix mechanical strength [43].

The addition of a binder such as low viscosity HPMC or PVP formulations can result in better powder wetting, larger granules and stronger HPMC matrices [58, 77, 143, 149–152]. Drug release properties are not affected by the type and concentration of the binder used, as drug release is primarily controlled by the high viscosity of HPMC. This overwhelms any impact that the binder may have. HPMC granules produced by aqueous low or high-shear granulation have high densities which make them difficult to pass through a sieve prior to drying. Wet or dry milling can be used in order to break up large HPMC agglomerates [152]. Granule drying is typically achieved using fluid-bed equipment, and the screened granules are then lubricated and compressed into matrix tablets.

Dry granulation by slugging or roller compaction is an alternative to direct compression and wet granulation. Typically, the reasons for using these processes are to improve the flow and dosage uniformity of moisture-sensitive matrix formulations [153]. During the roller compaction, a powder blend is transformed into ribbons by applying pressure between two counter-rotating rolls. The ribbons are then milled into free-flowing granules and compacted into tablets. The method is continuous, relatively simple, cost-effective, environmentally friendly and particularly suitable for moisture- and/or heat-sensitive materials [154, 155]. There is some loss of material compressibility and typically the tensile strength of tablets is lower than that of directly compressed matrices [156, 157].

It has been reported that the many process variables in dry granulation, including the roller pressure and the ratio of feeder screw speed and roller speed, have little effect on the physical properties of the manufactured matrices or their drug release profiles [158, 159]. Sheskey et al. [79] have studied the effects of scale-up on the robustness of a model HPMC matrix formulation containing theophylline. When scaling up from laboratory to pilot plant, roller-compaction scale and equipment conditions caused slight variations in the physical properties of the tablets, but did not affect the drug release profiles of the resulting matrices.

Figure 3.8 compares the influence of HPMC concentration and manufacturing process (direct compression, roller compaction or high-shear granulation) on the

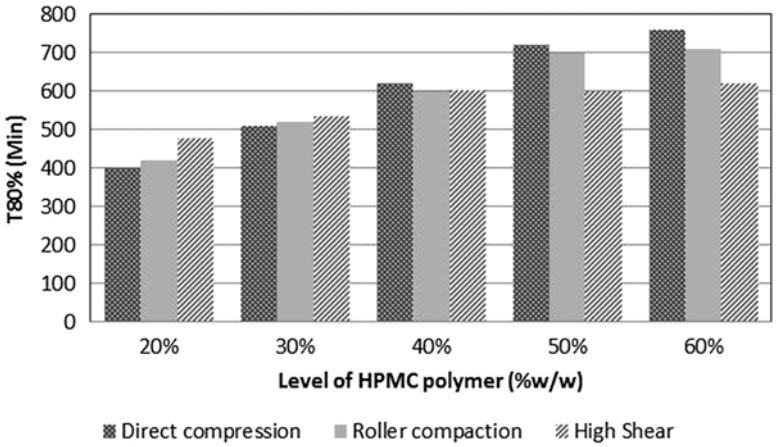

Fig. 3.8 Effect of manufacturing method and level of HPMC on $T_{80\%}$ values for release of theophylline *Formulation*: METHOCEL™ K4M (30 %), theophylline (10 %), lactose (59.75 %) and magnesium stearate (0.25 %) *Conditions*: USP apparatus 2, 50 rpm, 900 mL deionised water. Reproduced with permission from the Dow Chemical Company®, ™ Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

release of theophylline in formulations containing 30–40 % HPMC. Drug release was not affected by the manufacturing method. Martin et al. [157] have shown how roller compaction can increase the powder flow and density of polymer blends comprised of HPMC, polyvinylacetate phthalate (PVAP) and carbomer. The roller-compacted polymer granules were successfully incorporated into a verapamil HCl matrix formulation, resulting in tablets with good mechanical properties and drug release profiles similar to other matrix tablets manufactured by direct compression. However, when converting an existing manufacturing method, it is critical to evaluate the effect of each manufacturing process, as other reports have indicated that granulation can sometimes generate faster drug profiles than direct compression [68, 160].

3.6.2 Compression Force

Many studies have shown that typically compression force has little or no effect on the drug release rate of HPMC matrices [21, 81, 107, 161]. However, certain matrix formulations, which had been manufactured at a relatively low compression force, have exhibited initial bursts of drug release [107, 108], and the authors recommended using a higher than minimum compression force. In other studies, it has been shown that compression force may have a significant effect on drug release, dependent on the type of filler used [86, 87]. Figure 3.9 shows that an increase in compression force from 4 to 14 kN resulted in slower release of theophylline from HPMC formulations containing three different fillers.

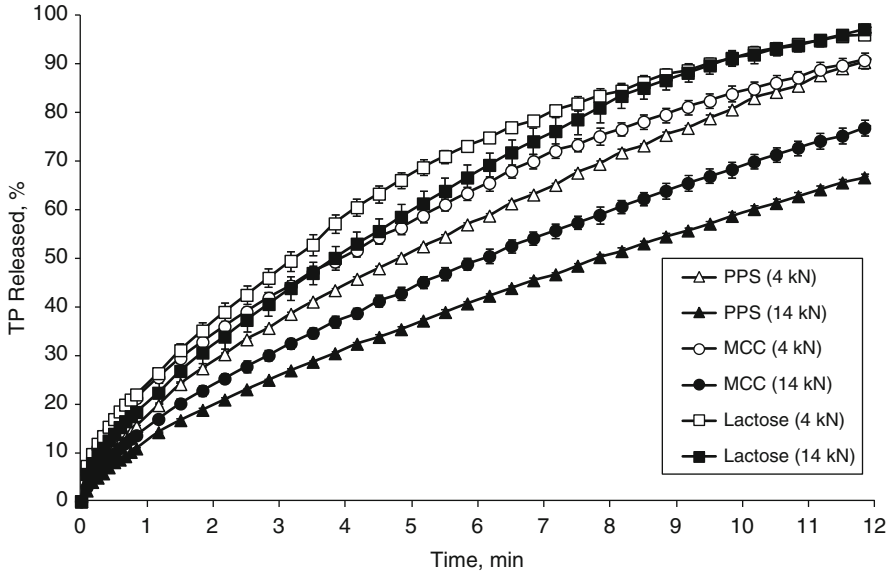

Fig. 3.9 Effect of low compression force on theophylline (TP) release from HPMC matrices containing different fillers *Formulation*: 30 % theophylline, 20 % HPMC (METHOCEL K4M), 49.25 % filler [partially pregelatinised starch (PPS), microcrystalline cellulose (MCC) or lactose], 0.5 % colloidal silicon dioxide, 0.25 % magnesium stearate *Conditions*: USP apparatus 2, 100 rpm, 1,000 ml water. Reproduced from [87] with permission through the copyright clearance centre

In formulations containing a high concentration of water-soluble ingredients (drugs or fillers) and a relatively low content of HPMC (20 % or less), capillary forces may be involved in faster water transport into the matrix during the initial stages of drug release. Application of different compression forces may produce significantly different matrix porosities [162] or may change the dimensions of inter-particulate voids [163]. This can govern both the rate of penetration of fluid into the tablet and the release of the dissolved drug and result in modified drug release kinetics. Tablets made at low compression force tend to have relatively high porosity, and can show faster drug release during the initial dissolution phase or an initial burst of drug due to a partial initial disintegration (Kabanda et al. [43]). Once the polymer on the surface of the matrix is hydrated, and a uniform gel layer is established, the dissolution profiles are similar to tablets manufactured at higher compression forces.

3.6.3 Tablet Size and Shape

It is well understood that for any matrix system undergoing diffusion and erosion, the size and shape of the tablet can significantly impact on the drug release rate [34, 61, 164–167]. Siepmann et al. [168] have developed mathematical models for diffusional drug release from HPMC matrices and have investigated the effect of the

aspect ratio (radius/height) and the size of cylindrical matrices on drug release in diffusion-controlled systems [169]. They found that as small cylindrical tablets have a larger surface area: volume ratio (SVR), drug release from small tablets is typically faster than release from large cylindrical matrices. Skoug et al. [170] have shown how a matrix split into two halves provided an SVR 16 % greater than a whole tablet, and resulted in more rapid drug release. However, HPMC matrix tablets possessing similar SVR values show similar release rates, both within the same tablet shape and amongst different shapes, e.g. oval, round concave, flat-faced bevelled-edge and flat-faced round tablets [171, 172]. Tablets with the same surface area but different SVR values exhibit dissimilar drug release.

3.6.4 Film Coating of HPMC Matrices

There are a multitude of reasons why extended release matrices might be coated with an immediate release film coat. These include (1) to improve their appearance, (2) for identification, (3) to disguise an unpleasant taste or odour, (4) to help the patient to ingest the tablet easily, (5) to protect tablet ingredients from exposure to light, environmental oxygen and moisture, (6) to minimise the amount of dust generated during packaging especially for highly toxic drug substances and (7) to facilitate product handling and packaging.

In general, the film coating of matrices results in an improvement in tablet mechanical strength, but imparts no significant effect on drug release profile [172, 173]. Levina [86] has investigated the influence of four commonly used aqueous IR film coating systems on the performance of extended release HPMC matrices containing chlorphenamine maleate and theophylline. It was found that the coating [4 % weight gain (WG)] increased tablet mechanical strength up to 44 % but did not influence drug dissolution profiles, both initially and after 12 months storage under different stability conditions. Similar results have been reported for HPMC matrices containing metformin HCl, in which no effect on drug release rate was recorded when the tablets were coated [174].

In cases where it is challenging to obtain the desired drug release profile, coating the matrix may be a useful strategy. Examples have included attempts to obtain zero-order release with a highly soluble drug, or a release profile with a significant lag time. Water-insoluble film coatings can be one method of achieving these goals. Colombo et al. [175] and Bettini et al. [34] have investigated hydrophilic matrices which were partially coated with cellulose acetate propionate. The rate of drug release could be modulated by varying the amount of the coating applied and its location on the matrix. The researchers applied these impermeable coatings to one or two faces of a cylindrical hydrophilic matrix and then monitored the effects on tablets swelling and drug release. They exhibited drug release rates inversely proportional to the area of the applied film coat were obtained. Drug release kinetics approached linearity through a slowing of tablet swelling. Colombo et al. [175] have quantified the changes in HPMC matrix relaxation and drug diffusion rates by measuring the surface exposed during polymer swelling and drug release as a function

of coating coverage and location. Drug release was only slightly influenced by the viscosity of the polymer used in the matrix [34].

3.6.5 Barrier Membrane Film Coatings

Extended release of highly water-soluble drugs can be difficult to obtain over long time periods. Usually, more than 80 % of the drug is released in less than 8 h, making it difficult to develop "once-a-day" dosage forms. To overcome this challenge, a hydrophilic matrix can be film coated with insoluble cellulosic or acrylic polymers. In these cases, the film coating acts as a physical barrier which restricts the swelling of the tablet, reduces the diffusion volume and slows the dissolution kinetics. The control of matrix swelling depends on the composition of the film: if the film is not sufficiently flexible and elastic, it will either form a reservoir device or it will break or rupture around the periphery of the tablet.

Bettini et al. [34] partially coated HPMC matrices with an impermeable film and found that the presence of the coating changed the swelling kinetics of the matrix, and reduced erosion. Dias et al. [176, 177] used aqueous ethylcellulose coating (EC) Surelease® (at 4 % weight gain) to overcome the initial burst in drug release from HPMC matrices containing venlafaxine HCl (Fig. 3.10a). This is a feature often seen with highly water-soluble drugs. It was observed that 90 min into the dissolution study, the axial relaxation of the matrix caused the film to rupture along the circumference of the tablet sidewall (Fig. 3.10b). This happened consistently for every tablet tested, resulting in reproducible drug release profiles. It can be assumed that, in the early stages of the matrix hydration, the swelling and internal forces created by the HPMC polymer are weak and drug release is controlled by its diffusion through the ethylcellulose membrane. In contrast, later, when significant quantities of dissolution liquid have ingressed into the tablet, the internal forces increase sufficiently to break the coat [176].

In other cases, HPMC matrices coated with an insoluble polymer have resulted in drug release profiles that are too slow or incomplete. To overcome this, permeability enhancers can be included in the film coating formulation [178, 179]. Dias et al. [180] have coated HPMC matrices up to 4 % weight gain, with ethylcellulose dispersion which contained 0–20 % w/w of low viscosity HPMC. Figure 3.11 shows how drug release rate increased significantly when this permeability enhancer was used.

For certain therapeutic indications, it may be beneficial to introduce a lag period before the onset of extended drug release. A lag phase in drug release can also be desirable for achieving chrono-pharmacotherapy, for site-specific targeting to the small intestine or colon, or to increase the systemic absorption of drugs which are poorly soluble in the upper gastrointestinal tract [178, 181, 182].

Dias et al. [180] have coated HPMC matrices with aqueous EC dispersions from 2 to 8 % weight gain and produced lag times which varied between 1 and 5 h, in addition to obtaining slower drug release rates. Another approach for obtaining a lag phase followed by nearly zero-order release has been to use a combination of extended and delayed release coatings [183].

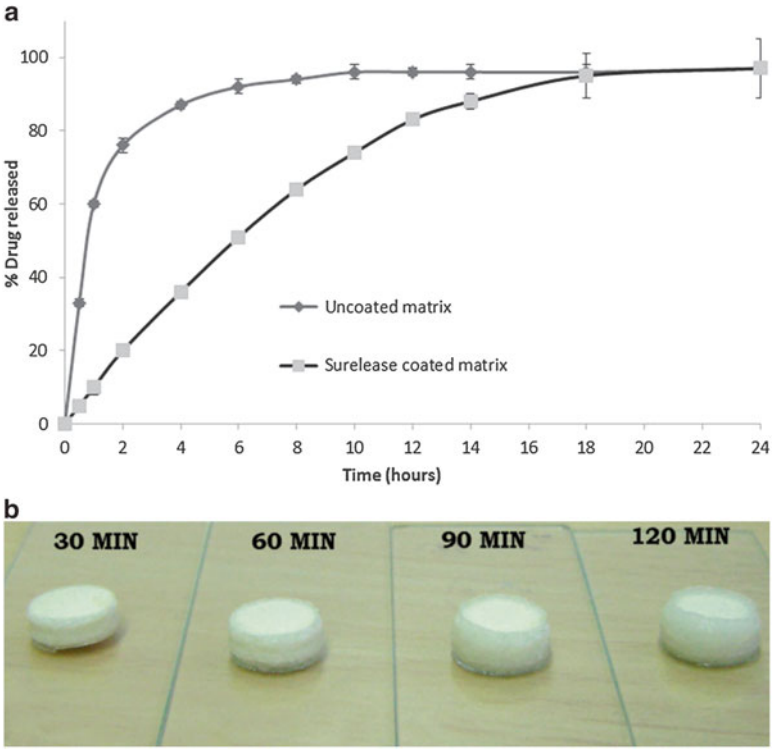

Fig. 3.10 The consequences of applying ethylcellulose coating on HPMC matrix tablet A. Venlafaxine HCl release from uncoated and Surelease (4 % weight gain)-coated matrices B. Swelling of matrices and barrier coating rupture during dissolution testing. *Formulation*: Venlafaxine HCl (12.5 %), HPMC (METHOCEL K15M CR; 30.0 %), partially pregelatinised starch (25.0 %), microcrystalline cellulose (31.5 %), colloidal silicon dioxide (0.5 %) and magnesium stearate (0.5 %); 300 mg tablets. *Conditions*: USP apparatus 2, 100 rpm, 900 ml water. Reproduced with permission from Colorcon Inc

3.6.6 Drug-Layered Hydrophilic Matrices

For some therapies it can be advantageous to formulate a biphasic dosage form that provides an initial immediate release dose, followed by a dose delivered by extended release [184]. In the first phase of drug release, the dose required to promptly relieve symptoms can be made available soon after administration, whilst in the second phase, the slow release portion maintains an effective drug plasma level over a prolonged period. Dias et al. [180] have shown how HPMC matrices coated with a drug-containing polymeric dispersion can achieve an initial rapid dose, followed by extended release of the sparingly soluble drug zolpidem tartrate (Fig. 3.12). 37 % w/w of the dose was drug layered onto the matrix, using an Opadry PVA-based coating system. If was found that drug in the outer layer was released within 15 min

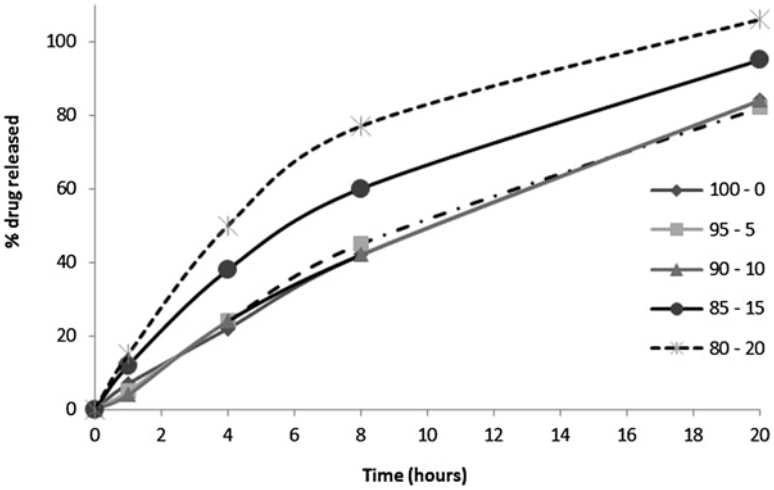

Fig. 3.11 Drug release from metoprolol succinate extended release HPMC matrices coated with aqueous EC dispersion containing 0–20 % of low viscosity HPMC as a permeability enhancer. *Formulation*: Matrices containing 28.58 % metoprolol succinate, 35 % METHOCEL K4M CR, 14 % MCC, 21.43 % PPS, 0.5 % colloidal silicon dioxide and 0.5 % magnesium stearate, coated to 4 % weight gain with Surelease E-7-19040, containing 0, 5, 10, 15 or 20 % w/w of low viscosity HPMC as a permeability enhancer. *Conditions*: USP apparatus 2, 100 rpm, 900 ml water. Reproduced with permission from Colorcon Inc. [180]

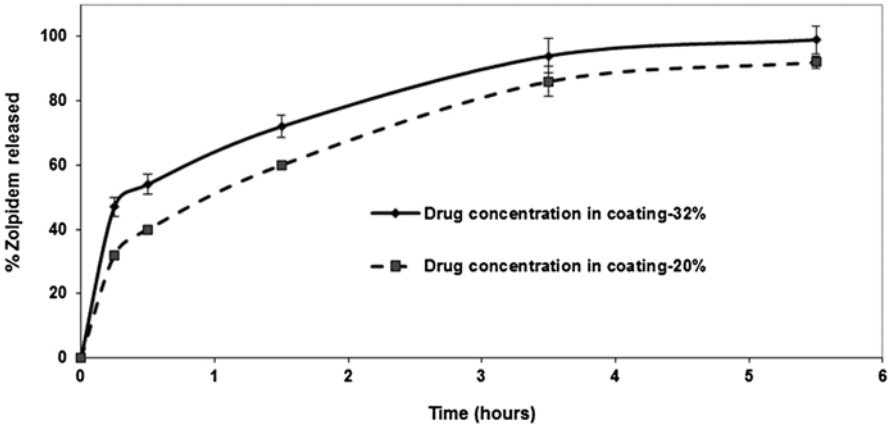

Fig. 3.12 Zolpidem tartrate release from HPMC drug-layered matrices. *Formulation*: Matrices weighing 200 mg, comprising 4.25 % zolpidem tartrate, 15.19 % microcrystalline cellulose, 45.56 % w/w lactose, 34.00 % METHOCEL K100 LV, 0.5 % w/w fumed silica and 0.5 % w/w magnesium stearate. Matrices were coated using a dispersion comprising of 4.29 % zolpidem tartrate, 0.06 % w/w sodium lauryl sulphate and 1.32 % w/w Opadry® II 85 Series. *Conditions*: USP apparatus 2, 50 rpm, 900 ml 0.1 M HCl. Reproduced with permission from Colorcon Inc. [180]

by dissolution of the coating, whilst the remaining drug was released over 5.5 h. Rapid dissolution in the initial phase was facilitated by incorporation of sodium lauryl sulphate in the drug layering dispersion. The dose fraction in each phase can be adjusted to achieve the desired dissolution profile. For example, when the drug-layered dose fraction was increased from 20 to 32 %, drug release in the first 15 min increased from 32 to 47 %.

3.7 The Influence of Hydro-Alcoholic Media on Drug Release from HPMC Matrices

In order to address safety concerns over the concomitant use of alcohol with extended release dosage forms, a number of studies have been conducted in which dissolution testing of HPMC matrices was performed in hydro-alcoholic media [185]. Roberts et al. [186, 187] have found that although ethanol media gave more rapid initial aspirin dissolution and retarded hydration of the polymer, it did not result in a dose-dumping effect. Skalsky et al. [188] have investigated the sensitivity of HPMC matrix formulations in ethanol concentrations up to 40 % v/v using several highly water-soluble drugs. They reported unchanged drug release in all the media tested. Levina et al. [189] and Levina and Rajabi-Siahboomi [190] have studied the effect of media containing 0, 5 and 40 % v/v of ethanol on the hydration, gel formation and drug release from HPMC matrices containing felodipine, gliclazide or metformin HCl. None of the matrix formulations investigated resulted in dose dumping when exposed to 5 or 40 % v/v ethanol solutions for up to 12 h. In the case of metformin HCl, drug release in hydro-alcoholic media was slightly slower, but this could be related to lower drug solubility in the ethanol water mixture.

3.8 Conclusions

HPMC matrix systems have been well studied, and there are many successful products on the market that utilise this versatile technology. Over the past 30–40 years, an increasing number of new extended release drug applications (NDA) have been filed with the Food and Drug Administration (FDA). This is evidence that this technology can provide significant therapeutic benefit and good patient acceptability, along with advantages, such as ease of development and manufacturing, stable formulations and broad regulatory acceptance. From a commercial perspective, HPMC matrices are economical to develop and manufacture because they can use available tableting equipment and processes without further capital investment. The flexible chemistry of HPMC polymers and the availability of a wide variety of viscosity grades offer the opportunity to formulate extended release matrix dosage forms for a wide range of drugs with varying solubility and doses. HPMC matrices will continue

to be one of the preferred routes for extended release dosage form development. In cases where their intrinsic properties prove insufficient, simple modifications, such as combinations with other polymers or the application of various coatings, can be considered in order to obtain more robust formulations or specific drug release profiles.

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Chapter 4
Natural Polysaccharides in Hydrophilic Matrices

Colin D. Melia and Peter Timmins

4.1 Introduction

Since the early descriptions of the use of 'hydrophilic gums' to sustain drug release from compressed tablets [1], an enormous variety of polymers have been investigated in this application. In fact, a search of the scientific and patent literature will confirm that almost any material which hydrates sufficiently rapidly and forms a hydrated continuous surface diffusion barrier has at some time been considered as a candidate release-control agent in hydrophilic matrix tablets.

Polymers derived from natural sources are an obvious choice. A wide variety are already used in foods. Many have interesting and useful properties for hydrophilic matrices because, unlike cellulose ethers, they form regular supramolecular structures which can influence the properties of the gel layer. These food biopolymers are primarily plant gums, seaweed extracts or microbial exopolysaccharides, and whilst a few mucopolysaccharides and proteins (such as zein) have been used in hydrophilic matrix applications, the vast majority are polysaccharides. Not surprisingly, the focus has been on mainstream polysaccharides which have worldwide approval for food or pharmaceutical use, but a wider range of other edible biopolymers and their chemically modified forms have also been investigated. Studies of new hydrophilic matrix polymers are reported on a yearly basis, usually with the aims of demonstrating the usefulness of locally sourced materials or to support claims of novelty in patent applications. They are most often plant gums. Rarely do

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Table 4.1 Natural and modified natural polysaccharides used in studies of hydrophilic matrix tablets in the scientific literature. This list is not exhaustive

Type	Origin
Starches and their derivatives	
• Pregelatinised	Physical or chemical treatment of native starches
• Cross-linked high amylose	
• Substituted starches	
• Retrograded	
• Freeze-dried	
• Amylodextrins	
Charged polysaccharides	
• Xanthan gum	Bacterial fermentation
• Alginates	Seaweeds
• Carrageenans	Seaweeds
• Pectins	Plants
• Chitosan	Crustaceans
• Hyaluronic acid	Animal tissues Bacterial fermentation
Neutral polysaccharides	
• Galactomannans: guar gum, locust bean gum, tara gum and many others	Plants
• Glucomannans: konjac	Plants
• Dextran	Bacterial fermentation
• Scleroglucan	Bacterial fermentation

they show extra useful properties over materials already studied. Table 4.1 lists examples of the more common natural polymers that have appeared in the hydrophilic matrix literature. Other reviews can provide more extensive lists of the wide range of natural polymers studied [2–5].

At the molecular level, the world of natural polysaccharides is varied and complex. Native polymers usually have a regular molecular arrangement and commonly undergo molecular ordering, forming structures such as helices in the hydrated state. If time and molecular mobility allow, this can develop into a longer range order, such as the crystalline regions that grow during starch retrogradation. This behaviour contrasts sharply with cellulose ethers, which are predominantly amorphous. The possession of ionic side groups adds another layer of complexity to their behaviour, as their solubility, solution structure and viscoelasticity can be markedly altered by changes in the ionic and pH environment that surrounds them. Charged natural polymers also have the potential to ion pair with oppositely charged polymers and drugs.

Each of these molecular characteristics has the potential to influence the diffusional and erosion properties of the gel layer, and they can be important factors in the drug release behaviour of hydrophilic matrices based on these polymers.

Modified derivatives of native polymers can be manufactured through physical or chemical processing. These can add side-chain substituents, cross-linking; reduce the molecular weight; or make other morphological changes which have potential to influence polymer hydration and drug release kinetics. In cases where such modifications introduce interchain cross-linking, and polymer solubility is reduced but swelling capacity remains, then matrix drug release behaviour can become more like that of a hydrogel. Alternatively, when modification results in significantly reduced swelling, then drug release mechanisms may emerge that are more typical of non-swelling ('inert') matrices.

4.2 The Advantages and Disadvantages of Natural Polymers

Although a diverse range of natural polysaccharides are available as food ingredients, the global pharmaceutical industry remains constrained in its use of novel excipients, and consequently cellulose ethers dominate the hydrophilic matrix market and literature. Table 4.2 illustrates some of the perceived disadvantages of using natural polymers in hydrophilic matrices and perhaps also more widely in pharmaceutical development and manufacturing. Regulatory acceptance is a critical factor, but characteristics such as chemical purity, physical uniformity, processing characteristics, reliability of supply, and excipient compatibility are also seen as important material attributes. Many natural polysaccharides, fairly or unfairly, have been perceived to be unreliable in these contexts. Combined with the paucity of information in the literature and a poor understanding of drug release mechanisms with respect to formulation variables, these factors have perhaps limited the use of natural polymers in hydrophilic matrices. However, many studies also reveal some interesting characteristics of natural polymers which, from a position of knowledge, can be

Table 4.2 Some perceived disadvantages of natural polysaccharides in hydrophilic matrices

Batch variability in:
• Chemical composition
• Physical properties
• Behaviour during pharmaceutical processing
Limited knowledge base of:
• Extended-release capability
• Processing characteristics and scalability
• Formulation incompatibilities
• Hydration and gelling behaviour
• Characterisation methods
• Toxicology
• Stability
Availability of pharmaceutical grades
Reliability of supply
Regulatory acceptance
Unclear advantages over existing materials

Table 4.3 Some potential advantages of natural polysaccharides in hydrophilic matrices

Property	Potential advantage
High molecular weight	High viscosity. Lower polymer content required in matrix
High gel strength	Enhanced resistance to gel layer erosion
Ordered molecular conformations when hydrated	Enhanced viscoelastic properties of gel layer Enhanced resistance to pH, salts, etc., e.g. xanthan gum
Synergistic combinations with other polymers	Enhanced viscoelastic properties of the gel layer
Charged side groups	Enhanced affinity for water, more rapid hydration and development of gel layer. Avoidance of 'initial burst' effects
Ion-mediated cross-linking	High gel strength and enhanced resistance to gel layer erosion
Ion pairing with drugs	Potential for enhanced extended release
Lack of Hofmeister effects	Improved compatibility with drugs, salts, buffers in comparison with alkoxy cellulose ethers such as HPMC
Tablet binding properties	Enhanced tablet strength, e.g. amylodextrins
Local availability	Environmental and economic advantages. Transport costs. Convenience

exploited to advantage in hydrophilic matrix formulations. Some of these are listed in Table 4.3.

At the present time, only a few natural polymers have achieved commercial application as hydrophilic matrix polymers. A short non-comprehensive list would include high amylose cross-linked starch (Contramid®), xanthan gum (in Brufen Retard®), alginates (in Isoptin SR (Ranbaxy) and xanthan/galactomannan combinations (TimerX®). A search of FDA-registered oral extended-release formulations in 2009 showed 9 products containing alginates and 21 containing xanthan gum [6].

4.3 Modified Starches

Starches and their derivatives are used extensively in foods and pharmaceuticals, and their almost universal availability and low cost make them obvious choices as potential hydrophilic matrix polymers.

Native starches are poor matrix formers because at body temperature, starch polysaccharides are not released from the crystalline structure of the granule. As a result, native starch grains swell independently and do not become sticky or form a gel layer. Granular starches are therefore used as disintegrating and bulking agents in immediate-release tablets. However, there is an extensive range of 'modified starches' which have been treated to allow release of the internal polysaccharides, and which have been developed to widen the functionality and usefulness of starch in food and consumer products. Modified starches are manufactured by the physical, chemical or enzymatic treatment of native starches with the principal objective of releasing free starch polysaccharides from the native starch grain. This improves the extent of swelling and the overall water holding capacity of the starch. It also

allows viscosity development and gelling at low temperatures. Other modifications can be undertaken to improve the quality of starch gels with respect to their clarity and texture, stability to acid and heat and freeze-thaw stability. Others confer resistance to unwanted molecular changes arising from retrogradation and enzyme degradation. Many of these enhanced properties are useful in hydrophilic matrix applications.

An excellent summary of the different starch modifications has been provided by Singh [7]. Physical modification of starches is undertaken by heat, moisture or solvent-based processing, with the simplest example being 'pregelatinisation' through high-temperature spray or drum drying. These processes disrupt the internal granule structure, release carbohydrate chains and provide the cold-water solubility essential to their functioning as a hydrophilic matrix polymer. The chemical modification of starches is undertaken by oxidation, acid, enzymes, cross-linking or derivatisation by etherification, esterification or grafting reactions. A wide variety of starch derivatives are commercially available, and many have been investigated as potential hydrophilic matrix polymers.

4.3.1 Amylose/Amylopectin Ratio

The branching of carbohydrate chains within the native granule means that starch modification processes facilitate the release of two distinct molecular fractions of starch: amylose and amylopectin. Amylose (which is α-D-(1–4) linked) is linear and water soluble, whereas amylopectin, (with additional α-D-(1–6) linkages), is branched, insoluble but water swellable. The amylose/amylopectin ratio varies with the botanical source of the starch and is a key parameter that dominates the behaviour of modified starches in hydrophilic matrices [8].

4.3.2 Pregelatinised Starches

Early literature was focussed on the use of thermally pregelatinised starches in hydrophilic matrix formulations. Nakano et al. [9] compared pregelatinised starches from different botanical sources and suggested that the differences in swelling reflected the amylose/amylopectin content of the native starch. They also showed how matrix drug release could be accelerated by α-amylases and acid hydrolysis in a low pH environment. Van Aerde and Remon [10] showed how different starch modifications could result in either an immediate or an extended-release profile and explored the influence of common tableting excipients. In these early studies, the modified starches were poorly characterised, and therefore Hermon and Remon [8, 11, 12] undertook experiments using more closely controlled pregelatinised starches. They investigated the influence of pregelatinisation conditions, manufacturing process (drum drying, extrusion, spray drying) and amylose/amylopectin ratio on matrix-relevant properties

such as swelling capacity, gel strength and powder flow. They concluded that only a fully pregelatinised starch could form an effective matrix gel layer and that lubricant type, compression force and the pH of the dissolution medium all had significant effects on drug release [11]. An in vivo study in dogs found that amylose/amylopectin ratio was a major factor. Whereas a 70 % amylose starch provided little retardation of drug release, a high amylopectin starch provided good extended plasma profiles regardless of the thermal treatment used in pregelatinisation [12]. A human volunteer study of a matrix containing 70 % drum-dried pregelatinised corn starch also failed to show sustained release characteristics [13]. Pregelatinised starches can show considerable variation in compressibility [14], but the use of new botanical sources of pregelatinised starches for matrix development continues to be described [15].

4.3.3 Cross-Linked High Amylose Starch

The problem of high amylose starches being unable to sustain drug release was addressed by chemical cross-linking, and lightly cross-linked high amylose starch (CLHAS) has since become the most widely investigated modified starch in the context of hydrophilic matrices. Cross-linking is most commonly achieved by epichlorohydrin or glycidol and the density of cross-linking is a critical parameter [16, 17]. The cross-link density (CLD) was defined as the percentage by weight of cross-linking agent added to the starch during the cross-linking reaction. It was found that a CLD of 2–6 could provide extended release of theophylline up to 24 h, whereas a CLD of 15 resulted in complete drug release after only a few hours [18] (Fig. 4.1).

Significant changes in water binding and swelling capacity were found to occur between CLD 6 and 11 [19] and this transition probably relates to a change in the

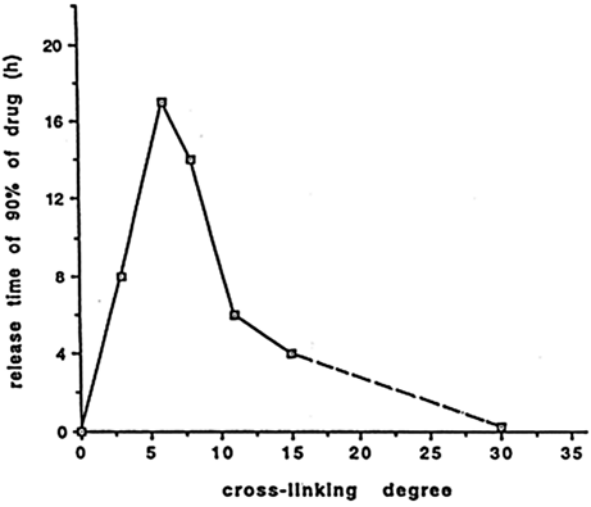

Fig. 4.1 The influence of polymer cross-linking on drug release ($T_{90\%}$) from a high amylose starch matrix. Original title: The influence of cross-linking degree of CLA tablets on the theophylline release time (tablets of 500 mg containing 50 mg of drug). Reproduced from [18]. Carbohydrate polymers by PERGAMON (Reproduced with permission of PERGAMON in the format reuse in a book/textbook via Copyright Clearance Center)

ability of the polymer to swell, disentangle and coalesce effectively into a gel layer or become a polymer that has become too extensively cross-linked and a rubbery hydrogel. In the latter case, the cross-linked hydrogel particles swell but would remain independent and act as disintegrants. Some evidence for this is provided by Ravenelle [20] who reported sponge-like compression and decompression behaviour typical of a particulate hydrogel, in matrices which hydrated up to 200 % in 24 h.

In matrices prepared from lightly CLHAS, there is evidence of changes in the molecular conformation of starch within the gel layer. This may influence polymer swelling, gel permeability and drug release. Lenaerts [21] has proposed that low CLD allows single amylose helices to form double helices within the gel layer, providing a more compact arrangement which reduces the outward swelling of the matrix. Higher degrees of cross-linking prevent this transition and maintain single coil structures in a more disordered arrangement, allowing greater swelling on hydration [18]. When the CLHAS has an optimally low degree of cross-linking, the pure polymer matrices exhibited water uptake kinetics and swelling profiles which were independent of compression force. This is a characteristic typical of hydrophilic matrices. Drug release was found to be insensitive to pH changes between 1.4 and pH 6 and sucrose concentrations up to 0.1 M, but swelling in 0.1 M NaCl was reduced by 25 % [22].

The matrix hydration process has been described in considerable detail. A surface gel layer is formed after 5–10 min and swelling of the matrix occurs in both axial and radial directions. Although there is evidence of water reaching the centre after 30 min, slow water penetration occurs over several hours eventually resulting in a fully 'equilibrated' gelled core [21].

CLHAS has also been incorporated in press-coated matrices to provide more complex drug release profiles, for example, to incorporate a lag time or combine an immediate and extended-release dose. In one study, the press-coat resulted in a release profile with a lag time of around 10 h. This was claimed suitable for targeting matrix release to lower regions of the gastrointestinal tract [23, 24].

In human studies, CLHAS (as Contramid®) matrices exhibited 24 h extended-release profiles [21], and there were claims of increased resistance to erosion and to intestinal amylases [25]. However, subsequent studies have shown that the low degree of cross-linking in CHLAS is not sufficient to render it immune to enzymatic degradation [26]. CLHAS has been marketed as the direct compression extended-release excipient Contramid® and further details can found elsewhere [25]. It has been utilised commercially in several products and a recent US patent application describes its use in a 24 h release Tramadol matrix [27].

4.3.4 Substituted Starch Derivatives

Chemically substituted starches are widely used in the food industry and many have been investigated as potential hydrophilic matrix polymers. These include carboxymethyl, aminoethyl, hydroxypropyl, phosphate and acetate derivatives with varying degrees of cross-linking and different amylose/amylopectin ratios. Many substituted starch derivatives can accommodate high drug leadings [28].

Carboxymethylated starches have been studied extensively, and their use in matrices merits the separate section below. Hydroxypropyl starch, used in the food industry to improve water holding and stability, is reported to improve the extended-release properties of high amylose, but not high amylopectin starch, and provide enhanced resistance to α-amylase under simulated gastrointestinal conditions [29]. Aminoethyl starches are ionised and mucoadhesive under acidic conditions and are therefore useful for vaginal matrices, whereas anionic starch derivatives show greater mucoadhesion in the neutral conditions of the buccal cavity [30]. Starch acetates, with their high degree of substitution, have been reported to behave as hydrophobic matrices [31, 32]. Starch phosphates provide matrices with strong gels [33]. The introduction of hydrophobic chains into the starch molecule has considerable effects on water uptake, and appears to progressively retard matrix drug release [34]. Onofre [35] has concluded that starches from different botanical sources require different types and degrees of chemical modification in order to achieve satisfactory sustained release properties in hydrophilic matrix applications.

Some studies have used different substituted starches in combination with differently charged drugs to probe the potential for ion-pair retardation of drug release [30, 35, 36]. However, it can be difficult to identify clear trends, in these studies because many other drug, polymer and dynamic processes contribute to drug release in hydrophilic matrices. For example, differences in the release of cationic drugs from neutral or carboxylated starch derivatives may not involve ion-pair interaction. Such differences could arise from (1) polymer hydration due to ion-pair charge shielding, (2) changes in polymer solubility or (3) an increase in chain/chain interactions due to hydrogen bond-mediated carboxyl dimerisation [28, 35].

4.3.5 Carboxymethylated Starch

Carboxymethyl high amylose starch has been studied in a range of hydrophilic matrix roles and exhibits some intriguing matrix properties. As a dry polymer in the acid form it had good direct compression properties, but the matrices cracked on hydration. Co-formulation with an electrolyte diluent (sodium chloride) prevented cracking, and the matrix provided almost linear *in vitro* drug release profiles for a number of soluble drugs [37]. This was not the case with all drugs as with acetoaminophen, the release kinetics were the typical curved profiles seen in hydrophilic matrix tablets and they exhibited a mixture of diffusion and case II relaxation [38]. Matrices of carboxymethylated starch also showed the swollen surface gel layer typical of a hydrophilic matrix. In acid media, they showed moderate swelling and little surface erosion and were resistant to the hydrolytic effects of acid soak time. In vitro tablet integrity was remarkably long, and when co-formulated with NaCl, they maintained their shape and provided extended drug release for up to 24 h [39]. However, changing the degree of carboxymethyl substitution completely changed the

drug release behaviour of the matrix. At low degrees of substitution (DS 0.1–0.2), the polymer provided extended release in both acid and neutral media, whereas at higher DS (0.9–1.2), matrices exhibited a delayed release profile and they eroded rapidly at pH 6.8. This behaviour could be useful for targeting matrix drug release to different regions of the intestine [40].

Another significant application of carboxymethylated starch has been the protection of biotherapeutic agents in the gastrointestinal tract. Carboxymethyl starch matrices are suitable because they remain compact and relatively unswollen in acid media and they can therefore avoid significant gastric digestion of biological agents in the stomach and then deliver it intact to the intestine [41]. Biological studies have included lyophilised *Escherichia coli* bacteria [41], a protease inhibitor [42], and the F4 fimbrial antigen of *E. coli* [43]. The latter is a veterinary vaccine which has been shown to retain its in vivo effectiveness as an immunostimulant when delivered in these matrices [44]. In the case of pancreatic enzymes, carboxymethyl starch matrices were able to carry a 70–80 % drug loading, and there was a 70 % survival of enzyme activity under gastric conditions. An additional advantage is that carboxylated starch is a poor substrate for the incorporated pancreatic amylases [45]. Carboxymethyl starch has undergone complexation with a cationic polymer, chitosan, and these matrices show less swelling and slower drug release and may be suitable for colon targeting [46]. This matrix has also been utilised for the intestinal delivery of probiotic bacteria [47], therapeutic enzymes, and for the treatment of inflammatory bowel diseases [48]. Other carboxymethyl starch complexes, for example, with lecithins, have also shown promise for the delivery of anti-inflammatory drugs to the colon [49].

4.3.6 Amylodextrins

Amylodextrins are short chain starches manufactured by enzymatic hydrolysis of pregelatinised starches. Their physicochemical properties, such as cold-water solubility, depend on the manufacturing process and the starch fraction from which they are derived [50]. An amylodextrin derived by enzymatically de-branching pregelatinised potato amylopectin has received considerable attention in the literature, as a purposely developed excipient for the easy direct compression of high-strength extended-release matrices [51]. At high polymer loadings, it has good binding properties and compatibility, and in one study, tablets had twice the crushing strength of their microcrystalline cellulose equivalents [52]. This type of matrix containing acetaminophen was found to exhibit zero-order release in vitro and ‘constant’ drug plasma levels over 14 h in vivo [53]. Drug release could be modulated by the amount and solubility of the added diluent [51, 52]. Because amylodextrins are themselves manufactured enzymatically, they are relatively insensitive to α-amylase degradation. The matrix drug release mechanism is interesting. On hydration they exhibit swelling, polymer relaxation, and a clear solvent front, but little gel formation and

significant peripheral core cracking [54]. In terms of matrix behaviour, these tablets may lie at the boundary between hydrophilic matrix and non-swelling inert matrix behaviour. Matrix behaviour may depend on the amylodextrin manufacturing process, as a pullulanase de-branched dextrin has shown good cold-water solubility and a surface gel layer typical of a hydrophilic matrix [55].

4.3.7 Freeze-Dried, Retrograded and Extruded Starch Hydrophilic Matrices

Freeze-drying provides highly porous powders, with a high-specific surface area. This offers the prospect of rapid hydration and gel layer development, a highly desirable characteristic in a hydrophilic matrix polymer. Freeze-drying also produces a brittle polymer morphology which is highly compactable. These aspects have been used to advantage in pregelatinised starches [56] and amylodextrins [50]. Freeze-dried, pregelatinised, amorphous waxy maize starches, for example, have been shown to produced highly compact tablets which, on hydration, develop thinner gel layers and longer extended-release characteristics than the same starches pregelatinised by oven heating [56]. However, freeze-drying can also result in powder flow problems [57]. Freeze-drying processing conditions can have a significant effect on the characteristics of the final material, and freeze-dried starch can provide anything from an immediate fast-dissolving tablet to extended-release matrices, depending on the molecular properties of the material used [15].

The heat processing of starches under certain temperature/hydration/time conditions can induce molecular reorientation and crystalline growth in starch gels in a process known as retrogradation. The production of a wet slurry, in which temperature cycling has produced a retrograded starch, and then drying to a glassy gel has been advanced as an alternative to manufacturing hydrophilic matrices by compaction. On hydration, retrograded starches produce denser and less swollen gels which have a greater resistance to digestive enzymes [58]. Retrogradation may also play a part in the molecular level gel layer structure of high amylose cross-linked starches [21] and in other starch matrices where there is considerable molecular freedom. It is already an established method for producing starches ‘resistant’ to amylase, and used in low-calorie foods [59].

Continuous hot melt extrusion has been used to prepare extended-release hydrophilic matrices directly from native starches. A recent study showed how 10 h dissolution profiles could be obtained from small (5 mm) matrix tablets, at drug loadings up to 70 %, using starches from several botanical sources [60]. The many variables that can be controlled, (for example, the degree of starch crystallinity), suggest that this could become a viable alternative to conventional tablet manufacture.

4.3.8 *Amylases: An Additional Mechanism of Drug Release*

Amylase digestion represents an additional accelerating drug release mechanism in starch-based hydrophilic matrices. Unmodified starches undergo enzymatic digestion by hydrolysis of α-1,4-glucosidic bonds by saliva and pancreatic α-amylases. As a result, amylases are often included in in vitro dissolution media when starch matrices are tested. The behaviour of cross-linked starch (CLHAS) matrices in the presence of α-amylases has been investigated many times. Early studies claimed that high amylose starch matrices with a cross-link density of 2.7–4.0 were unaffected by amylases [24]. However, when dosage forms were subjected to the more vigorous agitation of USP apparatus 3 dissolution tests, enzymatic erosion became a significant factor in drug release. The effects were dependent on amylase concentration, but could be reduced if 10–20 % of HPMC or PEO was included in the matrix [26]. In an alternative approach, α-amylase has been used intentionally in CLHAS matrices to create an enzyme-controlled drug release system which will improve the bioavailability of low solubility drugs [61]. Figure 4.2 shows how incorporated amylases can accelerate the drug release kinetics of these matrices. Alternatively a range of enzyme-resistant starches have been introduced to reduce the calorie content of foods [59] and we should expect more reports of their utilisation in reducing matrix erosion, in the near future [62].

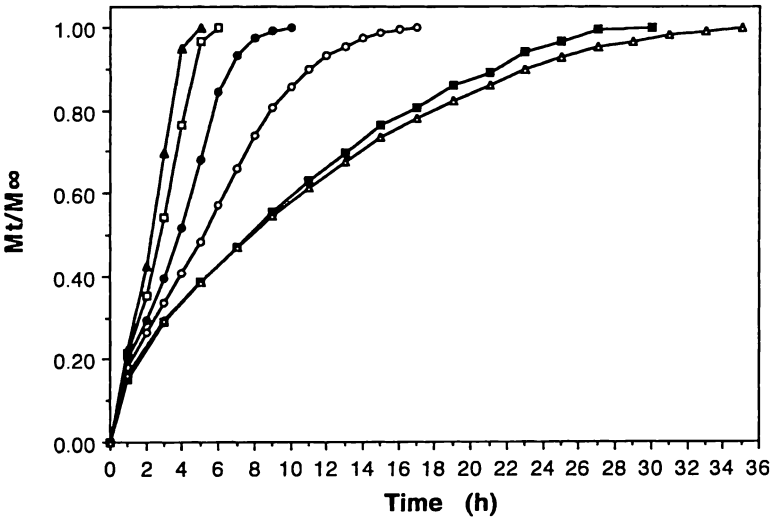

Fig. 4.2 The effect of incorporated alpha-amylase on the drug release characteristics of a cross-linked high amylose starch matrix. Original title: Release profiles from CLA-6 tablets (500 mg) containing 100 mg of theophylline and 0 (*filled square*), 1 (*open circle*), 2 (*filled circle*), 3 (*open square*), 5 mg (*filled triangle*) of α-amylase (5 EU/mg) or 15 mg (*open triangle*) of bovine serum albumin/tablet. Dissolution experiments were carried out in 1 l of 100 mM phosphate buffer, pH = 7.0 at 37 °C. Reproduced from [61]. Journal of controlled release: Official journal of the Controlled Release Society by CONTROLLED RELEASE SOCIETY (Reproduced with permission of ELSEVIER BV in the format reuse in a book/textbook via Copyright Clearance Center)

4.4 Other Neutral Polysaccharides

After starches, galactomannans are the most common neutral polysaccharides encountered in hydrophilic matrices [63]. They are plant polysaccharides comprising a poly (D-mannose) backbone with D-galactose branches. There is a wide variety available from different botanical sources and the family includes locust bean, guar, fenugreek, tara gums and many others. Konjac gum, a glucomannan, is a similarly branched polysaccharide with a polymannose/glucose backbone.

The water solubility of different galactomannans varies with their galactose content [64] which also varies with botanical source. The hydration properties of different galactomannans can therefore vary widely. Locust bean gum, for example, when used as a matrix forming polymer, showed less swelling, greater erosion and faster release of diclofenac than more effective polymers such as xanthan gum [65]. This probably arises from locust bean being a heterogeneous mixture of galactomannans of which only a limited fraction is water-soluble at low temperatures [66]. Guar gum is more soluble, has a higher solution viscosity and is an effective matrix polymer [67]. However, as this polymer is degradable by colonic microflora, the main literature focus has been on its potential for colon targeting [68]. Guar gum and konjac matrix slimming tablets for slimming have been associated with occasional reports of oesophageal blockage [69], and konjac is controlled in many countries as a recognised choking hazard in children — (see Chap. 1). Whilst galactomannans can be used alone as hydrophilic matrix carriers, they are more commonly encountered in 'synergistic' combinations with xanthan gum. This is discussed in the sections below.

A range of other neutral polysaccharides are encountered in hydrophilic matrix studies. These include dextrans [70], tragacanth and scleroglucan [5]. Scleroglucan is an interesting fungal polysaccharide, which is thought to adopt a triple helical conformation in solution. It has been reported to exhibit rheological tolerance in solutions up to 20 %w/v sodium chloride and over the pH range 0–13 [71]. The few studies of this material report that it forms hydrophilic matrices which are unaffected by environmental pH [72].

4.5 Charged Polysaccharides

A diverse range of charged polysaccharides and their derivatives have been studied in hydrophilic matrix applications. The most widely studied have carried carboxylic acid groups, carried either on uronic acid residues (e.g. alginates, pectins, hyaluronan), as ether substituents (carboxymethyl derivatives of starch, cellulose and guar) or on short glycosidic side chains (xanthan gum). Sulphated polysaccharides such as carrageenans have also been studied along with chitosan, a glucosamine polysaccharide which carries a cationic charge in acid environments.

Many charged natural polymers have good water solubility and provide good extended release when utilised in hydrophilic matrices [73–78]. However, their viscoelastic behaviour can change with pH, ionic strength and the type of dissolved

ions and drugs in their hydration environment. These changes can influence the hydration, solubility and rheological characteristics of the polymer, and this is reflected in matrix gel layer properties and in the mechanisms and kinetics of drug release. The response of different natural polymers ranges from changes in gel layer viscosity and gel strength, to more profound interactions that result in hydrogel formation or which precipitate the polymer. Charged polymers may confer some buffering capacity to the gel layer, which might temporarily protect against external changes in pH [79]. Chitosan is the only widely used cationic natural polysaccharide and is water soluble below pH 6.5. It has been widely investigated as a mucoadhesive agent [80], but unfortunately in extended-release matrices, its poor solubility at neutral pH can lead to unpredictable drug release behaviour at intestinal pH. As a result, its use in hydrophilic matrices has been limited to the role of a complexing agent [81].

Charged natural polymers in their soluble salt form are highly attractive to water, and they promote rapid swelling and gel layer formation when incorporated in a matrix. Rapid gel formation reduces liquid penetration, reducing the exposure of drug at or near the tablet surface, and as a result, these polymers are useful in reducing the initial burst of drug released from matrices that contain highly soluble drugs. Xanthan gum and sodium carboxymethylcellulose have been used for this purpose. This behaviour further suggests these polymers may also be useful in stabilising formulations which exhibit significant surface disintegration, a phenomenon sometimes observed in less robust matrix formulations which show sensitivity to erosion.

Certain ionic polymers such as alginates, pectins and carrageenan have affinities for specific cations with which they form cross-linked structures. This type of complexation radically affects the hydration properties and viscoelastic behaviour of the gel, but can vary with the polymer source. For example, the reaction of sodium alginates with calcium depends on the guluronate block length and mannuronate/guluronate ratio, which varies with botanical source. Amongst the carrageenans, kappa-carrageenan forms strong gels with potassium, iota-carrageenan forms weak gels with calcium, whilst lambda-carrageenan forms non-gelling viscous solutions [82]. In a few natural polymers such as gellan gum, the ion concentration required for gelation is so low that it renders the polymer virtually useless for hydrophilic matrices, but excellent for the preparation of hydrogels. In others, such as xanthan gum and scleroglucan, the dissolved ions induce a conformational change to a molecular ‘rigid rod’ which paradoxically then reduces the rheological sensitivity to higher concentrations of dissolved ions or changes in pH.

Charged polymers also have the potential to ion pair with oppositely charged drugs and polymers. Within the hydrophilic matrix literature, an emphasis is often put on polysaccharide/drug interactions as an important influence on drug release kinetics. However, most studies provide insufficient evidence for this to be clearly identified as a rate-controlling drug release mechanism. In some cases, drug/polymer complexation has been clearly demonstrated [83], and in the case of carrageenans, interactions with cationic drugs have been shown to have significant impact on drug release. The molecular chemistry of drug/carrageenan reactions, and their effect on matrix tablet performance has been studied in detail [84, 85].

4.5.1 Sodium Alginate

Alginates comprise a range of naturally occurring uronic acid polysaccharides, which are linear, unbranched, hydrophilic polymers mostly extracted from *Laminaria*, *Lessonia*, *Macrocystis* and *Durvillea* species of brown seaweeds. Alginates can also be obtained from bacterial sources [86] and these have found wide use in other biomedical and healthcare applications [87, 88].

Alginates are built from β-D-mannuronic and α-L-guluronic acid residues, linked by β1 → 4 and α1 → 4 glycosidic bonds, which occur as homogenous blocks of mannuronic or guluronic sequences or as mixed heterogeneous mannuronic/guluronic sequences. There are mannuronic-rich and guluronic-rich varieties, dependent upon the seaweed source [86]. The structure of alginate allows for interchain cross-linking of adjacent guluronate block sequences by certain divalent cations, notably calcium, to yield stiff gels. Although these ionotropically gelling forms of alginates appear in other drug delivery applications, they are rarely used in hydrophilic matrices and will not be described further. Alginates are available as pharmaceutical excipients in the free acid form, as sodium or potassium salts and as a propylene glycol ester. Early reports of sodium alginate in hydrophilic matrix systems demonstrated slow in vitro release of verapamil over 8 h, with only small differences in the release profile between pH 1.4 and pH 7.5 [89]. An in vivo evaluation in a dog model demonstrated how an alginate-based dosage form could provide sustained absorption of the drug under physiological conditions, and this work eventually resulted in a clinically important hydrophilic matrix tablet for extended oral delivery of verapamil hydrochloride, commercialised under the brand names Isoptin SR (Ranbaxy) and Calan SR (Searle/Pfizer).

Sodium alginate matrices behave much like HPMC matrices with respect to their mechanism of drug release. There is a gel layer formed by the hydration and swelling of surface polymer, an ongoing slow penetration of fluid, a diffusion of dissolved drug through and out of the hydrated layer and erosion of the gel layer. However, the ionic nature of sodium alginate adds an additional dimension of pH-dependent variation in polymer properties and behaviour. At pH values below the pKa of the uronic acid residues (3.38 for mannuronic acid and 3.65 for guluronic acid), alginic acid is formed. This free acid form is swellable but water insoluble. Therefore, when a sodium alginate matrix is hydrated in a low pH medium such as pH 1.2 simulated gastric fluid, the hydrated gel layer has very different characteristics to that formed at neutral pH. In one study, the hydrated layer formed at pH 1.2 was found to be tough and rubbery and it formed a tough 'rind' around the tablet [79]. Cross-sectional examination of this layer revealed a composite structure, comprised of partially hydrated polymer particles bound by regions of hydrated polymer. Clearly, there had been sufficient polymer dissolution to create interparticulate bonding and prevent disintegration, and this was attributed to the self-buffering of the first wave of ingressing acid by the sodium alginate. In contrast, a very different structure was formed at neutral pH, where sodium alginate matrices exhibited a uniformly hydrated viscous gel layer typical of a hydrophilic matrix. A comparison of the gel layer structures and drug release characteristics is shown in Fig. 4.3 [90].

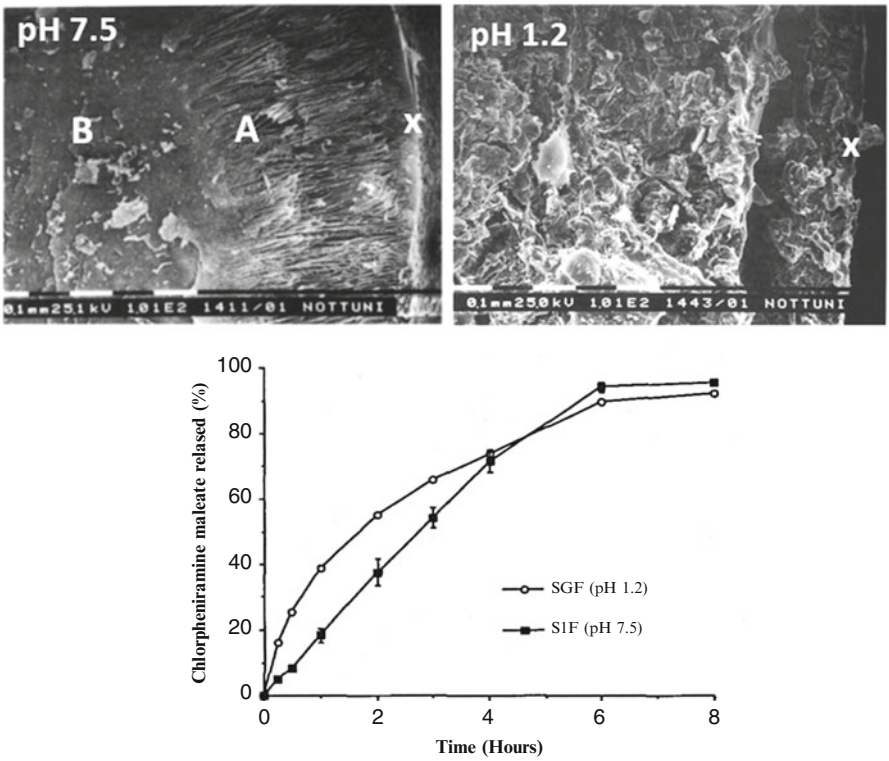

Fig. 4.3 The effect of pH on sodium alginate hydrophilic matrices. These illustrations show how different matrix gel layer structures are formed in acid and neutral media and how pH can affect the drug release profile of a soluble drug. The freeze-fracture SEM micrographs are cross sections through the surface hydrated layer of a sodium alginate tablet after 1 h hydration in pH 1.2 simulated gastric fluid or pH 7.5 phosphate buffer. Image brightness has been increased by 10 %. The pH 7.5 image is typical of a continuous hydrated gel layer seen with most hydrophilic matrices. The apparent structuring in region A is an artefact, a result of ice crystal formation in the low polymer outer regions of the gel layer. Region B is the inner gel where alginate concentration is too high to allow ice formation. X marks the edge of the gel layer. The second image shows that the gel layer has a different morphology at pH 1.2. It is a mass of particles, probably insoluble alginic acid, but which are bound together by polymer which must have previously dissolved. The dissolution graph shows the difference in drug release profile from alginate matrices hydrating in these different pH media (Reproduced from [90] with permission)

The matrix described above contained 49 % sodium alginate, but it can be anticipated that disintegration in acid media is more likely in formulations with lower polymer content because polymer particles are more widely dispersed in the tablet. At very low polymer contents (5 % w/w), alginic acid functions as a tablet disintegrant [82]. A matrix system containing sodium alginate with HPMC has been designed which swells but resists disintegration. It formed a matrix wetted almost to the core after 6 h immersion in pH 1.2 medium and a coherent, pasty mass [91]. These were conditions under which a low polymer content matrix containing only

sodium alginate would have disintegrated. By optimising the polymer ratio, it was possible to design a pH-independent release system for gastrointestinal delivery of basic drugs, by balancing the properties of the gel layer with the pH release characteristics of the drug. At low pH, the HPMC/sodium alginate combination provided a stiff hydrated gel layer which resisted erosion and allowed drug release principally by diffusion, but above pH4, a highly hydrated gel layer was formed, which allowed drug release to be driven by gel layer erosion. This allowed pH-independent drug release to be obtained for basic drugs that exhibit reduced solubility as the environmental pH was increased [92]. In the case of nefazodone hydrochloride, this principle could be used to mitigate a food effect seen with the immediate-release formulation of the compound [93]. Other reports of optimised ratios of sodium alginate with HPMC describe the utility of this dual polymer system for providing extended-release matrix tablet formulations of nicardipine hydrochloride [94] and cefpodoxime proxetil [95].

As sodium alginate is a natural product, there is risk of lot-to-lot variability in physicochemical properties. The uronic acid composition depends upon seaweed source [96], and this variation can affect polymer performance. Materials can be therefore produced that yield gels of different dilute solution viscosity at equivalent alginate concentrations. Differences in viscosity grade have been used to modulate release rate from hydrophilic matrix systems when sodium alginate is used as the sole rate control polymer [77, 97, 98]. However, one study showed how chlorpheniramine maleate release profiles were similar in acid medium (pH 1.2), irrespective of the viscosity grade of alginate used. This was attributed to the release mechanism being dominated by the precipitation of alginic acid to produce a hydrated, swollen, non-eroding layer around the tablet [98]. The tablet surface area to volume ratio was now likely to be the dominant influence on release rate, and this was the same in all tablets studied. Investigating the release of theophylline from sodium alginate matrices based on polymers with low (250 cps) and high (14,000 cps) viscosity but of undefined uronic acid composition showed that the low-viscosity alginate produced a tough gel layer in acidic media, whereas high-viscosity polymer swelled so much that the tablet laminated and the increased surface area led to a faster drug release [77]. The use of a guluronate-rich polymer in the matrix appears to encourage this lamination phenomenon, and adding pH modifiers to the formulation to raise the microenvironmental pH in the hydrated gel layer, can mitigate the occurrence of lamination in acidic media [99]. This effect can be so significant that, in a low pH environment, the swelling of low polymer content matrices (<20 %w/w) containing certain grades of alginate can result in matrix disintegration [100]. Other studies have demonstrated how different grades of alginate can exhibit similar swelling behaviour in acidic media [101]. However, in a different study of chlorpheniramine maleate sodium alginate matrices, it was noted that a high-viscosity alginate yielded faster release rates in acidic media than a lower viscosity alginate. This was attributed to a greater initial swelling of the higher viscosity polymer in the acidic medium, resulting in either a greater diffusivity of water and drug or a higher porosity gel matrix [97]. In higher pH media (pH 6.8), drug release rates followed alginate viscosity grade, with faster release being seen with the low-viscosity polymers [97, 98].

Mannuronate-rich alginates appear to hydrate more rapidly in acidic media than their guluronate-rich equivalents, and this can lead to slower drug release in acid media. However, guluronate-rich alginates retard drug release more than mannuronate-rich polymer in pH 6.8 buffer [97]. The stiffness of aqueous sodium alginate gels at equivalent concentrations increases with increasing guluronic acid content of the polymer, although alginate materials are often defined on the basis of a viscosity specification. This can result in two seemingly viscosity equivalent materials yielding dosage forms with very different performance. This results from the rheological properties of the hydrated gel being dependent on uronic acid composition and probably yielding different erosion properties in higher pH environments [78]. Rheological characterisation of the sodium alginate for use in hydrophilic matrix formulations is therefore a critical attribute for the assurance of performance, and intergrade and inter-batch variability of commercially available pharmaceutical grade sodium alginates has been studied with a view to establishing criteria to support quality-by-design approaches to its utilisation in drug products [102]. The steady shear behaviour of solutions at low sodium alginate concentration or the viscoelastic properties of solutions at high concentration have been suggested as appropriate characteristics for monitoring and control of alginates in hydrophilic matrices [102]. The uronic acid block composition can be characterised using circular dichroism and ^{1}H NMR [103] although the latter technique is disadvantaged in that it requires a partial hydrolysis of the polymer. The application of solid-state NMR has allowed the direct examination of the intact polymer to determine uronic acid composition, molecular weight, water content and intrinsic viscosity. This includes polymer that has been diluted with another excipient and compressed into a tablet [104]. The ability to make these measurements, and an understanding of how polymer variability affects drug release, can allow development of very robust formulations based on sodium alginate.

4.5.2 Xanthan Gum

Xanthan gum is widely used as a thickening and suspending agent in foods and liquid medicines. It is a branched polysaccharide, with charged trisaccharide side chains regularly spaced along a cellulose backbone. In water, the xanthan molecule adopts a flexible coil structure, but in the presence of a minimum amount of dissolved ions, a coil → helix transition occurs in which the trisaccharide chains collapse onto the backbone. At room temperature, this transition is reported to be complete at salt concentrations above ~0.01 M [105]. This result in a helical ‘rigid rod’ conformation which provides xanthan gum solutions and gels with a high gel strength, and gives them a viscosity resistance to changes in temperature, pH and ionic strength [106].

The use of xanthan gum in hydrophilic matrices was described in 1987 [107] and it has been utilised commercially in the extended-release product Brufen Retard® and several other products.

Xanthan gum offers some enticingly desirable properties as a hydrophilic matrix polymer. The molecular weight of xanthan is high ~10^6 Da [82] which results in high solution viscosities and gel strengths. These are further enhanced by molecular ordering into rigid helices. Xanthan solutions also have a good viscosity tolerance to high concentrations of aqueous ions, conditions which might cause Hofmeister 'salting out' of HPMC. The effectiveness of xanthan gum as an extended-release matrix carrier has been established in several studies. Sujjaareevath [65] have shown how 50 %w/w xanthan gum can extend the release of diclofenac Na for up to 10 h in mini-matrix tablets as small as 3 mm, and many other studies have shown effectiveness in the 10–30 %w/w polymer range. Xanthan gels exhibit shear thinning [108], but whilst this may occur at the uppermost surface of the gel layer in a hydrophilic matrix tablet, observational evidence suggests that the underlying static layers have a high gel strength which resists erosion. This is evidenced at the end of in vitro dissolution tests, when it is common to find a hydrated 'ghost matrix' remaining in the dissolution vessel.

The effect of different ionic environments on the performance of xanthan matrices has been the focus of several studies. Andreopoulos [109] has shown how xanthan matrices exhibit greater liquid uptake in water than in ionic buffers. They suggested that this resulted from the change in gel layer density as a result of the coil → helix transition. Other studies show how the drug release profile changes in shape when ions are introduced into the dissolution medium. One study is shown in Fig. 4.4. In water, matrices showed linear release, suggesting a significant role for erosion, whereas in 0.1 M NaCl, the drug release profile shifted to a classical root time curve, suggesting diffusion-dominated drug release. A simple explanation would be that xanthan adopts a random coil, entangled gel layer in water which is more susceptible to erosion, whereas in salt solutions, xanthan adopts the helical rod conformation, resulting in a gel layer more robust to erosion forces.

At ionic strengths above the coil → helix transition, xanthan solutions are notably viscosity resistant to changes in ionic strength. However, there is considerable evidence that ionic strength does have significant effects and several studies have described how the ionic strength of the dissolution medium can significantly affect both the swelling and the drug release behaviour of xanthan matrices [110–112]. Hodsdon [90] has shown how a change from 0.05 M to 0.25 M pH 7.5 phosphate buffer can significantly alter many aspects of polymer hydration behaviour. These include particle swelling kinetics, liquid uptake and the overall swelling of formulated xanthan gum matrices. Talukdar [110] reported slower matrix swelling rates in higher ionic strength media and that regardless of the ions involved, with an equivalent ionic strength resulted in similar polymer swelling kinetics. They reported greater swelling of xanthan in alkali than in acid environments which they attributed to ionisation of the side-chain glucuronic acid groups (pKa 3.1). Despite the presence of these anionic groups, however, Baumgartner [113] have reported no evidence for calcium cross-linking of xanthan gum matrices when exposed to internal or external calcium ions. Dhopeshwarkar and Zatz [114] have shown how xanthan matrices exhibit similar rates of drug release (of a soluble drug, chlorpheniramine maleate) at pH 1.2 SGF and at SIF pH6.8. This happened only after the gel layer

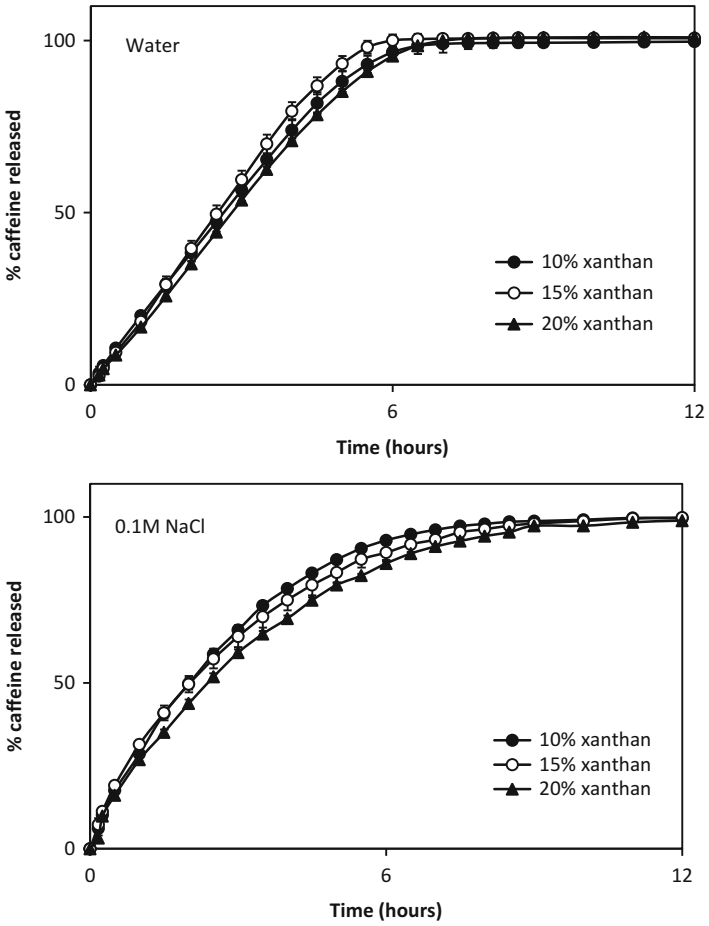

Fig. 4.4 Xanthan gum matrices undergoing dissolution in water and 0.1 M NaCl. These graphs show the change in drug release profile when salt is added to the dissolution medium. The change in shape suggests a change in gel layer properties, possibly as a result of the coil → helix transition undergone by xanthan in the presence of ionic species. The figure legend indicates the percentage of xanthan gum in the matrix. Matrices were 250 mg, round flat-faced matrix containing by weight xanthan gum q.s., caffeine 10 %, magnesium stearate 0.5 %w/w and diluent q.s. which was a 2:1 ratio of lactose and microcrystalline cellulose. USP apparatus I, 100 rpm, 900mls, 37 ± 0.5 °C. Mean ($n = 3$), ±1 S.D. Data from Y. Oni, A. Inchley, C.D. Melia. 2014 Formulation insights group, University of Nottingham 2014. The research was sponsored by Boots UK, Nottingham

had become established. This explains the pH sensitivity previously reported: differences in polymer swelling influence the establishment of the gel layer but not necessarily extended-release behaviour. Fu [115] have also reported how extended release of theophylline was independent of the dissolution medium pH. In the case of indomethacin, a drug with pH-dependent solubility, the free acid form of drug was found to induce less swelling of a xanthan matrix tablet than its sodium salt [111].

This can be attributed to the higher water affinity, solubility and the increased osmotic effects of an ionised salt within the gel layer.

At relatively high polymer contents, xanthan matrices show similar release characteristics to matrices that contain high-viscosity HPMC2208. For example, soluble drugs exhibit root time release kinetics, and poor solubility drugs show more linear release profiles. Peh and Wong [116] have shown how diltiazem HCl release is affected by the drug/polymer/diluent ratio in exactly the same way as high-viscosity HPMC matrices, and in both cases, a matrix containing 30 % polymer gave release rates that were independent of pH and agitation speed. An MRI imaging study has measured the moving fronts within a 75 % xanthan gum matrix and found that whilst the position of the swelling front was the same in all media studied, the position of the erosion front was strongly dependent on pH and ionic strength. They concluded that the erosion characteristics of the gel rather than solvent penetration determined gel layer thickness in the different media [117]. Gohel [118] have used a mixture of xanthan gum with HPMC to produce an optimised formulation of the highly soluble drug metoprolol succinate. The inclusion of the more rapidly hydrating xanthan gum obviated the initial drug burst from the purely HPMC formulation.

However, whilst xanthan and HPMC have many characteristics in common, there are three important properties which differentiate their behaviour in hydrophilic matrices. In certain circumstances, these can be exploited to advantage.

1. **Low polymer content**. Xanthan gum can provide extended release at polymer contents lower than standard high-viscosity HPMC 2208 grades. Dhopeshwarkar [114] demonstrated how in acetaminophen matrices 5 % xanthan gum could provide the same release profile as 15 % of a high-viscosity HPMC2208 (Methocel K4M). Mannion [119, 120] showed how a matrix containing 5 % xanthan gum could provide 24 h extended release of ibuprofen, a polymer content too low for most HPMC formulations.
2. **Salt tolerance**. Xanthan tolerates highly ionic environments which can disrupt early gel layer formation in HPMC matrices though Hofmeister effects [121]. Oni [122] has shown how matrices containing 10–30 % w/w xanthan gum can provide extended drug release in environments up to a remarkable 2 M NaCl. In contrast, 10 % HPMC 2208 (Methocel K100M) matrices disintegrated in <0.1 M NaCl and 30 % matrices in 0.6 M NaCl. Xanthan matrices exhibited longer extended-release times and more compact gel layers as the salt concentration increased [122] (Figures 4.5 and 4.6). Whilst this is purely an academic study and such salt concentrations are unlikely to be encountered in vivo, but this tolerance of extreme ionic strength suggests xanthan gum may be useful when matrices contain high valency buffers or drugs [123].
3. **Synergistic interactions**. Xanthan gum can exhibit strong ‘synergistic’ rheological interactions with certain polysaccharides, notably galactomannans, glucomannans and carrageenans. The enhanced viscoelastic properties this provides

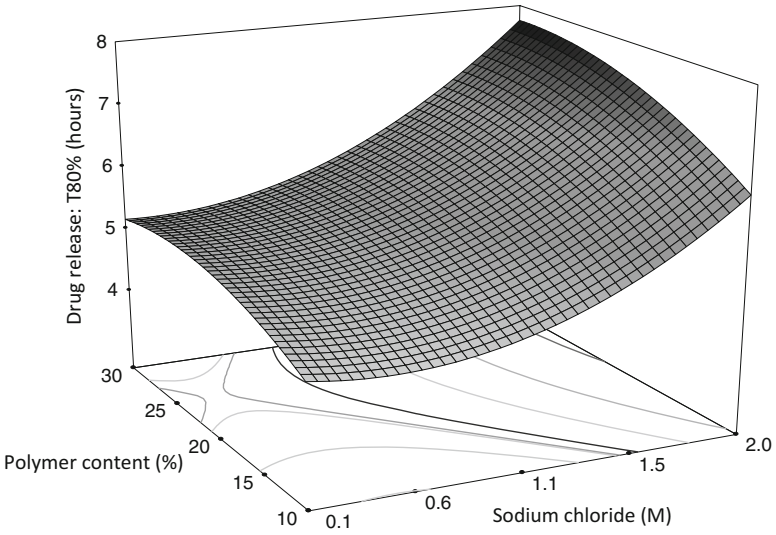

Fig. 4.5 Drug release from xanthan gum matrices with respect to matrix polymer content and sodium chloride concentration in the dissolution medium. T80 % is the time taken to release 80 % drug in a USP1 dissolution test at 900 ml, 100 rpm 37 °C. Round flat-faced matrices (250 mg) containing xanthan gum q.s., caffeine 10 %, diluent q.s. (2:1 lactose spray dried, MCC in a ratio) and magnesium stearate 0.5 %. Data from Y. Oni, A. Inchley, C.D. Melia. 2014 Formulation insights group, University of Nottingham 2014. The research was sponsored by Boots UK, Nottingham

may help reduce the total polymer content in the matrix and would be useful when designing a swallowable matrix for high-dose drugs. This topic is discussed in more detail in Sect. 4.6.2.

In common with other hydrophilic matrix polymers, the compressibility of xanthan powders depends on moisture content and the particle size and morphology of the different commercial grades. Takludar [111] has reported how the xanthan gum, used in their studies, exhibited similar compression characteristics to high-viscosity HPMC. Dhopeshwarkar and Zatz [114] have demonstrated that under direct compression, smaller particle size fractions of xanthan are more effective in extending drug release than large particle size fractions, a feature common to HPMC and other matrix polymers. A study of wet granulation and scaleup has illustrated how granulation variables such as water and impeller speed can impact on matrix tablet properties and drug release rates in the same way as HPMC formulations [124].

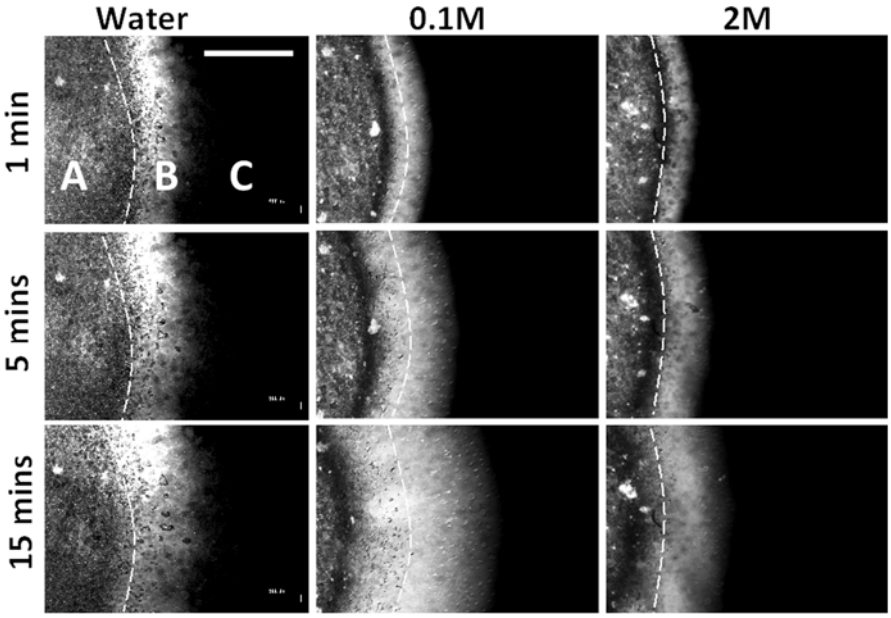

Fig. 4.6 Early gel layer growth in xanthan gum matrices in water and different concentrations of sodium chloride. The images illustrate how gel layer thickness is influenced by the hydration medium. Confocal fluorescence images (Ex568/Em > 585 nm) of xanthan gum matrices hydrating at 37 ± 1 °C. Region A is the unwetted core, B the hydrated gel layer, C is the bulk hydration fluid. The dotted line marks the original dry tablet boundary at $t = 0$. The xanthan gum has been labelled with the fluorophore rhodamine B isothiocyanate. The white scale bar is 1 mm. Data from Y. Oni, L. Jasmani, W Theilemans, J. Burley, A. Inchley, C.D. Melia. 2014 Formulation insights group, University of Nottingham 2014. The research was sponsored by Boots UK, Nottingham

4.6 Natural Polymer Mixtures in Hydrophilic Matrices

Hydrophilic matrix tablets which incorporate mixtures of polymers, abound in the patent and scientific literature. Patents describe the use of almost every binary combination and many other more complex polymer mixtures. Polymer blends are used to (1) optimise the in vitro or in vivo drug release characteristics for a particular drug, (2) provide extra robustness to fragile matrix formulations, (3) enhance resistance to challenging environments and ultimately (4) support claims of patent novelty. Natural polymers have been used in combinations with cellulose ethers and other natural polymers, or have been granulated with insoluble polymers or hydrophobic materials to enhance their extended-release potency.

In this section, we will describe only those mixtures which contain at least one soluble, swellable natural polysaccharide. The behaviour of polymers in these blended matrices can be broadly divided into two categories.

4.6.1 Mixtures in which the Polymers do not Significantly Interact

In many cases, individual polymers in a mixture appears to act independently, and each contributes its own characteristics to the drug release process. This has been used to advantage when (a) high- and low-viscosity polymer grades are used to obtain an intermediate release profile [6], (b) changes in polymer solubility can counteract drug solubility changes and provide pH-independent drug release [91] or (c) a rapidly swelling second polymer is added to reduce the initial burst of a highly soluble drug [118]. The gel layer structure in these cases has only rarely been investigated, and whilst polymers of the same type may be miscible, different polymers are more likely to exist as phase-separated domains within the gel layer. Miscibility between polymers is the exception rather than the rule, and rheological studies of concentrated mixed systems confirm that phase separation is the norm in hydrated polysaccharide gels [125, 126]. Phase separation arises from polymers being thermodynamically incompatible, but in the gel layer, this would be enhanced by polymer particles undergoing swelling in localised positions in this unmixed environment.

Different polymers within a polymer mixture may also hydrate and swell to different extents. For example, in partially pregelled starch/HPMC mixtures, there is a composite structure, with starch acting as a filler dispersed within a continuous phase of highly swollen HPMC [127]. Later work has provided evidence that different pregelled starch particles can swell and dissolve to different extents within the gel, reflecting the degree of pregelatinisation experienced by individual particles and the amount of amylose (swellable and soluble) and amylopectin (swellable) released in this process. The result is hydrated starch particles embedded in a swollen continuum of HPMC (Fig. 4.7). Composite structures of this type can provide high gel strengths. The disperse phase also increases the tortuosity of drug diffusion pathways within the gel, further retarding the diffusion of soluble drugs. These effects and the contribution made by highly swollen and dissolved fractions of pregelled starch may provide a basis for claims that pregelled starch contributes actively to the gel layer of HPMC matrices [128].

4.6.2 Mixtures which have the Potential for Significant Molecular Interaction

The situation becomes even more interesting when the polymers have the potential to directly interact. ‘Synergistic’ combinations of polymers have been chosen from the food science literature with the intention of enhancing the properties of the gel layer in hydrophilic matrix formulations. It is important to recognise that very few combinations of chemically different polysaccharides undergo these types of specific interactions [129] and that phase separation is more likely to be the dominating

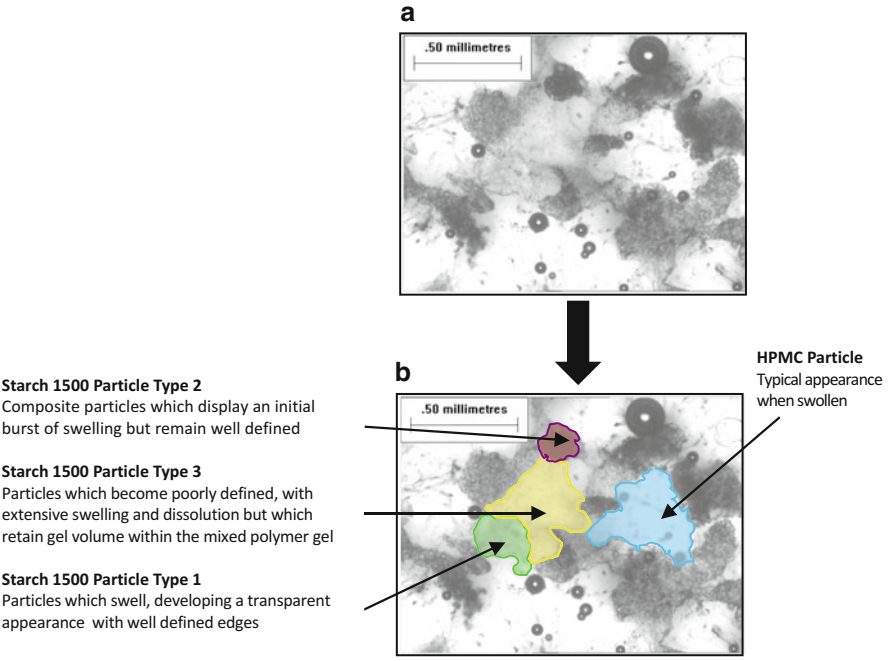

Fig. 4.7 Optical microscope images of a hydrated mixed powder bed (a mixture of HPMC and pregelatinised starch particles) showing how starch (darker areas) becomes embedded in a continuum of swollen HPMC. Approximately equal numbers of HPMC2208 (Methocel K4M) and partially pregelatinised starch (Starch 1500) particles were hydrated between two microscope slides at 20 ± 1 °C, in 0.154 M sodium chloride containing 0.003 M Coomassie Blue, with optical images taken in transmission. Images were acquired 5 min post-hydration. Image A is the original image which shows how HPMC swelling (white regions) dominates the swollen bed. Image B is an interpretation in which staining appears to indicate the presence of different particle swelling types within the hydrated bed. It is postulated that these may relate to the degree of pregelatinisation of individual starch particles within Starch 1500 (Reproduced from [165] with permission)

feature in a gel layer that contains polysaccharide mixtures. Nevertheless, interacting polymer systems offer the enticing possibility of enhanced gel layer viscosity, higher gel strength, and a reduction in polymer content. Therefore, synergistic combinations (usually xanthan gum with a galactomannan) are regularly revisited in the hydrophilic matrix literature.

Polymers can interact by undergoing (1) non-specific electrostatic interactions, for example, between anionic and cationic polymers, or (2) more specific interactions which result in molecular ordering and supramolecular structures. These boundaries are not absolute, and in hydrophilic matrices that deliver, for example, biotherapeutic proteins, there is the potential for highly complex interactions in addition to phase separation of the protein drug. Anionic natural

polysaccharides can also be combined with neutral polysaccharides such as HPMC, mimicking the role of sodium carboxymethyl cellulose in the interaction described in Chap. 2.

Matrices in which polyionic complexes form between oppositely charged species include combinations of chitosan with alginates, pectins and xanthan [81, 130] and the interactions of carboxylated starch which are described above [44]. In addition to providing extended release, and greater gel strength, these polyionic complexes can also be exploited to protect acid-labile biopharmaceuticals [42].

Synergistic combinations in the hydrophilic matrix literature most commonly involve xanthan gum with galactomannans and glucomannans. In solution, these plant polysaccharides interact specifically with xanthan to form supramolecular structures which impart gelling characteristics and enhance solution viscosity [131]. The polymer ratio, the type of galactomannan involved and the electrolyte concentration are important variables which influence this type of interaction [132]. The role of heat in enabling a strong interaction is conveniently ignored in the hydrophilic matrix literature, but fortuitously, room temperature interactions have also been identified [119, 133].

Figure 4.8a shows how a cold-mixed blend of xanthan gum with a water-soluble locust bean gum can significantly enhance the elastic modulus (G′) in dilute solution. There is a polymer ratio that provides the greatest enhancement, and Fig. 4.8b shows how this ratio also provides the most extended drug release profile [134]. A xanthan/locust bean gum combination has become a successful commercial matrix technology, TimerX®, which has underpinned a number of successful marketed products [135]. In vitro tests of the TimerX® system showed how drug release profiles appeared to be insensitive to changes in pH over the physiological range (pH 1.2–7.5) and also to ionic strength changes at each pH, except when the ionic strength in the medium was zero [136]. Xanthan interactions with locust bean gum occurs with fractions of locust bean gum which are soluble at low temperature, and the use of a cold-water-soluble locust bean gum has shown how these mixtures can provide longer release times than xanthan gum alone [119, 134]. Such combinations can be remarkably potent as hydrophilic matrix polymers: one study showed how ibuprofen release from a 12 mm matrix containing 5 % of the optimised polymer blend released only 50 % of drug in 24 h [119]. Whilst the solubility of ibuprofen is relatively low in the gel layer, and it may be expected to be released primarily by erosion, other studies suggest these mixtures can also enhance extended release of soluble drugs [137]. Synergistic polymer combinations with other galactomannans have been described [64] and a study of xanthan/konjac matrices by Alvareez-Mancenido [38] offers a useful lesson in the geographical source variability of plant gums. It showed considerable differences between US-, European- and Japanese-derived grades of konjac. Other polymer mixtures in which rheological synergy has been explored include kappa-carrageenan with galactomannans and spray-dried starch/Carbopol mixtures [138].

Both polyionic and ‘synergistic’ polymer interactions have the potential to markedly influence the hydration, erosion and diffusion barrier properties of the

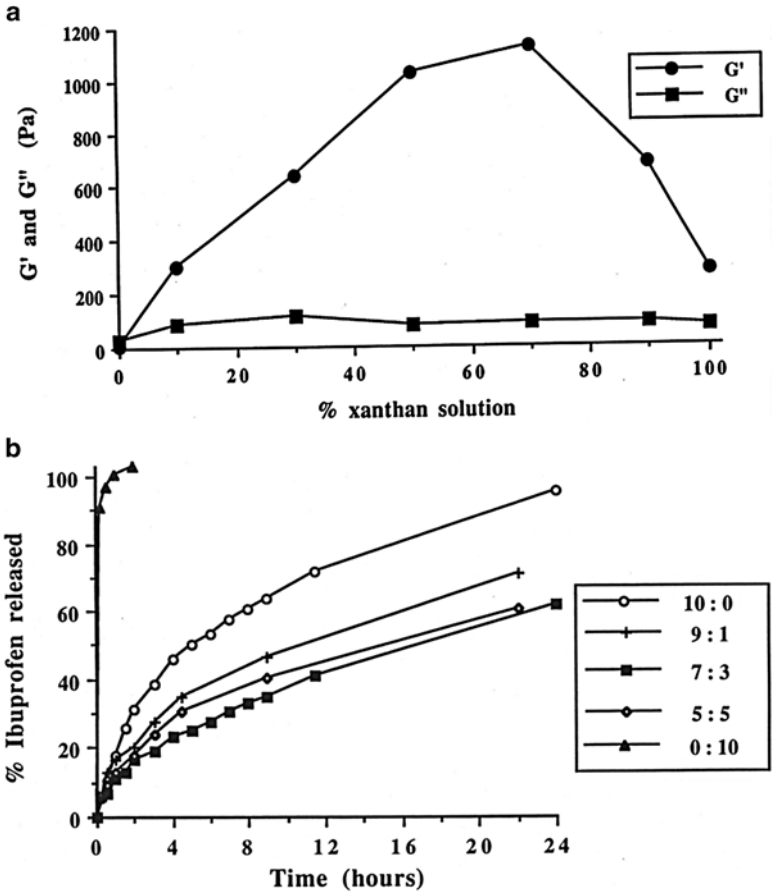

Fig. 4.8 Mixtures of xanthan gum with cold-water-soluble locust bean gum: (**a**) rheological behaviour and (**b**) matrix drug release. Graph (**a**) shows the elastic (G′) and loss (G″) moduli of 1 % cold-mixed solutions of xanthan gum with locust bean gum at 37 °C. The *x*-axis shows the proportion of xanthan gum in the polymer mixture. Graph (**b**) shows ibuprofen release from matrices containing different ratios of xanthan gum with locust bean gum. Note how the most extended drug release is obtained from the mixture that has the highest G′ value in graph **a** (a weight ratio of 7:3 xanthan to locust bean gum). Matrix composition by weight: xanthan gum 5 %, ibuprofen 33.3 %, microcrystalline cellulose 60.6 %, magnesium stearate 1 %, silicon dioxide 0.1 %. USP apparatus 1, 100 rpm, 900 ml pH 7.5 buffer, 37 °C. Mean ($n=3$) (Reproduced from [120] with permission)

hydrophilic matrix gel layer. Polyionic interactions which result in charge shielding will reduce water affinity, whilst the development of molecular structures in an entanglement-based gel can influence factors such as gel layer thickness, diffusion barrier properties and erosion resistance. Changes in polymer swelling rates will also affect early gel layer formation. These aspects are all key factors that can influence drug release kinetics in hydrophilic matrix systems.

4.7 Natural Polymers in Hydrophilic Matrices for Site-Specific Delivery to the Gastrointestinal Tract

Hydrophilic matrices containing natural polymers are especially useful for drug delivery to specific regions of the GI tract and numerous examples can be found in other literature reviews elsewhere [2, 10, 164].

4.7.1 Colon Targeting

Many natural polysaccharides have been investigated as colonic delivery carriers. These polymers are poorly digested in the upper GI tract, but are fermentable by the bacterial enzymes of the colonic microflora [139–141].

Pectin has been widely studied [142]. An important factor for dosage form survival is low polymer solubility and swelling in the upper regions of the GI tract, and in pectins this has been achieved by using (1) a high methoxyl or amidated pectin [142, 143], (2) calcium or zinc ion cross-linking [7, 144] or (3) complexation with oppositely charged polymers (low methoxyl pectins are best for this purpose) or (4) by adding HPMC to enhance matrix robustness [145]. Calcium pectinates have been reported to enhance enzymatic pectinolysis [146] and compression-coated matrices can provide the delayed release required to reach the colon. There is evidence that pectin itself may influence the incidence of colon cancer, depending on botanical source [142]. Pectin source and batch inconsistency may result in poor reproducibility of colonic delivery [73]. It has been noted that multiple unit dosage forms are dispersed around the colon and have longer retention times than single matrices, and may be more effective in delivering anticancer chemotherapy [147].

Guar gum is rapidly fermented by faecal bacteria [147], and hydrophilic matrices, either monolithic or compression coated, disintegrate in colon contents [148, 149]. This has provided opportunities for the targeted delivery of colon relevant drugs such as albendazole, 5-ASA and dexamethasone [68, 141]. Other natural polymers have been demonstrated to have potential for colon targeting in a hydrophilic matrix. These include dextran [150], and konjac/xanthan combinations [151].

4.7.2 Buccal and Mucoadhesive Delivery

In the case of buccal adhesive tablets that are formulated on the hydrophilic matrix principle, natural polymers can provide both the adhesive power and the extended-release properties required [152]. Properties such as polymer viscosity and water transport play a major role in maintaining the mucoadhesive bond, and in general the mucoadhesive strength of natural polymers follows the rank-order

cationic > anionic > non-ionic [80]. However, whilst many natural polymers have been investigated in this application [153], they have not ranked highly in comparison with their synthetic counterparts, particularly against polycarbophil and carbomer [154].

4.7.3 Gastro-Retentive (Floating) Tablets

Hydrophilic matrices containing natural polymers have been widely utilised in 'gastro-retentive' tablets. The aim is to create an extended-release matrix that floats on the gastric contents [155, 156], and natural polymers are usually part of a polymer blend, formulated with carbonates, effervescent mixtures or low-density foam to provide buoyancy [157, 158]. Xanthan gum is a common component [159–161] because it can provide the high viscosity and gel strength which will ensure matrix longevity. Other hidden advantages of xanthan include viscosity tolerance to multivalent salts, high ionic strength and low pH environments. It has also been reported that xanthan exhibits good adherence to gastric mucosa, whereas 'synergistic' xanthan mixtures do not [162]. Multilayer and compression-coated matrices are used to further modulate the drug release profile and to avoid drug compatibility problems, with natural polymers usually being located in the extended-release layers [163].

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Chapter 5
Applications of Polyethylene Oxide (POLYOX) in Hydrophilic Matrices

Lawrence M. Martin and Ali R. Rajabi-Siahboomi

5.1 Introduction and Background

Hypromellose (HPMC) has long been the polymer of choice for matrix applications, but many other high-viscosity water-soluble polymers have been also investigated. Polyethylene oxide (PEO), a hydrophilic linear polymer, is an alternative to HPMC in hydrophilic matrices. The physical and chemical properties of PEO make it a suitable candidate for use on its own or in combination with other polymers in hydrophilic matrix formulations.

5.2 The Chemistry and Properties of Polyethylene Oxide (POLYOX)

Polyethylene oxide (PEO) is a nonionic linear polymer produced by the catalytic polymerization of ethylene oxide. It can be represented by the formula $[–CH_2–CH_2–O–]_n$, where n ranges from ~2,000 to 100,000. While it is structurally similar to polyethylene glycol (PEG), PEG has a significantly shorter chain length and, depending on its molecular weight (from 200 to 35,000 Da), is a liquid or waxy solid. PEO polymers have significantly higher molecular weights than PEG (100,000–7,000,000 Da) and are free-flowing white crystalline powders [1]. PEO possesses some degree of reactivity associated with its polyether structure, but end group reactivity is low due to the small number present in the high molecular weight grades [2].

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PEO is soluble in water and forms viscous, pseudoplastic solutions. Above 98 °C, aqueous PEO solutions undergo phase separation, due to precipitation of the polymer which causes the solution to appear cloudy. The temperature of this cloud point can be depressed by dissolved ions [3, 4].

Pharmaceutical grades of PEO are manufactured by the Dow Chemical Company and are distributed globally by Colorcon Inc. under the trade name of POLYOX™ water-soluble resins (WSR). Some typical physicochemical properties of POLYOX are shown in Table 5.1 [6]. The grades are distinguished by differing average molecular weights and solution viscosities (Table 5.2). POLYOX polymers are

Table 5.1 Typical physical properties of POLYOX™ polyethylene oxides

Appearance	Off-white powder
Crystalline melting point (°C)	62–67
Odor	Slightly ammoniacal
Melt flow temperature (°C)	>98
Volatiles content, as packaged (wt % at 105 °C)	>1.0
Max alkaline earth metals (wt % as CaO)	1.0
Powder bulk density, lb/ft^3 (kg/m^3)	19–37 (304–593)
Polymer density (g/cc)	1.15–1.26
Moisture content, as packaged (%)	<1
Heat of fusion (cal/g)	33
Particle size: average through (wt %)	
10-mesh (US standard)	100
20-mesh (US standard)	96

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Table 5.2 Molecular weight and viscosity grades of POLYOX™ polyethylene oxide water-soluble resins

	Approximate molecular weight	Viscosity range in water at 25 °C (cP)		
		5 % solution	2 % solution	1 % solution
WSR N-10	100,000	30–50		
WSR N-80	200,000	55–90		
WSR N-750	300,000	600–1,200		
WSR 205	600,000	4,500–8,800		
WSR 1105	900,000	8,800–17,600		
WSR N-12K	1,000,000		400–800	
WSR N-60K	2,000,000		2,000–4,000	
WSR 301	4,000,000			1,650–5,500
WSR coagulant	5,000,000			5,500–7,500
WSR 303	7,000,000			7,500–10,000

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highly hydrophilic, and they hydrate rapidly in aqueous media to form viscous gels exhibiting high swelling capacities. These properties, coupled with the wide range of molecular weights available, make them suited to application in several controlled-release technologies, particularly in osmotic and hydrophilic matrix tablets. Despite its high molecular weight, POLYOX is highly crystalline and has a melting point temperature around 65 °C, above which, the polymer becomes thermoplastic. At temperatures far above the crystalline melting point, high molecular weight polymers of POLYOX still retain a very high degree of crystalline character. For this reason, when formulating extended-release oral solid dosage forms, the low molecular weight PEO grades are more suitable for hot-melt extrusion applications, whereas the high molecular weight grades will provide better sustained-release dissolution profiles.

POLYOX is susceptible to autoxidative degradation through a mechanism which involves the formation of hydroperoxides and cleavage of the polymer chain [2, 8]. The resulting reduction in molecular weight of the polymer can be seen as a progressive loss of viscosity in aqueous solution. The rate of molecular weight degradation increases at elevated temperatures and can be catalyzed by metal ions such as ferrous, cuprous, cupric, and silver ions. The number of chain cleavages occurring in a given time is independent of polymer molecular weight. Because scission of longer polymer chains leads to a wider polydispersity than in shorter chains, the higher molecular weight grades of PEO experience a greater rate of viscosity reduction than lower molecular weight grades [6]. Figure 5.1a compares the change in viscosity over time for a high (5,000,000 Da) and a low (200,000 Da) molecular weight grade stored at 23 °C [9]. Product stability can be improved by minimizing the long-term exposure of the polymer to high temperatures [10], and so POLYOX should be stored in sealed drums at or below 25 °C. It may require a retest of product viscosity prior to use after prolonged storage. Figure 5.1b shows how a POLYOX (MW = 200,000) stored at 23 °C experienced less than a 10 % loss of viscosity over 2 years. At 40 °C, the same material experienced a 20 % viscosity loss over the same time period.

The inclusion of antioxidants can reduce the viscosity loss by terminating the free radicals generated during autoxidation. In the case of extended-release matrices, a range of antioxidants have been tested, including ethylenediaminetetraacetic acid (EDTA), propyl gallate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ferrous sulfate, and ascorbic acid. Lower degradation rates have been observed, particularly in the presence of ascorbic acid and BHT [11, 12]. The effect of BHT on POLYOX stability is shown in Fig. 5.2 in which samples with and without BHT were tested during extended storage at 23 °C. The sample containing 500 ppm BHT showed a significantly lower reduction in solution viscosity than the sample containing no antioxidant [9].

Pharmaceutical grades of POLYOX already contain BHT, but supplementation of BHT at levels of 100–1,000 ppm (0.01–0.10 % w/w) may be required for additional protection and stability of the formulation [13]. The BHT content of a formulation may be reduced through sublimation or oxidation when exposed to heat or air in fluid bed operations such as granulation and drying. Additional BHT can be

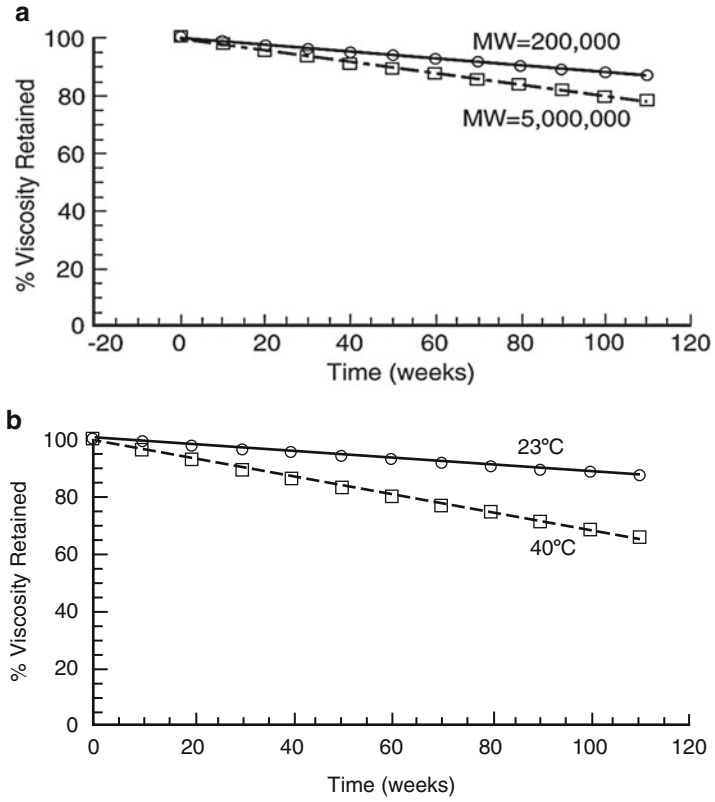

Fig. 5.1 Viscosity changes in POLYOX™ during storage. (**a**) Solution viscosity of high and low POLYOX™ molecular weight grades during extended storage at 23 °C. (**b**) Effect of storage temperature on the viscosity of POLYOX™ molecular weight 200,000. Reproduced from [9] with permission from the Dow Chemical Company. ™ Trademark of the Dow Chemical Company ("Dow") or an affiliated company of Dow

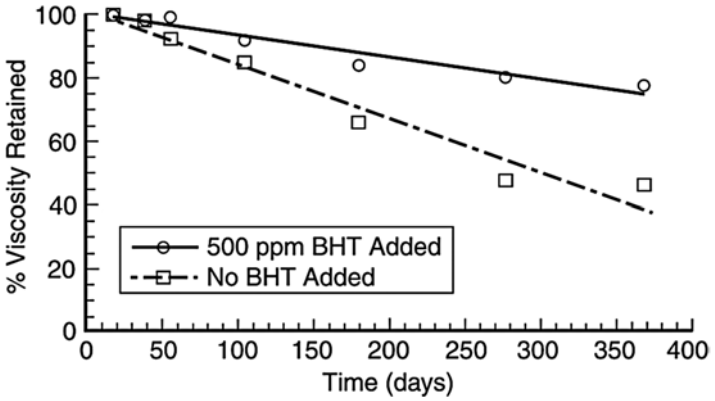

Fig. 5.2 Effect of BHT on POLYOX™ viscosity during storage. Solution viscosity changes during extended storage at 23 °C. Reproduced from [9] with permission from the Dow Chemical Company. ™ Trademark of the Dow Chemical Company ("Dow") or an affiliated company of Dow

blended into the formulation during the lubrication process (e.g., addition of magnesium stearate) to ensure a sufficient concentration of antioxidant in the final tablet.

The stability of formulated dosage forms containing POLYOX can be also influenced by the inclusion of incompatible excipients. The stability of extended-release matrices containing theophylline with various fillers has been investigated by L'Hote-Gaston et al. [14]. It was found that formulations containing soluble sugar derivatives (e.g., lactose, mannitol) developed increased drug release rates after 3 months of accelerated stability testing, whereas no change was observed in the case of insoluble or partially soluble fillers such as dicalcium phosphate, microcrystalline cellulose, and partially pregelatinized starch (Starch 1500®). The authors concluded that aerobic autoxidation of lactose and mannitol may have generated active oxygen species which promoted depolymerization reactions resulting in a loss of polymer viscosity.

5.3 Flow and Compaction Behavior

The physical and mechanical properties of POLYOX have been characterized with reference to its performance in tablet manufacturing processes in extended-release matrix applications [15]. POLYOX has a granular or spherical morphology and an average particle size of approximately 150 μm. The inclusion of 1.5 % silicon dioxide as a glidant in POLYOX further enhances the flow properties of the raw material. Table 5.3 shows Carr's compressibility index values for POLYOX grades. The generally low values of <25 % indicate the material will have good excipient flow in common processing operations. In the production of POLYOX compacts using a rotary tablet press, the high flowability of POLYOX has allowed tablets to be produced with low tablet weight variability across a range of turret speeds. POLYOX matrices with high breaking forces and low friability are achieved as a result of the plastic deformation and low elastic recovery of the polymer. Measured ejection forces for the various grades of POLYOX are very low and are insensitive to turret speed, suggesting that the polymer has an inherent lubricity. Owing to this highly ductile and plastic deformation behavior, formulations that contain higher levels of polymer may experience tablet edge defects such as crowning or flashing as the polymer flows around the punch tips on compression. This can be minimized by avoiding excessive compaction forces during tablet production.

Table 5.3 Carr's compressibility index values for various molecular weight grades of POLYOX polyethylene oxides

Grade	Average molecular weight	Carr's compressibility index (%)
WSR 1105	900,000	20.5
WSR N-60K	2,000,000	19.0
WSR 301	4,000,000	17.0
WSR 303	7,000,000	16.5

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5.4 Factors Influencing Drug Release from POLYOX Matrices

5.4.1 Hydration and Swelling Behavior

The kinetics and mechanisms of drug release from swellable, hydrophilic polymer matrices are dependent on the dynamics of gel formation, the properties of the hydrated gel, and front movements within the hydrating tablet [16–18]. The general characteristics of swelling matrices are directly applicable to POLYOX-based formulations. POLYOX hydrates and swells rapidly on contact with water, forming a viscous gel layer around the tablet. The properties of the gel control the release of drug from the tablet and depend on the molecular weight of the polymer, its concentration in the formulation, and the properties of the other formulation components. Strong, high-viscosity gel layers can be promoted by the use of higher molecular weight grades of POLYOX and higher polymer concentrations. In a similar manner to HPMC hydrophilic matrices, drug release from POLYOX matrices appears to be controlled by drug diffusion and matrix erosion or a combination of both [19, 20]. In some cases, POLYOX can achieve near zero-order drug release due to its rapid hydration and suppression of initial drug release bursts. In the examples above, polymer swelling and erosion occur at similar rates, and the rate of polymer swelling at the rubbery-glassy front is similar to the rate of polymer erosion at the interface of the tablet surface with the dissolution media. This behavior, known as "front synchronization," promotes zero-order drug release from the matrix. It has been reported that the use of lower PEO molecular weights encourages earlier synchronization so that steady-state release is more rapidly achieved [16].

The unique properties and swelling and hydration behavior of POLYOX have led to its incorporation with other polymers in hydrophilic matrices to provide benefits which may not be achievable with either polymer used alone. For example, blends of POLYOX and HPMC have been used to further modulate drug release profiles and also to prevent the burst release of highly soluble drugs [21, 22]. The inclusion of POLYOX in HPMC matrices has also been used to achieve high degrees of swelling, to provide enhanced gastro-retention of the dosage form [23].

5.4.2 The Effect of Drug Properties on POLYOX Matrices

Drug loading and drug solubility are important factors to consider when developing hydrophilic matrix formulations. In the case of highly soluble drugs, it is generally understood that diffusion through the gel layer is the primary release mechanism. Drug release also occurs by surface erosion of the gel layer, and this mechanism is particularly important for poorly soluble drugs, which continue to dissolve for some time after being released from the tablet. A wide range of release profiles may be obtained by changing the POLYOX content of the matrix and the polymer molecular weight. The physicochemical properties of the drug and especially drug

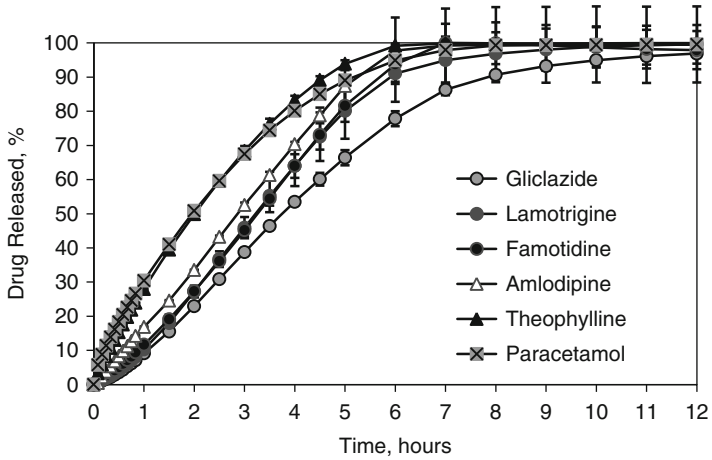

Fig. 5.3 Effect of drug solubility on the release profile of POLYOX WSR 1105 matrices. Matrix composition was drug 15 % w/w, POLYOX WSR 1105 35 % w/w, microcrystalline cellulose 49 % w/w, fumed silica 0.5 % w/w, and magnesium stearate 0.5 % w/w. Tablet weight 200 mg. Drug solubilities at 37 °C: gliclazide (<0.055 mg/ml), lamotrigine (0.17 mg/ml), famotidine (1 mg/ml), amlodipine besylate (3.16 mg/ml), theophylline (8 mg/ml), and paracetamol (20 mg/ml). USP Apparatus II with quadrangular baskets, 100 rpm, purified water 1,000 ml at 37.0 ± 0.5 °C. Reproduced with permission from Colorcon Inc.

solubility are also key parameters of release. They can influence POLYOX hydration, swelling, and gel characteristics and therefore can facilitate or hinder media penetration into the tablet [24]. For example, it has been shown that increasing the drug content of diltiazem hydrochloride (solubility 100 mg/ml) increased water influx into high molecular weight POLYOX matrices and increased drug release rates [16]. Drug solubility and content may not significantly affect the drug release profiles in formulations using low molecular weight grades of POLYOX as the swelling and erosion processes occur faster than the rate of drug diffusion through the gel layer. Dissolution medium pH in general does not affect drug release from POLYOX matrices unless the solubility of the drug itself is pH dependent [25]. Interactions between the drug and polymer are unlikely, because of the nonionic nature of POLYOX [26].

Figure 5.3 shows the drug release profiles for POLYOX matrix formulations containing different drugs with a wide range of aqueous solubilities. It can be seen that drug solubility influences drug release and that lower solubility drugs produce slower release profiles, closer to zero-order release as a result of their erosion-dominated mechanism. High-solubility drugs do not achieve zero-order release due to the high contribution of diffusion through the swollen POLYOX matrix [27], and they give a typical diffusional first-order release profile as also shown in Fig. 5.4. The use of high molecular weight grades of POLYOX can achieve reproducible drug release profiles which parallel the release profiles that are obtained from matrices containing high-viscosity HPMC (e.g., METHOCEL™ K100M).

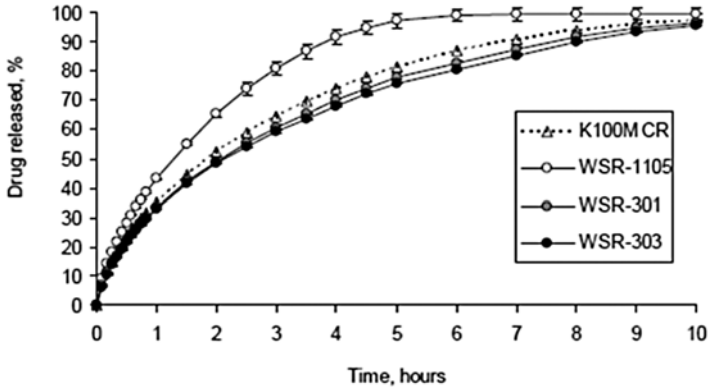

Fig. 5.4 A comparison of drug release from matrices containing HPMC or POLYOX. HPMC was METHOCEL K100M CR, and this is compared with various molecular weight grades of POLYOX WSR. The drug metformin HCl is highly soluble. Matrix composition was metformin HCl 50 % w/w, POLYOX or HPMC 30 % w/w, microcrystalline cellulose 19 % w/w, fumed silica 0.5 % w/w, magnesium stearate 0.5 % w/w. Tablet weight 1,000 mg. Reproduced from [28] with permission from Colorcon Inc.

5.4.3 The Effect of Polymer Content and Molecular Weight

Polymer molecular weight can have a significant influence on drug release. The wide range of POLYOX viscosity grades available provides a means to achieve desired release profiles for drugs with varying dose and solubility characteristics. By increasing the polymer molecular weight in a formulation containing a fixed content of POLYOX, the drug release rate is decreased, by retarding the diffusion of dissolved drug and increasing the gel strength of the hydrated gel layer [29]. In a similar manner to HPMC, the impact of increasing molecular weight reaches a threshold value, beyond which further increases in POLYOX molecular weight have little effect. This occurs particularly in the case of highly soluble drugs (e.g., metformin hydrochloride) which have high rates of diffusion through the gel (Fig. 5.4) [6, 28]. Drug release profiles can also be modulated by varying the concentration of the polymer in the formulation. A minimum polymer level of 20–30 % w/w is initially recommended to ensure a robust and consistent drug release performance. Adhering to this guideline is especially important for POLYOX-based matrices, as stability-related viscosity loss may result in drug release variability on storage. Keeping POLYOX levels above this minimum level can avoid these problems and ensure matrix robustness and retardation of drug release.

Figure 5.5 shows the effect of polymer content on the release rate of the highly water-soluble model drug metformin hydrochloride from matrices containing POLYOX WSR 1105. Polymer levels below 15 % w/w were unable to provide extended release of the drug, but increasing polymer content produced more

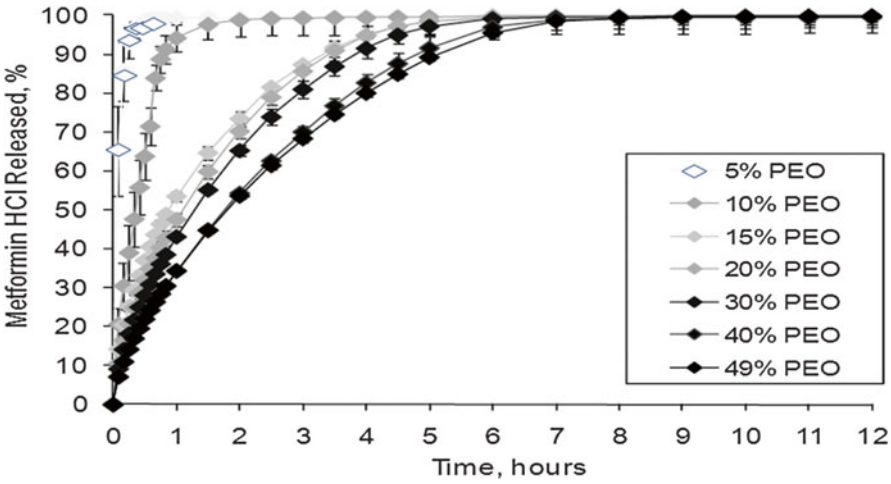

Fig. 5.5 Effect of polymer content on the release of the highly soluble drug metformin HCl from POLYOX matrices. Matrix composition was metformin hydrochloride 50 % w/w; POLYOX WSR 1105 5 %, 10 %, 20 %, 30 %, 40 % or 49 % w/w; microcrystalline cellulose 0–44 % w/w; fumed silica 0.5 % w/w; and magnesium stearate 0.5 % w/w. Tablet weight 1,000 mg. Reproduced from [28] with permission from Colorcon Inc.

extended drug release profiles, until an apparent threshold level was achieved at 40 % w/w. At this polymer level, diffusion of this highly soluble drug through the gel layer probably dominates any further increases in gel strength and erosion resistance.

5.4.4 The Effect of Fillers

Excipients in matrix formulations can impact on drug release profiles by modifying the ingress of solvent and the properties of the gel layer. Soluble excipients may dilute the polymer in the swollen matrix, and therefore drug release rates may increase through lowering of gel viscosity, increasing diffusion of drug through the gel layer, and promoting erosion. Insoluble fillers do not increase the water content of the gel layer and do not appear to increase drug release rates [30].

The effects of different solubility fillers have been studied in theophylline POLYOX matrices [14]. Highly soluble fillers such as lactose and mannitol gave the most rapid extended-release profiles, while insoluble fillers such as dicalcium phosphate, microcrystalline cellulose (MCC), provided slower drug release. Partially pregelatinized starch (Starch 1500) provided the slowest release profiles of all the fillers in the study. Despite its partial solubility in water, this diluent may slow the penetration of the swelling front into the core through its independent swelling properties.

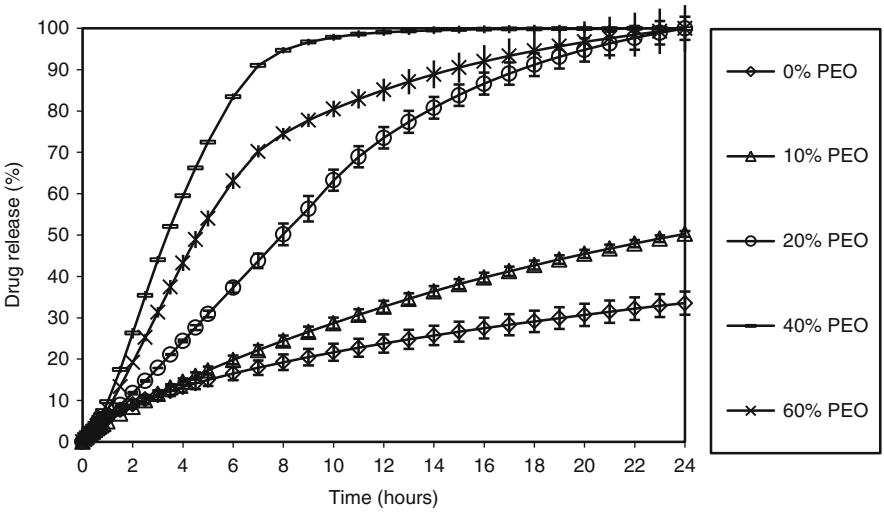

Fig. 5.6 Effect of polymer content on the release of the poorly soluble drug gliclazide from POLYOX matrices. Matrix composition was 15 % w/w API, 0–60 % w/w POLYOX WSR 1105, 25–60 % w/w microcrystalline cellulose, 0.5 % w/w fumed silica, and 0.5 % w/w magnesium stearate. Tablet weight 200 mg. USP Apparatus II with quadrangular baskets, 100 rpm, purified water 1,000 ml at 37.0 ± 0.5 °C. Reproduced with permission from Colorcon Inc.

Formulation of a poorly soluble drug in a hydrophilic matrix generally requires the use of a soluble filler. However, due to compatibility issues between soluble sugars and POLYOX, it means that less soluble fillers such as Starch 1500 and MCC are preferred. Matrix formulations of poor solubility drugs (below 1 mg/ml) with MCC as a filler show that the drug release rate increases as the concentration of POLYOX is increased [27]. Further studies showed that the poorly soluble model drug gliclazide which contained solely MCC had long disintegration times and, therefore, very slow release. However, addition of POLYOX at low levels enabled the tablet to disintegrate, resulting in faster drug release rates (Fig. 5.6). As the concentration of the polymer increased, sufficient gel layer formation occurred, and a classical hydrophilic matrix performance was achieved with 20 % w/w POLYOX in the formulation [27].

5.5 The Processing, Manufacture, and Testing of POLYOX Matrices

5.5.1 Processing and Manufacturing Considerations

POLYOX hydrophilic matrices can be manufactured using conventional tableting processes including direct compression, wet granulation (high shear or fluid bed processes), and dry granulation (roller compaction).

Direct compression is usually preferred for the production of pharmaceutical tablets due to its simplicity, fewer operational steps, and lower cost in comparison with granulation processes. When formulation properties are suitable, tablets can be manufactured by simply blending drug with excipients, polymers, and a lubricant and then feeding the mixture directly into the tablet manufacturing process. However, the selection of excipients is critical in direct compression formulations in order to ensure powder blends resist segregation and remain uniform in composition during processing. The raw materials must also have good flowability and compressibility and must be of similar particle size distribution to other ingredients so that the drug and other components are distributed evenly within each tablet.

POLYOX as a raw material has good flow properties due to its spherical particle morphology and the inclusion of silicon dioxide as a glidant. It is also a highly compressible and plastically deforming material, which imparts low friability to tablets at tensile strengths below those required in conventional tablets. Direct compression formulations of POLYOX matrices have been investigated and have demonstrated good tablet weight uniformity, low friability, and extended-release characteristics for a variety of drugs [31–34]. Compaction behavior of different polymer molecular weight grades was similar, but the inclusion of other highly compressible excipients in the formulation was recommended to allow production in high-speed tableting operations [35]. The reduced processing steps involved in direct compression also minimize the process-related loss of BHT from POLYOX, and additional BHT may not be required to ensure stability of the finished dosage form.

If simple blending cannot provide a uniform mixture or if the resulting powder is subject to segregation or is poorly compressible, then further processing using wet or dry granulation will be required prior to tablet manufacture. Wet granulation usually involves the production of granules through addition of a liquid or polymeric binder solution to the powder blend, increasing the average particle size. It reduces the potential for segregation by binding particles together. In formulations containing high levels of POLYOX, the addition of a polymeric binder to the granulating liquid is generally not needed due to the high degree of self-binding provided by the polymer.

High shear, wet granulation of matrices containing high levels of POLYOX has been achieved using solvent-based or hydro-alcoholic granulating liquids. These approaches reduce agglomerate formation and the occurrence of lumps, which would otherwise arise from the rapid swelling of POLYOX on exposure to water. However, as environmental and safety concerns over the use of solvents have driven interest toward aqueous processes, water-only granulation of POLYOX has also been explored [36]. It was found that adding 10 % w/w water rapidly and omitting the subsequent mixing process (wet massing) was sufficient to granulate pure POLYOX batches without agglomeration. Localized over-wetting of formulations containing POLYOX can rapidly lead to lump formation, and this can be avoided by using an atomizing spray nozzle and keeping wet massing times to a minimum [37]. Polymer molecular weight has no impact on granulation properties.

Owing to the low melting point of POLYOX and its highly plastic nature, formulations containing high levels of polymer may be mechanically sensitive to friction

and high shear generated in wet granulation processing equipment. Lower chopper and impeller speeds than those used for HPMC-based formulations may therefore be required. A buildup of material on the leading edges of the blades or at the base of the bowl can indicate excessive mixing speeds or an improper water addition rate. Flakes, strings, ribbons, or other dry agglomerates in the granulation can indicate high-friction areas where powder is compressed and extruded from pinch points, such as under the impeller blade or chopper bushing.

Solvent or water can be removed from wet granules in low temperature drying operations (<50 °C) using a tray or fluid bed drier. Milling the granules can be challenging due to the tendency of POLYOX to deform rather than to break under an applied force, and milling screens with sharp, grater-type perforations may be more effective than standard punched metal screens when milling granules containing POLYOX. The residence time in the mill should be kept to a minimum to reduce heat buildup and prevent excessive granule attrition. A portion of the formulation's POLYOX content may be withheld from the granulation process to reduce the plastic characteristics of the batch during milling. It will also reduce loss of antioxidant during wetting and drying. This withheld portion of POLYOX can then be added to the batch as an extragranular component during the blending of the lubricant. Additional BHT should also be blended into the batch during this stage.

Roller compaction provides a means of granulating POLYOX matrix formulations in a water-free process, avoiding the process challenges associated with hydration of the polymer and drying of wet granules. Formulation powders are blended together and compacted between two counterrotating rollers to form ribbons, which are then milled into granules of a desired size distribution to produce a free-flowing blend of uniform composition. Because the formulation is not subject to heat, water, or solvents, dry granulation processes are suitable for sensitive active ingredients and they reduce the potential for BHT loss. The process should be conducted at compaction pressures lower than conventional formulations because of the plastic deformation and low yield strength of POLYOX. Excessive pressure during roller compaction can result in material sticking to the rollers or low compactability of the resulting granulation. Changing to smooth rollers may reduce sticking problems if encountered with the use of textured rollers. The inclusion of intra- or extragranular excipients which deform by brittle fracture (e.g., calcium phosphates) can maintain granulation workability and provide good compaction properties during the tableting process. The milling of the roller-compacted ribbons can be challenging because of the polymer's tendency to melt and plastically deform, and so milling equipment and parameters should be chosen to minimize residence time and exposure of the formulation to frictional heat. If necessary, a portion of the POLYOX content in the formulation may be withheld and blended extragranularly prior to tableting [38].

Matrix tablets of a POLYOX-based acetaminophen formulation produced by dry granulation have been found to exhibit reduced tensile strength and increased friability compared with similar tablets produced by direct compression [39]. Extragranular addition of a filler excipient was found to improve the strength and friability of the roller-compacted tablets, and the authors concluded that the dissolution performance of the matrices was not affected by roller compaction.

5.5.2 Film Coating Considerations

Tablet film coatings can provide a number of benefits for hydrophilic matrices. For example, pigmented film coatings can be used to distinguish multiple strengths of a controlled-release product from their immediate-release counterparts, reducing the chances of dosing errors or an accidental under- or overdose. Film coating also improves tablet swallowability, decreases esophageal transit time [40], and can improve the stability of the marketed dosage form by providing a barrier to oxygen, light, and moisture.

The impact of film coating has been studied in POLYOX matrices. One study has investigated the influence of an immediate-release film coating, Opadry® II (Colorcon), on the drug release stability of POLYOX matrices containing propranolol hydrochloride. The film coating was found to increase the mechanical strength of the matrices without impacting on the drug release profile. After 6 months of storage at 40 °C/75 % RH, the drug release profile of the film-coated matrices remained unchanged, whereas uncoated POLYOX matrices showed a small increase in their drug release rate (Fig. 5.8a, b). The mechanical strength of coated matrices also remained unchanged after 6 months of storage at 40 °C/75 % RH, while the strength of uncoated matrices was reduced by 25–50 % under the same conditions [42].

5.5.3 Dissolution Testing Considerations

The in-vitro drug release profiles obtained from hydrophilic matrix tablets are influenced by the hydrodynamic conditions of the dissolution test. Different dissolution apparatus and stirring intensities apply varying degrees of stress to a hydrating matrix, and this can impact on drug release rates, by modifying matrix swelling and erosion behavior. The influence of different dissolution methods and hydrodynamic conditions on POLYOX-based matrices has been investigated in which the release of metformin hydrochloride was determined in deionized water at different stir speeds and in a range of dissolution apparatus [43]. Although reproducible first-order release profiles were obtained using all the methods used in the study, the authors found that the use of stationary quadrangular baskets (QB), as shown in Fig. 5.7, with USP Apparatus II produced the lowest drug release variability (Fig. 5.8). The quadrangular basket provided a consistent presentation of the matrix to the dissolution medium because it prevented the tablet from sticking to the bottom of the vessel or floating on the surface. The vertical positioning of the basket within the vessel was important in maintaining reproducible release rates, due to a region of relatively low fluid velocity just above the paddle. Paddle speed was found to have a significant impact on metformin hydrochloride release, with faster speeds resulting in faster drug release. This can be attributed to the high solubility of the drug and the relatively low molecular weight grade of POLYOX WSR 1105 used in the formulation.

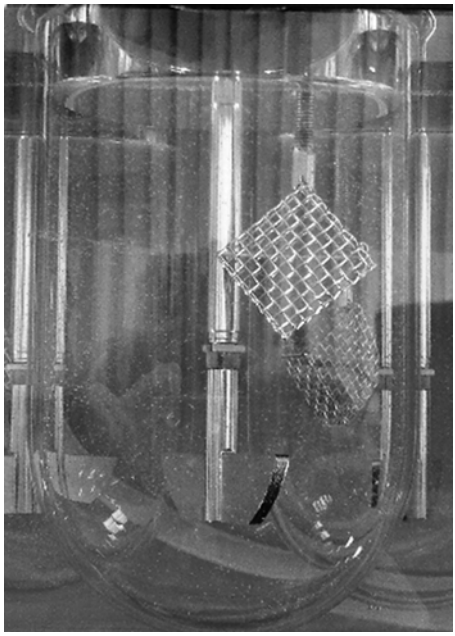

Fig. 5.7 USP Apparatus II with quadrangular baskets: a useful dissolution test geometry for POLYOX matrices. USP Apparatus II with an 8-mesh (2.38 mm) stationary quadrangular basket positioned within the vessel perpendicular to and 3 cm above the paddle. This geometry was used for the drug release results shown in Figs. 5.3, 5.6, and 5.8. Reproduced from [41] with permission from Colorcon Inc.

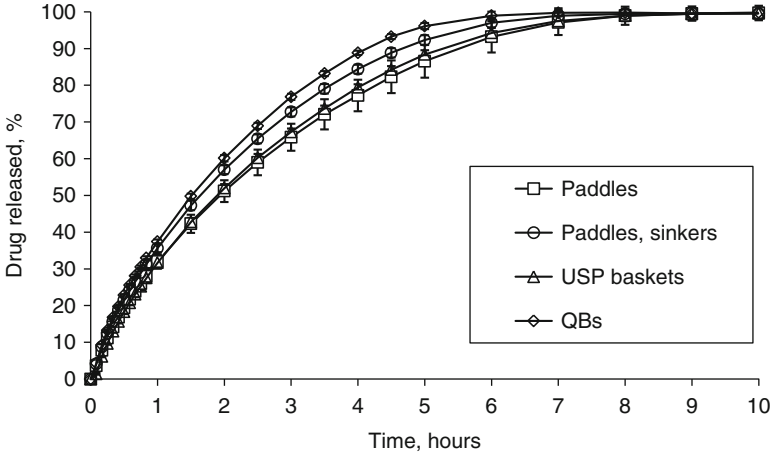

Fig. 5.8 Effect of different dissolution apparatus on the release of metformin hydrochloride from POLYOX matrices. The dissolution medium was 1,000 ml of purified water at 37.0±0.5 °C. 100 rpm stir speed for all apparatus. QBs, quadrangular baskets. Matrix composition was metformin HCl 50 % w/w, POLYOX WSR 1105 30 % w/w, microcrystalline cellulose 19 % w/w, fumed silica 0.5 % w/w, and magnesium stearate 0.5 % w/w. Tablet weight 1,000 mg. Reproduced from [41] with permission from Colorcon Inc.

Another study has found that the release of a lower solubility drug (theophylline 8 mg/ml) from POLYOX-based matrices was less sensitive to stirring speed [16]. Matrices incorporating medium and high molecular weight grades of POLYOX were resistant to increases in drug release rates when USP II stirring speeds were raised above 100 RPM, suggesting that POLYOX matrix performance can be robust in the face of challenging hydrodynamic agitation.

Hydrophilic matrix tablets contain significantly greater quantities of drug than immediate-release dosage forms, and the controlled-release capabilities of the polymer act as a safety mechanism to ensure a large dose of the drug is not prematurely released. However, the concomitant ingestion of alcoholic beverages has been highlighted by the FDA as a critical failure mode for some extended-release formulations as it may induce "dose dumping" effects. The robustness of POLYOX matrices to hydro-alcoholic media has been evaluated [44]. POLYOX matrices containing metformin hydrochloride (water solubility 500 mg/ml) or gliclazide (<0.1 mg/ml) have been subjected to dissolution testing in media containing up to 40 % w/v ethanol. Reproducible drug release profiles were obtained in all the media tested, and there was no dose dumping from any formulation. Drug release profiles in hydro-alcoholic media deviated from those in water due to the different solubilities of drugs and polymers in each environment, and the release profile variability between tablets increased when tested in the presence of alcohol. The authors concluded that POLYOX matrices showed no potential for dose dumping and delivered consistent drug release characteristics in both water and hydro-alcoholic media.

5.6 The Use of POLYOX Matrices as an Abuse Resistance Strategy

The use of high molecular weight POLYOX in matrix formulations not only provides extended release but also results in crush- and abuse-resistant tablets. Crush resistance is related to the highly plastic nature of the polymer. Heat extraction of drug from the POLYOX matrices is also impeded by the low melting temperature of the polymer because it creates a molten mass. Solvent extraction of the drug is similarly inhibited due to the formation of a viscous polymer solution that hinders syringe loading and injectability [45]. A commercial product using POLYOX as a physical abuse-resistance barrier is oxymorphone ER (Opana ER™, Endo Pharmaceuticals Inc. and Purdue Pharma L.P.). This employs the INTAC® technology (Grünenthal) which uses high molecular weight polyethylene oxide in a proprietary hot-melt extrusion process which results in a matrix with high mechanical strength and resistance to crushing.

5.7 Regulatory Considerations

POLYOX resins comply with the standards set by the US Pharmacopeia/National Formulary (NF) and the European Union. They are approved for use in Japan and Europe and meet the requirements of the Food Chemicals Codex and the International Codex Alimentarius Commission. POLYOX has an FDA Inactive Ingredient Database (IID) limit of 543.9 mg per tablet for oral applications (FDA IID, June 2010) [46].

POLYOX NF (pharmaceutical) grades have a maximum free ethylene oxide content of 0.001 % (10 ppm) and are acceptable for use in the USA (USP 36—NF 31) [47]. The POLYOX LEO (low ethylene oxide) grades have a maximum free ethylene oxide specification of 0.0001 % (1 ppm) and are acceptable for pharmaceutical use in the USA and Europe [48].

POLYOX contains amorphous fumed silica (1.5 %) as a glidant to enhance its flowability. Butylated hydroxytoluene (BHT) is added to all POLYOX NF grades as an antioxidant and stabilizer at levels ranging from 100 to 500 ppm depending on the molecular weight of the polymer.

5.8 Safety and Handling Considerations

Like many excipients, POLYOX can be flammable as a powder and it has been evaluated for explosivity [49]. It has been reported that POLYOX is not unusually hazardous, but its low minimum ignition energy (MIE) makes it susceptible to ignition in the air by static discharge or other sources. Equipment and operating procedures for handling POLYOX powders should be therefore designed to prevent the formation of explosive mixtures and control the effects of explosions.

POLYOX powders also present a significant slip hazard, due to their high lubricity when wetted. During dispensing, blending, or other processing steps, fine airborne dusts are generated which settle invisibly on floors and other surfaces. Post-processing cleanup should therefore use a sweeping or vacuuming step to remove dry powder before wet cleaning is commenced. A cleaning solution of 10 % sodium carbonate (soda ash) can remove POLYOX films from floors while minimizing the potential for slip-related injuries.

5.9 Conclusions

The unique properties of polyethylene oxide, its excellent flowability, compactability, and high swellability, make it an excellent candidate polymer for controlled-release matrix applications. Hydrophilic matrices of POLYOX may be produced by conventional tableting processes such as direct compression, dry granulation, and wet granulation. POLYOX offers suitable polymer properties which can be used on its own or

in combination with other polymers, and these matrices may exhibit gastric floating (gastro-retentive) properties due to their high swelling and low density. The broad range of molecular weight grades provides the formulator with the ability to tailor release profiles for different drugs across a wide range of dose and solubility combinations. In some formulations and for some APIs, the rapid hydration of PEO can provide near zero-order release profiles not otherwise attainable from HPMC matrices.

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Chapter 6
A Formulation Development Perspective on Critical Interactions Affecting the Performance of Hydrophilic Matrix Tablets

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6.1 The Significance of Interactions on the Performance of Hydrophilic Matrices

Hydrophilic matrices remain a cornerstone controlled-release (CR) technology. There are many reasons for their continued popularity despite advances in other extended-release (ER) technologies such as pellets and osmotic tablets. The reasons, which are discussed in detail in previous chapters, include their formulation simplicity, their capacity to be manufactured on conventional tabletting machinery, their ability to accommodate high drug loadings and the relatively low cost and lack of toxicity of the polymers [1–3].

However, hydrophilic matrices require additional ingredients to facilitate their ease of manufacture and stability and allow the accurate, efficacious and reproducible delivery of drug to the body. This formulation process raises the possibility of interactions between the active drug substance and the formulation additives. In the case of hydrophilic matrices, interactions can arise between both inert and active formulation components and the rate-controlling polymer. These have the potential

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to significantly influence drug release characteristics and subsequently the observed pharmacokinetics in vivo. The interaction can take various chemical or physical forms and can change the properties and functionality of the polymer thereby altering the physical performance of the dosage form. Therefore, during the development of a successful hydrophilic matrix ER formulation, potential interactions need to be identified and avoided or mitigated where necessary.

Interactions can be intra-matrix, where formulation excipients interact with each other, or extra-matrix where there is an interaction between formulation components and the dissolution media. When a problem is observed, an appropriate mitigation strategy must be put in place to minimise or eliminate the risk.

This chapter focuses on cellulose ethers and considers their reported interactions and incompatibilities with drugs, electrolytes, surface active materials and other excipients. It ignores polymer–polymer interactions, as these are dealt with in other chapters. As will become apparent to the reader, a precise mechanism by which these interactions occur, and how and why they impact on drug release kinetics, can be difficult to elucidate, and they are often poorly understood. Solution studies are often undertaken with the results then extrapolated to matrices; however, the gel layer of a hydrophilic matrix is a complex environment in which many dynamic and competing physicochemical processes contribute to the retardation of drug release. In the absence of detailed experimental investigations and conclusive evidence, many theories are speculative.

In writing this chapter, the principal aim is to aid the formulation development process by highlighting and describing these interactions to the extent that is possible from the present literature. It is the requirement and responsibility of the formulation development scientist to apply these case studies to ensure the successful design of a robust controlled-release drug product.

6.2 Interactions Between Salts and Cellulose Ethers

The influence of salts on both polymer solutions and matrix behaviour has been extensively investigated by a number of groups. There are many reasons why salts are co-formulated within hydrophilic matrix formulations. Sodium chloride (NaCl) has been used as a lubricant and diluent in direct-compression tablet formulations [4–7]. It has also been used as a channelling agent [8] and as an osmotic agent [9, 10] in the cores of controlled-release tablets. The inclusion of ionic buffers for microenvironmental pH control can be a useful strategy when the gastrointestinal solubility of weakly basic or weak acid drugs causes bioavailability problems [11]. The counterions associated with drugs also have the potential to elicit salt effects, an aspect noted but rarely investigated in the literature [12].

Salts may also present an extra-matrix challenge, as salts in gastric media may change the behaviour of the polymer and the kinetics of drug release from HPMC matrices. These salts are encountered in dissolution test media, in gastrointestinal fluids, or as a result of the intake of food and drink. It is therefore necessary to

explore how cellulose ether matrices interact with salt solutions as an extra-matrix challenge. Chapter 12 details the efforts to bridge the impact of interactions in the in vitro dissolution test to the in vivo environment of the body.

6.2.1 Mechanism of Salt Interaction with Cellulose Ethers

Solutions of many cellulose ethers are thermo-responsive. On heating, they undergo a thermally induced, reversible gelation which often results in visible phase separation. This arises as a result of extensive intra- and interchain associations between hydrophobic-rich areas of the polymer chain and the formation of a three-dimensional network [13]. In solutions at low temperatures, the polymer is a random coil with little polymer–polymer interaction [14]. The strong solute–solvent interaction protects the hydrated polymer molecules against agitation [15]. However, as temperature is increased, polymer molecules lose their water of hydration, also known as the water sheath, and with sufficient dehydration, polymer–polymer associations occur between the hydrophobic methyl side groups. This results in a macroscopic phase separation which is often seen as insolubility of the gel or polymer precipitate. This is accompanied by a sharp rise in viscosity and an accompanying rapid increase in the dynamic storage modulus G'. The temperature at which this occurs is termed the sol–gel transition temperature and is most often assessed rheologically or through turbidimetric determinations of incipient precipitation temperature (IPT) or cloud point temperature (CPT) [14]. The interrelationship between gelation, clouding and precipitation is relatively poorly understood, and terms are used fairly loosely [16]. At low concentrations of HPMC, it is possible to produce a turbid solution before gelation has occurred, and the reverse is true at high temperatures. However, both properties are affected by electrolytes to a similar extent [17].

Studies of the influence of salts on solution thermal properties have been undertaken on many types of cellulose ether. Early studies were undertaken on methylcellulose [15, 18–20], later followed by hydroxyethyl cellulose, hydroxypropyl cellulose [21] and hydroxypropyl methylcellulose [17, 22, 23]. The pharmaceutical literature focuses on methylcellulose (MC), hydroxypropyl methylcellulose (HPMC) and ethyl hydroxyethyl cellulose (EHEC) with respect to salt effects on hydrophilic matrices. A wide variety of techniques are available to study the sol–gel transition in solution including turbidity measurements [17, 24], dynamic light scattering [25], differential scanning calorimetry (DSC) [13, 26], rheological measurements [27, 28] and ATR-FTIR spectroscopy [29], with methods described extensively in published literature.

Various salts have been found to alter the CPT and sol–gel transition temperature to an extent dependent on their type, valency and charge, and this can influence formulation properties as diverse as solution viscosity, disintegration time and drug release from HPMC matrices [1, 15, 17, 28, 30–32]. The majority of salts reduce the sol–gel transition temperature and CPT; however, some demonstrate the opposite effect and ‘salt in’ the polymer, consequently increasing the CPT. The rank order in

which the salts essentially 'salt out' nonionic cellulose ethers from water is known to follow the Hofmeister (lyotropic) series [17, 20, 22, 33]. The series for cations and anions is shown below, with 'salting out' power for both anions and cations decreasing from left to right. Several studies have shown that the effects of anions are more important than cations in 'salting out' polymers [2, 17, 22].

$$PO_4^{3-} > SO_4^{2-} > Cl^- > CO_3^{2-} > NO_3^- > SCN^- > I^-$$

$$Al^{3+} > Na^+ > Mg^{2+} > K^+ > Ba^{2+} > Ca^{2+} > NH_4^+ > Fe^{3+} > Cu^{2+} > Zn^{2+} > Pb^{2+}$$

Several mechanisms have been proposed in the literature to account for the observed effects of the salts on the thermal properties of cellulose ethers. The reduction in CPT of cellulose ethers has been explained through an interaction between salts and the hydration mechanism of cellulose ethers. Early theory attributed the reduction to an osmotic effect, whereby ions in solution compete with the polymer for available water molecules [20]. However, later work [14] suggested a more complex mechanism, since the relative 'salting out efficiency' of different salts varied widely, which would later be found to link with the Hofmeister series. Ions that have a greater affinity for water than HPMC are able to remove water of hydration from the polymer and disrupt the water sheath that solubilises the polymer. This results in dehydration or 'salting out' of the polymer as polymer–polymer interactions become more favourable [15]. Salts that lower the CPT of cellulose ether solutions will also lower the thermal gelation temperature, which is the temperature at which the polymer gels [17]. A linear relationship has been reported between increasing salt concentration and depression of thermal gelation temperature [17, 28, 34].

Liu and co-workers [31] attributed the ability of inorganic salts to affect the gelation temperature of HPMC on their water structuring capability. The effects of various inorganic salts and isotopic solvents on the thermal gelation behaviour of HPMC in aqueous solutions were examined by micro-differential scanning calorimetry and rheological measurements. It was found that salts which induced 'salting out', such as NaCl, promoted the sol–gel transition of HPMC at a lower temperature. An analysis of solvent isotope effects on the changes in the temperature at maximum heat capacity with salt concentration showed that interchain hydrogen bonding (hydrogen bonding between the hydroxyl groups of different HPMC chains) was involved in the sol–gel transition. Its strength depended on the temperature and salt concentration. It was demonstrated that the effectiveness of anionic species in changing the temperature at maximum heat capacity of the HPMC solutions was in the sequence of the Hofmeister series. Anionic species play a role in reducing the temperature of maximal heat capacity by their influence on the structure of the water, which in turn affects interactions between hydroxyl groups and water molecules, interchain hydrogen bonding and the strength of the water cages prohibiting hydrophobic association. Rheological and microcalorimetric results indicated that the change in the thermodynamics of gelation of the HPMC aqueous solution was related to the salt type and concentration, and the effect of monovalent salts was found to be more cooperative than that of multivalent salts on the sol–gel transition.

Elevation of the CPT of HPMC by sodium perchlorate, sodium iodide and sodium thiocyanate may be the result of the 'salting in' effect of perchlorate, iodide and thiocyanate anions respectively [22]. The increase in the solubility of the polymer is postulated to arise from the adsorption of the large anions of relatively low water affinity onto the macromolecule [19]. Such ions carry with them water molecules and thus concomitantly raise the degree of hydration of the polymer [18, 22, 35]. Nakano and co-workers (1999) have studied the effect of ions on CPT of HPMC using UV spectrophotometry at a wavelength of 600 nm. They found that HPMC solutions containing sodium thiocyanate and sodium iodide had a raised CPT and the anions appeared to disrupt the hydrogen bonding between water molecules sheathing the polymer. This increased the interaction of water with the polymer raising the energy required for dehydration and resulted in a higher CPT [22].

Salts can alter the disintegration characteristics of HPMC matrices by influencing the hydration properties of the polymer. The influence of salts, both internal and external, on the behaviour of dosage forms is discussed in the following sections.

6.2.2 Internal Influence of Salts on Dosage Form Behaviour

As discussed earlier, salts can be incorporated into matrices for many reasons. For example, citrate, phosphate buffers and alkalising agents such as carbonates and magnesium salts have been used for microenvironmental pH control to improve the solubility of weakly acidic drugs [36]. However, there is a paucity of information investigating the effect of incorporating salts into hydrophilic matrices. The inclusion of citrate in an HPMC matrix, for example, has been found to accelerate drug release beyond the anticipated improvement in solubility, leading to the conclusion that citrate was interfering with HPMC hydration through a Hofmeister effect, resulting in a weaker HPMC barrier [11]. Therefore water uptake was increased in the early stages of matrix hydration, with the effect of accelerating drug release. In a subsequent study [37], tris(hydroxymethyl) aminomethane (THAM) was proposed as an alternative suitable buffering agent for hydrophilic matrices, as THAM did not elicit a strong Hofmeister effect and did not depress the thermal gelation temperature of HPMC.

6.2.3 External Influence of Salts on HPMC Matrix Behaviour

Salts can also provide an external challenge to the hydrating matrix within the GI tract. Salts can originate from physiological challenge, such as the secretion of gastric acid within the stomach to provide a typical gastric ionic strength of 0.05–0.15 M, from the ions secreted in the small intestine and from the concomitant intake of foods, drinks and other medicines.

Lapidus and Lordi first reported how the presence of electrolytes within the experimental medium could influence drug release from HPMC matrices [38]. Numerous further researches have corroborated and elaborated on this early work, finding that chloride and phosphate [17, 23, 39] could also change drug release rate. As ionic strength of the medium was raised from zero, an enhanced swelling of the matrix gel layer was observed, leading to increasingly lower drug dissolution rates as a result of the increased diffusional path length. At increased ionic strengths, the erosional rate was increased [40]. Above a certain ionic strength, a value which varies according to the matrix formulation, polymer type and lyotropic classification of the salt, water activity was reduced to such an extent that uniform polymer hydration did not occur, and incomplete gel layer formation resulted in burst release of drug from the matrix [41]. Fagan et al. [23] reported that this catastrophic disintegration of hydrophilic matrices occurred because the salt (chloride and phosphate) concentration caused a lowering of the cloud point temperature of the polymer to that of the medium. Confocal microscopy images [42] have illustrated the early gel layer growth of HPMC matrices in a salt environment, depicting the increased swelling at lower ionic concentration that serves as a greater barrier to drug release, until 0.75 M NaCl when polymer particles clearly failed to coalesce into a gel layer. The failure to form a limiting diffusion barrier resulted in enhanced liquid penetration of the core, and the swelling of particles that did not coalesce culminated in surface disintegration.

Asare-Addo et al. [43] reported that the low viscosity grade of HPMC (K100LV) was more sensitive to increases in ionic strength than higher viscosity grades, with a greater erosional rate [40]. Additionally, HPMC2910 (METHOCEL E4M) was more sensitive to ionic strength changes probably associated to its higher methoxy substitution compared with HPMC2208 (K grade polymer). This can provide for increased polymer–polymer interactions which can be disrupted by the added ions manifesting as an increased sensitivity to ionic strength [44].

6.3 Interactions Between Sugars and Hydrophilic Carrier Materials

In comparison with the literature exploring the influence of salts on HPMC performance, there are only a few papers describing the effect of sugars on polymer properties and dosage form behaviour. In one of the early pioneering studies, Levy and Schwartz [19] demonstrated how sucrose and sorbitol reduce the sol–gel transition temperature of HPMC solutions. Lactose has also been reported to reduce the sol–gel transition temperature of methylcellulose, although it showed a lower potency than sodium chloride and other ionic salts [15].

The mechanism of interaction appears to be closely linked to sugar structure [45]. Punitha et al. (2014) found there were strong molecular interactions between the studied sugars (sucrose, fructose and lactose) and 0.4 M HPMC solutions and that the strength of the interaction was related to the sugar concentration. FTIR

studies showed lactose formed the strongest bonds with HPMC due to reduced steric hindrance compared to other sugars allowing strong hydrogen bond formation. A study with a copolymer solution (PPO–PEO) correlates with conclusions above [46] with equatorial hydroxyl groups on the sugar, and the molecular size of the sugar was found to be key in the interaction with water cages around hydrophobic groups on the polymer. With increased number of saccharide units, the reduction of lower critical solution temperature (LCST, CPT) was less pronounced. Williams et al. [47] suggested that the change in cloud point temperature was related to molar hydroxyl number, the orientation of the C(4) hydroxyl and the beta $1 \rightarrow 4$ linkage, all factors which influence sugar compatibility with the water structure and, by inference, the HPMC polymer hydration sheath.

Williams et al. [48] investigated the mechanism by which dissolved sugars influence drug release from HPMC matrices and structure–activity relationships with different sugars. It was found that low concentrations of dietary sugars retarded drug release in in vitro tests, but above a critical solute concentration [$S_{(CRIT)}$], there was marked acceleration of release, in a similar fashion to that observed with salts (discussed earlier in chapter). Studies of early gel layer formation suggested this resulted from sugar-induced suppression of HPMC particle swelling and coalescence, leading to gel structures with poorer diffusion barrier properties and reduced resistance to physical erosion. Sucrose, lactose, D-glucose, D-galactose and D-FRUCTOSE all exhibited this pattern, but $S_{(CRIT)}$ values varied widely between sugars (0.5 M lactose, 1.15 M D-fructose). The ability of the sugar to depress the polymer sol–gel transition temperature (Delta CPT) exhibited a linear relationship with $S_{(CRIT)}$ value.

A subsequent study investigated how the presence of internal and external sugars affects drug release [47]. In a model matrix containing 30 % HPMC (Methocel (TM) K4M), the inclusion of sugar as a tablet diluent was a key factor. Lactose–microcrystalline cellulose mixtures, dextrose and D-xylose all produced highly swollen, erodible matrices in 0.7 M sucrose which collapsed and rapidly released remaining drug after 1–4 h. In contrast, matrices containing microcrystalline cellulose as the sole diluent provided extended release in 0.7 M sucrose for 10 h. This suggests that internal and external sugars combine to disrupt the diffusion barrier properties of the gel layer.

Radwan et al. [49] report an indirect interaction between HPMC and drug release in high-sucrose solutions in dissolution tests. They found that water diffusivity in sucrose solutions decreased as concentration increased, with reduced water dynamics and reduced drug dissolution. The diffusivity was reduced additionally than for salt solutions at the same osmolality. They explained the difference between salt and sugar solutions by the presence of hydrogen bonding between sugar molecules, an effect not expressed in sodium chloride solutions.

Salts such as sodium chloride and sodium citrate can produce additive effects in combination with sugars and so can reduce the amount of sugar required to cause accelerated release. The amounts of sugar that would then impact drug release would be similar to concentrations found in high-sugar soft drinks [32].

Lactose is commonly used as a diluent within pharmaceutical formulations. It is well known that the presence of a highly water-soluble excipient, such as lactose, within hydrophilic matrices can increase soluble drug release rate, with several studies comparing lactose to less soluble alternatives such as dicalcium phosphate, microcrystalline cellulose and starch [50–55]. In these studies, the mechanism by which lactose increases release rate is thought to be owing to the increased uptake of water in the early phase of hydration, altering the drug diffusivity in the gel layer, with no suggestion of a direct interaction between HPMC and lactose. However, given the evidence of an interaction by Williams et al. [47], it would be prudent to assess the risk of seemingly inert excipients within a HPMC formulation.

6.4 Interactions of HPMC with Surfactants

The interaction between polymers and surface active agents, or surfactants, has been the focus of research within many different industries because of their potential to alter the polymer solution properties. Surfactants are amphiphiles which possess both hydrophilic (polar head group) and hydrophobic (nonpolar tail) domains. They can be anionic, cationic, zwitterionic or nonionic depending on their hydrophilic head group. At low concentrations, surfactants adsorb to interfaces such as air and water or water and oil. At an appropriate concentration (the critical micelle concentration or CMC), surfactants can associate into regular structures called ‘micelles’. In a hydrophilic solvent such as water, the important characteristic of micelles is that hydrocarbon chains (hydrophobic tails) constitute the inner part or core of the micelle whereas the polar head groups are positioned in a thin layer at the surface of the micelle. Surfactants can lower surface tension and can therefore be used to solubilise poorly water-soluble compounds or as wetting or emulsifying agents.

Surfactants have long been proposed as excipients which can modify drug release profiles from hydrophilic matrices [56–58], as they can change the viscosity of nonionic polymers [59, 60].

6.4.1 Mechanism of Surfactant Interaction with HPMC

The relationship between surfactant concentration and surface tension lowering is shown in Fig. 6.1 (dotted line), but in the presence of polymers, this behaviour can be modified. Whilst this diagram represents the generalised behaviour of these systems, the underlying molecular interactions can be complex and they depend on the properties of the individual polymer and surfactant. In the simple surfactant system, there is a lowering of surface tension with an increase in surfactant concentration, a result of surfactant adsorption at the interface. At a critical concentration, the critical micelle concentration (CMC), surface tension remains constant as surfactant micelles start to form [61, 62].

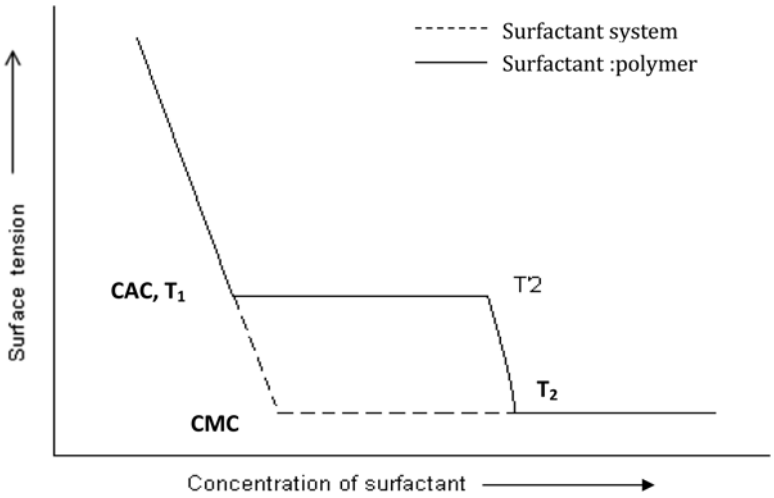

Fig. 6.1 Schematic plot of the surface tension of surfactant solutions as a function of surfactant concentration in the presence of polymer. *CAC* critical aggregation concentration, *cmc* critical micelle concentration, T_1 the onset point of CAC, T'_2 the saturated point of polymer–surfactant association, T_2 the cmc reached point (Adapted data from [61])

With a polymer–surfactant, there may or may not be a lowering of surface tension, depending on the surface activity of the polymer. At a certain critical concentration (the so-called critical association concentration, critical aggregation concentration or CAC), there is an onset of surfactant–polymer association. Above this concentration, there is no increase in surfactant activity and thus no further reduction of surface tension until the polymer is saturated with surfactant (T′2). Thereafter, the free surfactant concentration and surface activity start to increase again, and surface tension is further reduced until a critical micelle concentration (CMC) is reached (T2); after which surface tension remains constant [61, 62]. Silva [63] found there were three regimes as a function of SDS concentration. There was an initial decrease in viscosity, up to the CAC, followed by a drastic increase until the proximity of the PSP (T′2), when viscosity starts to decrease again. Surfactant/polymer systems that exhibit this behaviour include ionic surfactants and uncharged polymers, and examples include SDS/poly(vinylpyrrolidone) (PVP), SDS/PEO, (anionic or cationic) surfactant/poly(vinyl alcohol), PEO, PVP or MC [64, 65].

There are many factors which can influence the association between surfactants and polymers, and these include (1) temperature, (2) addition of electrolyte, (3) surfactant chain length, (4) surfactant structure, (5) surfactant classes, (6) polymer molecular weight, (7) amount of polymer and (8) polymer structure and hydrophobicity.

The interactions between nonionic polymer solutions and surfactant have been widely investigated. Nilsson [66] studied the interactions between HPMC and the anionic surfactant sodium dodecyl sulphate (SDS) in water using viscometry,

equilibrium dialysis, cloud point determinations, dye solubilisation and fluorescence spectroscopy. He proposed that SDS adsorbs in a cooperative manner as molecular clusters, forming small micelles, the cores of which are able to solubilise the methoxy-rich 'junction zones' (hydrophobic regions) of the HPMC polymer chain. This increases the polymer solubility and raises the cloud point temperature. Important rheological effects such as high viscosity are observed over a fairly limited composition range beginning at the onset of adsorption and ending long before adsorption saturation is reached. The maximum capacity of adsorption in HPMC was found to be of the order of one adsorbed amphiphile molecule per polymer monomer unit.

Since adsorption depends on the magnitude of the hydrophobic bonding free energy, the amount of surfactant adsorbed directly increases with increasing surfactant alkyl chain length according to Traube's rule [62]. This rule, for hydrocarbon surfactants, states that the concentration of surfactant at which a given reduction of surface tension is observed decreases in a regular progression with each $–CH_2–$ unit in the homologous series [67, 68].

There are also other types of surfactant–polymer interaction, for example, (1) surfactants and hydrophobically modified polymers, which results in an association structure, e.g. SDS/HM-HEC (or hydrophobically modified hydroxyethyl cellulose), and (2) surfactants and polyelectrolytes which are opposite-charged polymers and results in a strong intermolecular association, e.g. SDS/cationically modified cellulosic polymer (or Polymer JR, Union Carbide), cationic surfactants–anionic polyelectrolytes.

6.4.2 Behaviour of Surfactant/HPMC Solutions

There have been several studies that investigate the behaviour of aqueous solutions of HPMC in the presence of surfactants. Kulicke et al. [69] have investigated three highly substituted, hydrophobic grades of HPMC each in admixture with the anionic surfactant sodium lauryl sulphate (SLS). In the absence of anionic surfactant, the aqueous HPMC solutions showed predictable polymer solution flow behaviour. The most hydrophobic HPMC displayed clearly the effects of an SLS-dependent viscosity increase and the appearance of dilatant flow. At constant HPMC concentration (0.5 % w/w), a 15-fold increase in viscosity was observed in the critical micelle concentration range for SLS.

Wittgren et al. (2005) have used size exclusion chromatography (SEC) with online multi-angle light scattering (MALS) and refractometric index (RI) detection to characterise the surfactant–polymer interaction between various cellulose derivatives including HPC, HPMC and HEC and the surfactant sodium dodecyl sulphate (SDS) [70]. The more hydrophobic HPC and HPMC adsorbed surfactant to a significantly greater extent than HEC. The interchain interactions at compositions close to the critical aggregation concentration (CAC) were clearly seen for HPC and

HPMC as an almost twofold average increase in the apparent molecular mass of the complex.

Sovilj [71] used conductivity, viscosity and rheological measurements to study the interaction of HPMC with the anionic surfactant SDS in aqueous solutions. The concentration of SDS at which interaction starts [the critical aggregation concentration (CAC)] and at which it ends [polymer saturation point (PSP)] was determined, and an interaction mechanism was proposed. The linear relationship was found between the PSP and HPMC concentrations, whilst CAC remained constant. In addition, it was found that stability of the emulsions was influenced by the HPMC–SDS interaction.

A second paper [72] expanded these studies to examine a ternary system composed of two cellulose derivatives, anionic sodium carboxymethylcellulose (NaCMC) and nonionic HPMC and the anionic surfactant sodium lauryl sulphate (SDS). Rheological investigations showed that HPMC and NaCMC molecules interact with each other with a synergistic effect on viscosity. This synergistic effect disappears with SDS addition. In such a system, depending on the mass ratios of the components, various interactions between HPMC–NaCMC, HPMC–SDS and NaCMC–(HPMC–SDS) take place. Phase separation depends on the HPMC–SDS interaction and influences turbidity and viscosity of the system.

A study by Silva at al. [63] studied the interaction between SDS and HPMC, specifically looking at the effect of HPMC concentration and temperature. For dilute HPMC solutions (up to 0.5 %), the CAC remained constant, with an approximately constant calculated free energy of SDS association suggesting that the process of micellisation is slightly less spontaneous than in the absence of HPMC. When HPMC concentration increases above 0.5 %, there is an increase in the absolute value of free energy to surpass that of the system without HPMC. In a similar manner to the results of Sovilj, the polymer saturation point exhibited a linear relationship with HPMC concentration. As temperature increased from 25 °C to 50 °C, the SDS association process became more and more favourable. Su et al. [73] studied the same system, finding that the addition of SDS at different concentrations showed dissimilar influences on the gelation of HPMC; SDS at lower concentrations (≤6 mM) did not affect gelation temperature significantly except for enhancing the heat capacity, whilst SDS at higher concentrations (≤6 mM) not only resulted in the gelation of HPMC at higher temperatures but also changed the pattern of the gelation DSC thermograph from a single mode to a bimodal. They proposed that the bimodal graph was the result of SDS binding to the available sites of the HPMC chain either as a monomer or a small micelle of low aggregation number when SDS concentration was increased. One bonded micelle might be shared by two or more HPMC molecules, creating a three-dimensional network. Upon heating the HPMC/SDS mixture both the SDS micelles and water cages needed removing to expose the HPMC hydrophobic group, resulting in later association of HPMC hydrophobic chains with delayed gelation [73].

In an expansion of the work which had previously focused on the SDS–HPMC reaction, Joshi et al. [74] looked at three anionic surfactants [sodium *n*-dodecyl

sulphate (SDS) alongside sodium *n*-decyl sulphate (SDeS) and sodium *n*-hexadecyl sulphate (SHS)] and one nonionic surfactant (Triton X-100). The effect on the thermal behaviour of HPMC was different for anionic and nonionic surfactants. The anionic surfactants increased the energy barrier of the sol–gel transition through their binding to the hydrophobic parts of the HPMC chain, hindering free access at elevated temperature. Differences in the chemical structure and electrostatic interaction between the surfactant and HPMC molecules determined the magnitude of the effect. DSC curves for the nonionic surfactant Triton X-100 showed only a weak interaction between the surfactant and HPMC, owing to the lack of polar head group, resulting in minimal change to the gelation properties of HPMC.

6.4.3 Interaction Between Surfactants and Hydrophilic Matrix Dosage Forms

As anionic surfactants are able to increase the viscosity of cellulosic polymers, they have been incorporated into hydrophilic matrices to change release rate profiles. Daly et al. [58] were one of the first group to study the effect of adding a surfactant (sodium lauryl sulphate, SLS) to HPMC matrix formulations in an attempt to achieve a more sustained action. It was found that SLS retarded drug release, with the extent dependent upon the concentration of surfactant incorporated. The effect was found to occur for both cationic and anionic drugs, which lead them to conclude that retardation of drug release was unlikely to be the result of an interaction between a cationic drug and anionic surfactant.

Subsequent work by Feely and Davis [57] found that the retarding effect was both dependent on the concentration of the surfactant but also the drug and surfactant having opposite charges. The formation of a drug–surfactant complex with low solubility was their mechanism for retardation of drug release, rather than an increase in viscosity. Subsequent studies found that a cationic drug (propranolol) was able to interact with anionic surfactants, namely, SDS [56] and Eudragit S [75], to form an insoluble product, hence slowing drug release. A similar result was observed with captopril matrices, where drug release was altered depending upon the type and concentration of the surfactant [76]. Nonionic surfactants did not lead to extended drug release, indicating that the observed behaviour is restricted to anionic surfactants [58]. In a study where the anionic surfactant (SLS) decreased propranolol release rate owing to complexation, it was found that a combination of cationic (CTAB) and anionic surfactant (SLS) increased drug release rate, as the surfactants interact with each other, thus decreasing the number of interacting anionic molecules with the cationic drug [77]. Nokhodchi et al. [78] found that the presence of SLS within the matrix increased the drug release rate of theophylline, with kinetic analysis suggesting the contribution of erosion fell as the concentration of SLS rose.

The presence of a surfactant (SLS) within dissolution media has been found to accelerate release of a poorly water-soluble drug (nimodipine) from HPMC matrices

[79], owing to a combined effect of an increased solubility of the drug in the SLS media and accelerated erosion of HPMC matrix tablets by the surfactant. This mechanism differs from ionic hydrophilic drugs where drug–surfactant ionic interactions retard drug release.

Despite solution behaviour that suggests surfactants may increase viscosity of HPMC, this has not been shown to be a mechanism which affects drug release from hydrophilic matrices; instead drug release is altered through complexation and changes in drug solubility which are capable of modifying drug release profiles.

6.5 Interactions Between Drugs and HPMC

As discussed above, the performance of HPMC as an extended-release carrier material can be affected by incompatibilities with electrolytes and other small molecules. The disruption to HPMC solubility and gelation characteristics can manifest in failure of the pseudo-gel layer and consequently immediate drug release profiles. Drugs may possess the key structural elements with the potential to interact with HPMC. Highlighting and understanding the molecular structures responsible for cellulose ether incompatibilities would be of significant value for solid dosage form formulation scientists working in both academia and industry.

Beyond interactions with simple soluble species, there have been several reports that drugs may influence and alter the physiochemical properties of nonionic cellulose ethers, including the thermal properties, as shown in Table 6.1.

Table 6.1 Effect of commercial drugs on the thermal properties of nonionic cellulose ethers

Drug	Polymer	Thermal properties		References
		CPT (°C)	Sol–gel (°C)	
Nicotinamide	HPMC	↑		Hino and Ford [80]
Ibuprofen Na	EHEC HPMC	↑		Ridell et al. [81]
Propranolol HCl	HPMC	↑		Mitchell et al. [17]
Promethazine	HPMC	↑		Mitchell et al. [17]
Aminophylline	HPMC	↑		Mitchell et al. [17]
Tetracycline HCl	HPMC	↑		Mitchell et al. [17]
Theophylline	HPMC	↔		Mitchell et al. [17]
Quinine bisulphate	HPMC	↔		Mitchell et al. [17]
Chlorpheniramine maleate	MC		↑	Touitou and Donbrow [15]
Potassium phenoxypenicillin	MC		↑	Touitou and Donbrow [15]
Salicylic acid	MC		↓	Touitou and Donbrow [15]
Diclofenac Na	HPMC	↓	↓	Rajabi-Siahboomi [82]

Arrows denote: ↑ increase, ↓ decrease, and ↔ no change
CPT cloud point temperature, *Sol–gel* sol–gel transition temperature

6.5.1 HPMC–Drug Solution Interactions

Touitou and Donbrow [15] used viscosity–temperature curves to examine the effect of drugs on the sol–gel transition temperature of MC. Potassium phenoxypenicillin and chlorpheniramine maleate raised the sol–gel transition temperature of MC. The effect is explained on the basis that the drugs are adsorbed onto the macromolecule, carrying with them water molecules raising the degree of hydration of the polymer. No direct evidence to support this hypothesis was provided. The failure of compressed matrices of MC containing these drugs to undergo attrition or disintegration, unlike the matrices from which these agents were absent, suggests that these drugs were the cause of stabilisation of these matrices. Reduction of the gel point by salicylic acid may be a result of the formation of a complex of low solubility with the macromolecule.

Mitchell and co-workers [17] examined the effect of drugs on the thermal properties of HPMC solutions. Propranolol hydrochloride and promethazine hydrochloride were found to increase the CPT of HPMC. This effect on the solution properties was found to be more prominent at higher drug concentrations. Promethazine is amphiphilic and therefore behaves as a surfactant in solution and associates at concentrations greater than 0.5 % w/v. Propranolol hydrochloride is weakly surface active; therefore the response of HPMC in the presence of these drugs may be associated with the surface activity of the drugs. Aminophylline and tetracycline gave straight-line relationships between their concentration in solution and the observed CPT. Quinine bisulphate and theophylline did not affect the CPT. They suggested that the hydrating effect of the quinine molecule was counteracted by the dehydrating effect of the sulphate ions; however, no direct evidence to support this hypothesis was provided.

McCrystal and co-workers [83, 84] used differential scanning calorimetry to investigate the effect of propranolol hydrochloride and diclofenac sodium on the distribution of water in HPMC gels. An increase in the number of moles of bound water per polymer repeating unit was reported for diclofenac sodium, whereas propranolol hydrochloride had no effect. It was hypothesised that diclofenac sodium causes the polymer to ‘salt out’, making it less soluble and requiring more water to bind to the polymer to keep it in solution. These observations support the findings of Rajabi-Siahboomi [82] who found that diclofenac sodium reduced both the sol–gel transition temperature and CPT of HPMC solutions.

The effects of nicotinamide on the properties of aqueous HPMC solutions were studied by Hino and Ford [80]. Nicotinamide exhibited a ‘salting in’ effect on the HPMC solutions resulting in an increase in gelation temperature and CPT. It was proposed that these effects were considered to be due to the hydrogen bonding of nicotinamide to the hydrophilic groups of HPMC molecules.

The aqueous interaction of the sodium salt of ibuprofen with the cellulose ethers ethyl hydroxyethyl cellulose and HPMC has been investigated by cloud point, capillary viscometry, equilibrium dialysis and fluorescence probe techniques [81]. The amphiphilic drug, ibuprofen, formed micelles in pure water, as monitored by

fluorescence and microviscosity measurements. At the critical micelle concentration (CMC) of the drug, a marked increase in the CPT of the cellulose ethers was reported. Above the CMC, it was postulated that micelles of ibuprofen solubilise the hydrophobic parts of the polymer and therefore increase the CPT [81] as was discussed previously with surfactants.

In a follow-up study [85], fluorescence probe techniques together with microcalorimetry and dye solubilisation were used to study the interaction between nonionic polymers and anionic surfactants with different monovalent counterions in order to examine the effects of the counterion. The polymers used were the cellulose ethers hydroxypropyl methyl cellulose (HPMC) and ethyl hydroxyethyl cellulose (EHEC). The surfactants were dodecyl sulphates with potassium, sodium and lithium as counterions (KDS, NaDS, LiDS). The counterion influenced the interaction start concentration as well as the nature of the mixed aggregates formed. The interaction start, according to surfactant concentration, was found to be in the order KDS < NaDS < LiDS for both polymers and aqueous solution. From fluorescence measurements, it was found that the KDS-polymer aggregates shield pyrene from water better than the other surfactants, indicating larger aggregates with a more fluid interior. The microcalorimetry measurements confirm that the adsorption of the surfactants onto the polymer is endothermic and entropy driven at the start, and as more clusters are formed on the polymer chains, the process converts to being exothermic and driven by both enthalpy and entropy.

In a more recent study [86], the solution interactions between HPMC with two nonsteroidal anti-inflammatories—the sodium salts of diclofenac and meclofenamate—were investigated using tensiometric, rheological, NMR, neutron scattering and turbidimetric techniques. The two drugs behaved very differently, meclofenamate addition to HPMC solutions led to substantial increases in viscosity, a depression of the gel point and a marked reduction in the self-diffusion coefficient of the drug, whereas diclofenac did not induce these changes. Collectively, these observations are evidence of meclofenamate forming self-assembled aggregates on the HPMC, a phenomenon not observed with diclofenac Na. Any process that leads to aggregation on a nonionic polymer will not be strongly favoured when the aggregating species is charged. Thus, it is hypothesised that the distinction between the two drugs arises as a consequence of the tautomerism present in meclofenamate that builds electron density on the carbonyl group that is further stabilised by hydrogen bonding to the HPMC. This mechanism is absent in the diclofenac case and thus no interaction is observed. These studies propose for the first time a molecular basis for the observed often unexpected, concentration-dependent changes in HPMC solution properties when co-formulated with different NSAIDs and underline the importance of characterising such fundamental interactions that have the potential to influence drug release in solid HPMC-based dosage forms.

The effects of two cationic drugs [imipramine hydrochloride (IMP) and promazine hydrochloride (PMZ)] and one anionic compound [sodium salt of ibuprofen (IBF)] on the clouding behaviour of HPMC were investigated by Khan et al. [87]. Though all the three drugs increase the cloud point (CP) of HPMC, the effect was found to be minimum in the case of IBF. Further, the effect of adding salts

(NaF, NaCl, NaBr, $NaNO_3$, Na_2SO_4, Na_3PO_4, KCl, KBr, KNO_3) in the presence of drugs (IMP and PMZ) on the CP of HPMC was seen. Almost linear decrease in the CP was observed with the [salt] at fixed concentrations of these drugs, whereas in the absence of drugs, the drop in the CP was slight. The energetic parameters [Delta G(c)(0), Delta H-c(0) and T Delta S-c(0)] were evaluated and implied that the disruption of water structure becomes significantly prominent at lower concentrations of the drugs at fixed salt concentrations.

Incompatibilities between cellulose ethers and small aromatic molecules have been reported. The British Pharmacopoeia monograph for methylcellulose lists incompatibilities with chlorocresol, hydroxybenzoates and phenol [88]. Touitou and Donbrow [15] found that salicylic and p-hydroxybenzoic acid reduce the gelation temperature of methylcellulose solutions, a property which may be predictive of a cellulose's ability to form a functional gel layer [89]. Small aromatic molecular species are present in many drug molecular structures as key active moieties (e.g. nonsteroidal anti-inflammatory drugs, bronchodilators, anti-Parkinsonian drugs) and may therefore be co-formulated with HPMC and other cellulose ethers.

The influence of the physicochemical parameters of substituted aromatic molecules on the phase transition from sol to gel of hydroxypropyl methylcellulose (HPMC) was investigated using a homologous series of substituted phenols [90]. Using a turbimetric methodology, concentration-dependent suppression of phase transition temperature of HPMC was observed for phenol and its derivatives, including methyl-, nitro- and chloro-substituted molecules. Although no strong direct relationship between single molecular physicochemical properties of the phenolic compounds (such as pKa, LogP and other molecular descriptors) and ΔCPT was found for the compounds tested, a successful prediction of behaviour could be obtained by using a combination of parameters. This suggested that the interaction mechanism between HPMC and the substituted aromatic moiety is a complex summation of the different molecular physicochemical properties.

6.6 Interactions of HPMC Matrices with Fats

Dietary fats have the potential to interact with hydrophilic matrix tablets when ingested with food. Through in vitro drug release and combined imaging studies, it has been shown that fats can directly influence drug release from HPMC (Methocel K4M) matrices [91]. The model fat systems examined included milk (0.1–3.5 % fat) and the parenteral emulsion intralipid (R) (20–30 % fat). The matrix showed good extended-release properties for at least 12 h in these media (USP-1/USP-4), but at the highest fat concentration, release was retarded and shifted towards zero-order release. Confocal imaging studies using a water-soluble (fluorescein) and fat-soluble (Nile red) fluorophore provided evidence of phase separation of intralipid (R) at the surface of the emerging gel. Combined magnetic resonance imaging-USP-4 drug release testing provided further evidence for deposition of fat on the tablets. It was proposed that the aqueous portion of the emulsion is removed by the

hydrating matrix, causing coalescence and deposition of a fat layer at the surface, and these deposits cause slower drug release by reducing the matrix surface area available for release. Therefore, it was concluded that there is a risk of a direct interaction between fat emulsions and HPMC tablets, with resultant effects on drug release in vitro.

Franek et al. [92] discussed the influence of Ensure Plus® (a nutritional drink similar in composition in terms of fat, carbohydrate, protein content and calorific values to the FDA standard breakfast meal) on the release of drug from HPMC matrices. Akin to results seen by Williams (above), Ensure Plus was found to form a hydrophobic barrier around the tablet; able to decrease water penetration to retard drug release. This observed interaction between Ensure Plus® and the HPMC tablets may translate into decreased drug release rate in the fed stomach, which may decrease the amount of drug available for absorption in the small intestine and thus reduce systemic drug exposure and maximum plasma concentration.

6.7 Judicious Formulation Strategies to Mitigate Against HPMC–Excipient/HPMC–Drug Interactions

As a consequence of investigations into the interaction between HPMC and drugs and excipients, strategies have been developed in an attempt to mitigate the effect. Viriden et al. [93] found that the heterogeneity of substitution of particular HPMC batches can influence polymer interactions with model drugs. The cloud point of the most heterogeneous batch was more affected by the model drug substances, methylparaben and butylparaben, and mostly by butylparaben (the more hydrophobic of the model compounds, with the lowest solubility. The different clouding behaviour was explained by the heterogeneously substituted batches being more associative and the more lipophilic butylparaben being able to interact more efficiently with the hydrophobic transient cross-links that formed. Interestingly, tablet compositions of the heterogeneously substituted HPMC batches released the more soluble methylparaben at lower rates than butylparaben. The explanation is that the hydrophobic HPMC interactions with butylparaben made the gel of the tablet less hydrated and more fragile and therefore more affected by erosional stresses. In contrast, drug release from compositions consisting of the more homogeneously substituted batches was affected to a minor extent by the drugs and was very robust within the experimental variations. The study thus revealed that there can be variability in drug release depending on the lipophilicity of the drug and the substituent heterogeneity of the HPMC used.

In a subsequent study [94], the release of poorly soluble carbamazepine was found to be significantly affected by HPMC heterogeneity as polymer erosion was slower, and this is the dominant mechanism by which poorly soluble drugs are released.

Williams et al. [47] found that selection of a small HPMC particle size (<63 μm) or high-viscosity HPMC (Methocel K100LV) improved resistance of the matrix to increase external sugar concentration as a stronger gel layer was formed. By judicious

selection of excipient properties, the tolerance of HPMC matrices to highly challenging environments was significantly improved. Further studies in this area are warranted as opportunities for robust formulation design.

6.8 Conclusions

Although relatively uncomplicated from a conceptual point of view, the HPMC hydrophilic matrix has hidden complexities with respect to the design and development of a robust formulation. Many of these elements come from an appreciation of the interaction possibility between drugs, salts, fats, sugars and other materials with the HPMC polymer that can affect performance. When designing formulations with an objective to engineer dosage form robustness, the formulator should consider the possibility of interactions leading to changes to behaviour and performance of the dosage form both in vivo and in vitro. This chapter has reported the key studies in the area; it remains critical to assess the risks of interactions and design formulations accordingly to reduce the risk and maximise formulation robustness.

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Chapter 7
In Vitro Physical and Imaging Techniques to Evaluate Drug Release Mechanisms from Hydrophilic Matrix Tablets

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7.1 The Use Physical and Imaging Techniques in the Evaluation of Hydrophilic Matrices

As detailed earlier in this book, the crucial role of the gel layer in controlling drug release from hydrophilic matrix tablets has meant that it has been a natural focus for study. Early papers described methods for measuring gel dimensions and the kinetics of gel growth, while more recent publications describe the use of highly sophisticated techniques which probe the internal properties of the gel layer, the behaviour of excipients, and the early stages of particle hydration and coalescence that lead to the establishment of the gel barrier. These techniques may help us develop an understanding of the underlying processes, and may potentially provide evidence for the mechanisms of drug release.

Drug release from hydrophilic tablets is controlled by the physical changes in tablet structure associated with hydration, gelling, swelling, erosion and eventual

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dilution of the drug and polymer within the tablet. The rate-controlling processes are physical rather than chemical and are therefore well suited to being followed using physical methods. Physical characterisation of the dosage form enables changes in the state of the dosage form to be monitored, and followed with time in order to provide a correlation with the drug release profile. Following these changes with respect to time is particularly important because the dominant mechanism of drug release may change over the course of the drug release process. For example, even the simplest hydrophilic matrix, containing a water-soluble drug, undergoes several stages in its release cycle: at first, an 'initial burst' driven by drug solubility as drug within the gel layer dissolves during gel layer formation, then drug release by diffusion and erosion in a pseudo steady state, and finally the release of remaining drug by core collapse, or diffusion through a fully gelled matrix.

Various imaging techniques have been used to study gel layer growth, morphology, and other features that might promote or retard drug release. They offer a complementary approach to physical measurements often allowing hydration, swelling, and release to be followed with time in a single tablet. Those considered to provide the widest applicability and potential are described here, accompanied by selected studies to illustrate what information may be obtained. However, the list of techniques is not exhaustive and within the methods described there are many challenges and pitfalls. For example, it is often difficult in optical and NMR imaging to simultaneously determine with accuracy the position of the core/gel and the outer gel/aqueous boundaries. These boundaries are alternatively referred to as the 'diffusion front' or 'swelling front' and the 'erosion front' respectively. In addition, chemical and physical mapping techniques require suitable controls and calibration to be meaningful and produce data that provides confidence in its translation to the in vivo situation.

7.2 In Vitro Drug Release Testing and Characterisation

The environment in which a hydrophilic matrix tablet is hydrating may influence the relative contributions of the various mechanisms to release [1]. For a diffusional mechanism to contribute to drug release, the drug needs to have a sufficiently high solubility to dissolve within the gel layer and for its rate of dissolution in the gel layer to be faster than its rate of release into the bulk solution at the periphery of the gel layer. The concentration of drug dissolved behind the diffusion front, the region in which drug in the dry core exists in equilibrium with drug in the aqueous phase of the hydrated gel layer, is determined (1) by the amount of drug present, (2) the drug solubility in relation to the water concentration gradient within the gel layer, and in cases where the drug has a pH-dependent solubility [2], (3) and the pH microclimate within the gel layer [3]. In the case of an ionisable drug, both the dissolution of the drug and the pH of the ingressing hydration medium can influence the micro-environmental pH within the gel layer [4] and as a result can influence both the solubility of the drug and its rate of diffusion out of a matrix.

In addition to diffusion, drug is released through erosional mechanisms [5]. The release of drug by erosional processes is initiated by hydration but ultimately results from the disentanglement and dissolution of polymer particles at the surface of the tablet, and which is accelerated by mechanical forces. The rate of polymer dissolution is believed to be mass transfer limited [6] and is influenced by the degree of agitation of the dosage form, with the greater fluid movement causing a decrease in the diffusion layer thickness. Additionally, the loss of larger particles of hydrated gel is also observed, which appears to be a tablet disintegration process in direct response to shear stress. This occurs particularly (1) with low viscosity polymers, (2) at low polymer contents below the percolation threshold of the matrix, or (3) when a drug or excipient is present which reduces the ability of the polymer to form an effective diffusion barrier and allows liquid ingress into the tablet core [7].

During in vitro testing, the characteristics of the dissolution test apparatus are critical. The rate of fluid movement and shear stress generated within a particular dissolution apparatus, often described as the hydrodynamics, has the potential to influence both the rate of erosional release and the relative contributions of diffusion and erosion to the release mechanism at a particular time point during release. In summary, the dissolution medium composition, its pH, buffer capacity, solubilisation capacity, and hydrodynamics of the in vitro test apparatus all have potential to influence the mechanism of release and therefore require careful selection.

Compendial dissolution methodologies are often used in mechanistic studies as they are have standardised dimensions to a high level of precision and have been adopted worldwide. Environmental parameters such as pH and agitation rate can be well controlled.

The United States Pharmacopeia (USP) specifies standardised procedures which will provide a dosage form with a public specification from a method that is discriminating yet sufficiently reproducible. There are four different dissolution apparatus that are standardised:

1. USP Apparatus I (Basket)
2. USP Apparatus II (Paddle)
3. USP Apparatus III (Reciprocating Cylinder)
4. USP Apparatus IV (Flow-through Cell)

USP Apparatus I and II are the most frequently for solid oral dosage forms, employed with compendially recognised media volumes and rotation speeds (Fig. 7.1a, b). In the case of USP Apparatus 2 the use of sinkers and quadrangular baskets (see Chap. 5) has proved useful in cases where hydrophilic matrix buoyancy and/or vessel adhesion is a problem [8, 9].

USP Apparatus III (reciprocating cylinder) and IV (flow-through cell) are also available for use (Fig. 7.2a, b) and can be especially valuable for modified-release drug products with poorly soluble active ingredients or where a multi-pH dissolution method is required. As an example, the flow-through apparatus (USP IV) can be employed with an open-loop system and unlimited media, which is advantageous in that any pH changes are easily performed and sink conditions can be maintained indefinitely.

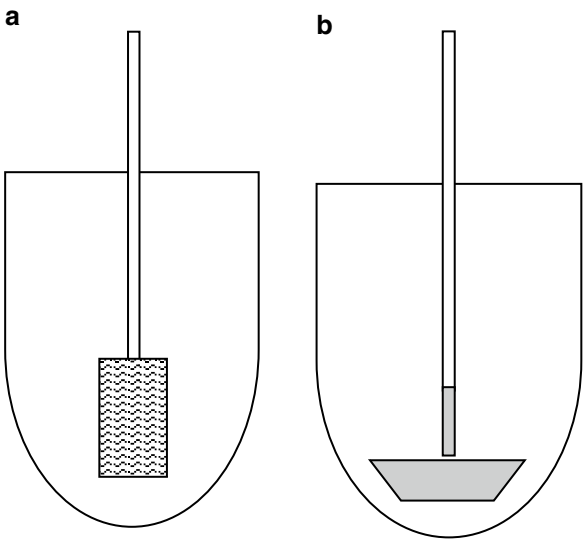

Fig. 7.1 (**a**) USP Apparatus I—rotating basket, typically 40-mesh size, at 37 °C and (**b**) USP Apparatus II—paddle, with or without sinker, at 37 °C

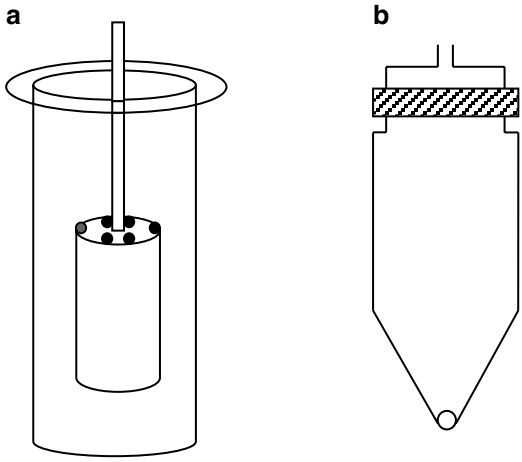

Fig. 7.2 (**a**) USP Apparatus III—reciprocating cylinder and (**b**) USP Apparatus IV—flow-through cell, with filter block at top and ruby bead sitting in aperture at bottom to be used with in conjunction with a piston pump to maintain a pulsatile flow of media

Importantly from a mechanistic perspective, the hydrodynamics and therefore the shear forces operating during a dissolution test differ significantly between the apparatus described above and with the operational parameters, such as agitation speed or flow rate, chosen. It is therefore important that the apparatus used and the parameters employed are specified when conducting mechanistic analysis as the conditions of the experiment can influence the relative contributions from different mechanisms of release.

The USP apparatus can provide well-controlled and characterised environments which are suitable for assessing in vitro drug release mechanisms and the influence of different environments such as medium composition, pH, or shear. With an appropriate choice of apparatus and experimental conditions they provide sufficient

discrimination and precision to establish good in vitro/in vivo correlations. However for the accurate prediction of in vivo performance and how gastrointestinal conditions such as fed versus fasted states might influence the drug mechanism, additional considerations are required. These are described in more detail in Chap. 12 of this book.

7.2.1 Advances in the Kinetic Modelling of Drug Release Data

A range of mathematical expressions have been developed to describe the course of in vitro drug release and the fit of various mechanistic models to dissolution data has been used to inform drug release mechanism. The majority of models applied are based on diffusion equations, utilising a case of Fick's second law of diffusion. Referring to the work of Higuchi [10], a diffusional drug release mechanism is demonstrated by a linear relationship between the drug release rate and square root of time. However, Siepmann and Peppas [11] explain that the basis on which the square root of time dependency relationship was developed rarely applies to matrix tablets. Also, it does not apply to swelling systems, as it was developed for thin, one-dimensional films and not three-dimensional systems like tablets. As discussed in earlier chapter, in hydrophilic matrix tablets, erosion of the tablet may play a role in the drug release mechanism and other mechanisms may also play a part in drug release due to the multi-component nature of a tablet dosage form.

The Peppas group therefore introduced the empirical power law equation:

$$M_t / M_\infty = kt^n$$

where M_t and $M\infty$ are the amounts of drug released at time $= t$ and infinity respectively, n is the release exponent, and k is a constant for the dosage form.

This equation has found wide utility in defining and describing drug release mechanisms [12]. The equation is typically only applied to a portion of the release profile (e.g. up to 60 % released [13]; however it is widely used to describe changes in mechanism associated with changes in formulation composition or process. Some workers have demonstrated how the equation can be applied to the whole release profile [14]. It is a significant disadvantage of this kinetic modelling approach that the exponent then represents the "averaged" release mechanism over the time period studied and does not allow for discernment of changes in mechanism over the progression of drug release. More recently, modelling efforts in this area have included very elaborate predictive mathematical models that have been developed based upon multiple complex front movements with the aim of better describing pharmaceutical dosage forms [15].

As analytical approaches have continued to evolve, elaborate predictive mathematical models have been developed which can describe multiple complex front movements, and which better describe the characteristics of real-world dosage forms. Additionally, numerical simulation approaches such as Finite Element

Method (FEM) [16] and Discrete Element Method (DEM) [17] have been utilised in order to simulate the multiple, and often interacting, drug release mechanisms that contribute to the experimentally determined release profile of a dosage form. The use of FEM simulation has been reported more frequently in this application than DEM, with FEM having being employed to describe the overlapping processes of water uptake, swelling, and erosion occurring during drug release from hydrophilic matrix systems [18–22]. Finite Volume Method (FVM), a process similar to FEM, has been successfully applied to the determination of tablet shape for higher strength version of an existing extended-release formulation, in order to ensure similar drug release and bioequivalence of the two strengths [23].

7.3 Physical Characterisation Studies

7.3.1 Swelling and Erosion Studies

The physical swelling on hydration of a hydrophilic matrix formulation can be assessed by performing physical swelling studies and a number of approaches have been described in the literature. Colombo et al. [24] describe the hydration of tablets between two Perspex sheets which enables the visualisation of radial tablet swelling, although this methodology involves the blanking off of two faces of the tablet and therefore prevents the direct correlation with drug dissolution from an hydrating compact fully exposed to liquid media.

Alternatively, tablets can be retrieved from the hydration medium and sectioned with a scalpel to enable assessment of hydration and gel layer thickness [25]. However the sectioning process is destructive and is difficult because the dry core has different resistance to cutting than the gel layer. This can introduce errors into the measurement.

In addition to hydration, erosion can be assessed. Many authors describe the use of gravimentric methods for assessing erosion and drug release, in which the quantity of formulation eroded over time is monitored by drying the sample to constant weight [26, 27]. This is a relatively crude approach that cannot distinguish the loss of different components (drug, polymer, solutes) without further chemical analysis of the tablet or dissolution medium.

A hybrid approach involving hydration, gravimetric, and drug release measurement was first published by Timmins et al. [28]. In this approach, the initial weight and dimensions (Fig. 7.3) of dry tablets were recorded. The tablets were then hydrated in a dissolution apparatus and removed at varying times in the experiment. By comparing the wet weight and dimensions of the swelled matrix (Fig. 7.4) with the initial measurements, the extent of hydration and depletion of the dry core was characterised. Furthermore, the dried weight of the residual samples could be compared with drug released during the dissolution test, in order to calculate the fraction of remaining ingredients, as a surrogate value for the extent of erosion. This was

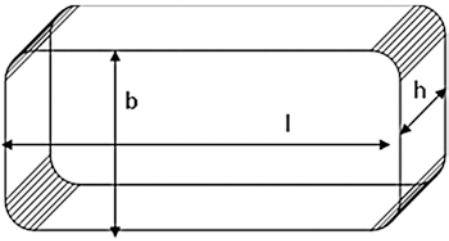

Fig. 7.3 Hydrophilic matrix tablet dimensions

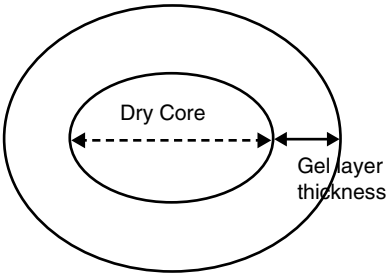

Fig. 7.4 Cross section of hydrated hydrophilic matrix tablet

defined as the fraction of ingredients remaining at a particular time point, as shown in the equation below:

At each time point t_x,

$$\text{fraction of remaining ingredients} = \frac{\text{actual dried weight}}{\text{theoretical dried weight}}$$

Where

$$\text{theoretical dried weight} = \text{initial tablet weight} - \left(\text{tablet strength} \times \text{drug release at } t_x\right).$$

This calculation is particularly important for dosage forms with higher drug loadings.

7.3.2 Measurement of Polymer Release

The direct measurement of erosion has been undertaken by quantifying the appearance of dissolved polymer in the dissolution medium [28, 29]. Polymer can be quantified using standard techniques such as size exclusion chromatography. Using this approach, Viriden et al. [30] have been able to demonstrate a relationship between substitution heterogeneity in HPMC and the polymer release of a hydrophilic matrix tablet. This work adds an intriguing insight into how HPMC polymer chemistry may influence erosion mechanisms.

A wet chemistry approach to the quantification of polymer has been described recently by Ghori et al. [31] who used a phenol-sulphuric acid assay to quantify sugars, including celluloses such as HPMC in the dissolution medium. They showed good correlation between polymer erosion rates determined using this assay and gravimetric techniques, for tablets containing binary blends of drug and HPMC. They concluded that the phenol-sulphuric acid assay allows erosion rates to be determined with fewer experiments and tablets compared to a gravimetric method. Non-polysaccharide polymers would require more modern instrumental approaches.

7.3.3 Texture Analysis

Texture analysis is a mechanical method in which a probe can be used to penetrate, shear, or cut a hydrated matrix tablet. The force required to drive the probe into the sample is monitored and can be used to identify textural interfaces or forces required to break materials. Textural analysis of hydrophilic matrix tablets has been employed in several studies in order to simultaneously determine the extent of gel layer thickness and its mechanical properties. This can provide information on gel layer and core properties in addition to the purely dimensional and gravimetric measurements described previously for swelling and erosion studies.

Yang et al. [32] have used a texture analyser technique to measure the resistance experienced by the probe as it approaches the core/gel interface in HPMC and PEO compacts. In so doing they determined the gel layer thickness which they defined as the distance between the detectable outer surface of the swollen compact and the outer surface of the core. The approach was shown to allow determination of relative front movement between the swelling front and erosion front as described by Colombo et al. [24]. They noted that the gel layer thickness in HPMC2208 matrix formulations was dependent upon molecular weight. Tablets prepared from high viscosity HPMC grades (Methocel K4M and K15M) showed similar force-displacement profiles and had similar gel thickness whereas low viscosity HPMC (Methocel K100LV) exhibited thinner gel layers. The authors proposed that this was probably due to greater erosion of the K100LV grades. The technique has been subsequently used by Pilay and Fassihi [33] to demonstrate increased gel layer rigidity in the presence of electrolytes such as sodium carbonate and tripolyphosphate.

Varma et al. [34] have employed texture analysis to explore an HPMC matrix formulation containing a basic drug and fumaric acid as a pH modifier. They showed that the presence of fumaric acid in HPMC matrices resulted in a change in the overall gel layer thickness, and the work done by the probe in the initial time points of the hydration experiment as compared to matrices without fumaric acid, suggesting a gel layer affording greater resistance to probe penetration when fumaric acid was present.

Although texture analysis can provide valuable information, care is required in the development of experimental methods sufficiently sensitive to probe the gel layer. Researchers have coated planar base surfaces with an organic coating to

render these surfaces impermeable to penetration by buffer solution and to achieve fixing of the sample onto a glass dish or slide prior to hydration [32]. In other work lateral surfaces have been also coated to prevent interfacial deformation of core/gel structure during probe advancement and confinement of swelling in the axial direction [33]. Yang et al. [32] have also used compacts cut in half diametrically and glued with the cut surface on a glass slide to enable the concurrent measurement of gel layer thickness and distance of water penetration by visual observation. Texture analysis of standard tablets samples have been undertaken to determine overall swollen tablet thickness and total tablet strength during hydration [35, 36]. However more sensitive analysis of gel layer structure can be challenging in unmodified tablets due to the semi-solid nature of the gel and its tendency to deform under pressure particularly on the lower surface of the hydrated tablet.

7.4 Imaging Hydrophilic Matrix Behaviour During Drug Release

7.4.1 Early Imaging Work

Imaging studies aimed to provide visual evidence of the often complex matrix behaviour and processes that contribute to drug release. For example, photography has been used since the inception of matrix dosage forms to illustrate morphological changes during hydration and drug release. The earliest studies often focused on simple measurements of dimensional changes in the gel layer and core. However, with the rapid advancement of instrumentation and greater accessibility of digital storage and processing in the 1980s and 1990s, it soon became apparent that more complex time-resolved information could be acquired.

In the late 1980s and early 1990s, a few pioneering studies applied more a more sophisticated imaging techniques to hydrophilic matrices. For example one early study combined cryogenic SEM with energy dispersive X-ray microanalysis (EDX) to explore gel layer structure and drug distribution [37]. Image interpretation was not without problems. Using a freeze-fracture technique on a thick object such as a tablet introduced artefacts in the more hydrated regions of the gel: (1) morphological detail in the outermost parts of the gel was destroyed by ice crystal formation and (2) freezing may have precipitated dissolved drug in areas of high concentration. However, the study provided clear evidence for an internal gradient of hydration within the gel, and the pattern of precipitated drug particles (diclofenac sodium) suggested that a drug concentration gradient also existed across the gel layer. Follow-up studies revealed the pattern of HPMC particle swelling at the core/gel boundary and revealed in detail how air bubbles formed in the gel layer from voids in the tablet [38]. Another paper showed how alginate matrices adopted very different gel morphologies dependent on the pH of the hydration medium [39]. The latter images are shown in Fig. 4.3 of this book.

In 1994, Ashraf [40] produced the first ^{1}H-NMR images of internal hydration in a hydrophilic matrix dosage form, in this case, a capsule containing HPC, while Gao and others [41] developed a convincing non-invasive optical imaging method for the study of gel layer growth kinetics. Partial imaging methods were also in use. Mitchell et al. [42] used a thermomechanical probe and a projected laser beam to measure matrix expansion, whilst others used penetrometry to probe the gel layer formation.

Conte and Maggi [43] compared gel layer thickness in hydrating Geomatrix tablets using a penetrometer attached to a texture analyser and a video microscope. The results obtained using each technique were similar, and it was possible to demonstrate the effect of applying a further rate-controlling barrier to one or two surfaces of the tablet. However, the destructive sectioning procedure was a significant disadvantage as it prevented time-resolved observations of gel layer development in the same sample.

Penetrometry was also used in combination with backscattered ultrasound by Konrad et al. [44] to measure the position of the gel layer/hydrating media interface: the so-called erosion front. Both methods produced similar results, although the ultrasound technique was preferable because of its non-destructive nature. However, there were limitations associated with the ultrasound method as tablet swelling can only occur in one plane owing to the sample holder, and it was not possible to simultaneously measure the position of the glassy core/rubbery gel interface (the swelling front).

7.4.2 Optical Microscopy

Valuable insights have arisen from the development of suitable optical microscopy methods, notably the collaborative studies between groups at the Universities of Parma, Pavia, and Purdue. In an early study, Colombo [45] calculated the surface areas of hydrating matrices by taking photographs at various time points during dissolution. Coating the tablet surfaces with an impermeable polymer modified both their swelling behaviour and drug release, and it was shown that drug release was directly dependent on the available surface area. Further studies by Bettini et al. [46] involved imaging HPMC tablets fixed in position between two Plexiglass discs, while drug release and changes in tablet surface area were monitored over the course of the experiment. A seminal investigation into the movement of internal fronts within the gel layer was later carried out within the same group [24, 47]. These studies utilised buflomedil pyridoxal phosphate (BPP), a model drug which is pale yellow in colour but stains aqueous environments with a rich orange colour as it dissolves. This colour differential allowed Colombo to visualise drug diffusion from its point of hydration (close to the gel/core interface) to the outer tablet, and in the process, discerned three distinct regions or ‘fronts’ in the swollen region of the tablet. These were subsequently interpreted as (1) the swelling front (i.e. the boundary between glassy polymer and the rubbery gel state), (2) the diffusion front

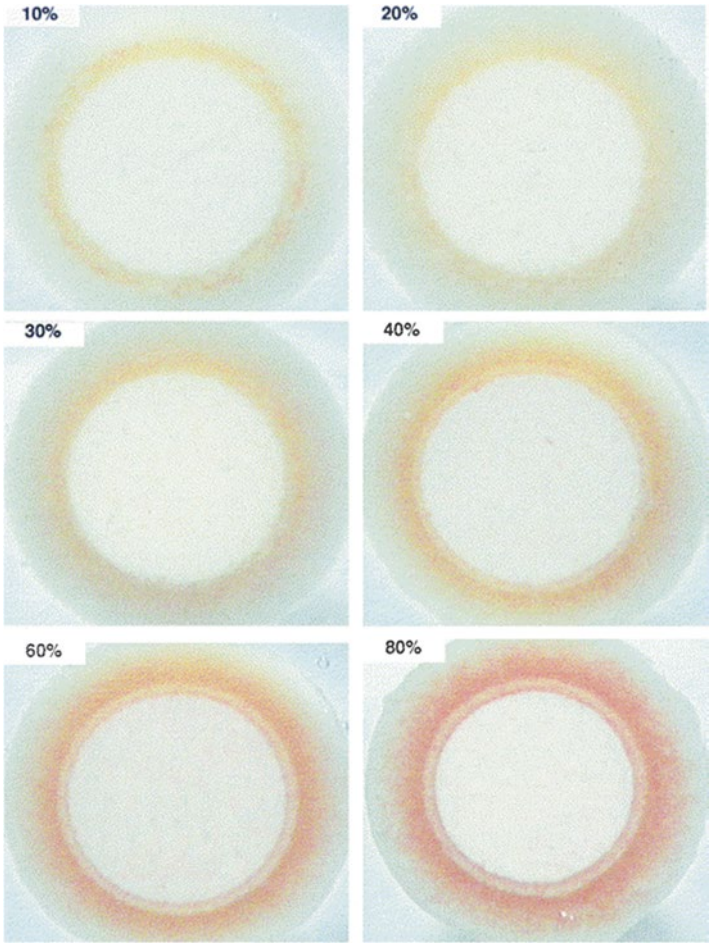

Fig. 7.5 Optical images of HPMC matrices containing different percentages of buflomendil pyridoxalphosphate BPP (w/w) taken after 120 min of swelling (from Colombo et al. [47])

(i.e. the boundary between the solid and dissolved drug in the gel layer), and finally (3) the erosion front (i.e. the outermost radial front, which forms the boundary between the gel layer and the outside hydrating medium). These three fronts and the distinct transition in the colour intensity across the gel layer are shown in Fig. 7.5, which portrays an HPMC tablet containing 60 % BPP after hydration for 1 h.

An optical imaging method developed by Gao and Meury [41] was later used by Vlachou et al. [48] to monitor the movement of swelling/diffusion/erosion fronts in HPMC tablets containing furosemide and the more soluble diclofenac (sodium salt). In this method, the hydrating tablet and macroscopic camera are entirely enclosed to block external light, and a visible light source (fluorescent light tubes) is positioned beneath the tablet. Acquired images were coded for scattered light on a grey intensity scale, with gel layer region of the tablet appearing white/grey in

colour (i.e. high scattered light intensity) against a black dry tablet core. The gel layers of matrices containing diclofenac were twice the thickness of gels in the furosemide tablets, and they showed clear separation of swelling and diffusional fronts. Critically, these visual observations were corroborated by drug release kinetics obtained experimentally using a USP dissolution apparatus and power law modelling of the release profiles. The study concluded that the release of diclofenac sodium occurred through diffusion and gel layer erosion (with a Power Law n exponent between 0.45 and 0.89). In contrast, the release of the less soluble furosemide was slower because it was primarily erosion mediated (i.e. $n > 0.89$), a result which also explained the inability to clearly define a diffusional front in the imaging study.

7.4.3 Magnetic Resonance Imaging

^{1}H-nuclear magnetic resonance (NMR) microscopy or magnetic resonance imaging (MRI) microscopy, has proved a useful non-invasive technique for examining matrix hydration and gel layer properties and behaviour in both simple and complex hydration media. Detailed descriptions of the principles of this technique and its application to controlled-release dosage forms are provided elsewhere [49–51], but in essence, magnetic resonance images are formed from the nuclear magnetic resonance (NMR) signal, which is generated by certain nuclei (e.g. ^{1}H, ^{19}F, ^{31}P, and ^{13}C) subjected to a strong magnetic field and irradiated with radio waves. These nuclei have a magnetic moment and consequently tend to align with an applied magnetic field. This results in a weak net magnetisation precesses when disturbed from equilibrium. The precessing magnetisation induces a small voltage in a surrounding tuned coil by the process of electromagnetic induction and it is this voltage which forms the NMR signal.

The great advantage over previous techniques was that NMR microscopy provided a method for the non-invasive internal imaging of hydrating hydrophilic matrices. The technique could provide time-resolved images in any direction so that unrestricted axial and radial gel properties could be examined. The principal disadvantage is that only certain paramagnetic atoms can provide a strong NMR signal. However in the case of hydrophilic matrix studies proton NMR imaging has allowed significant information to be gained on the internal spatial distribution and mobility of water during matrix hydration, and ^{19}F-NMR has allowed the changing distribution of fluorine containing drugs to be investigated.

Early studies in this area examined the changes in axial and radial dimensions of the gel layer with respect to hydration time and polymer grade, and observed the distribution of insoluble excipient particles in the gel layer [52]. Figure 7.6 shows a vertical section through a hydrated HPMC (Methocel™ K4M) matrix, revealing the unusual concave development of gel growth on the radial tablet surface, which is highly characteristic of these systems and probably arises through axial expansion.

Using MRI, Rajabi-Siahboomi et al. [53] showed that gel layer thickness in both the axial and radial directions was similar, and therefore, the greater overall tablet

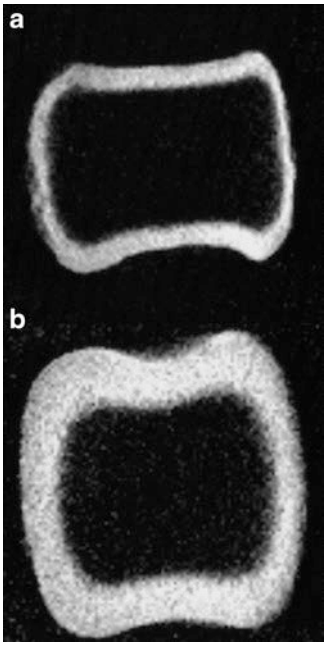

Fig. 7.6 ^{1}H MRI image showing a vertical section through a hydrating HPMC (Methocel®-K4M) matrix. The image reveals the unusual concave development of gel growth in the axial direction. (**a**) 10 min, (**b**) 30 min exposure to distilled water. From Bowtell et al. [52]

growth in the axial direction was caused by expansion of the dry core in the direction of uniaxial compression (and not due to increased gel swelling as originally thought). By determining the self-diffusion coefficient of water molecules in the gel, the authors were later able to show that the degree of mobility progressively decreased deeper within the gel, indicating that a polymer and water concentration gradient existed across the gel layer [54].

Fyfe and Blazek [55] quantified the relaxation rate in HPMC solutions of known concentration, and by comparing these values to corresponding relaxation data from a gel layer, provided a quantitative map of polymer concentration within the gel, which ranged from ~30 % (at the gel/core boundary) to <10 % at the erosion front. NMR techniques that allow the swelling and hydration behaviour of HPMC matrix tablets to be evaluated in situ are also evident. Using various hydrophilic polymers of varying viscosity grades, Baumgartner et al. [56] showed that polymer concentrations within the gel layer and gel layer thickness in dynamic tests could be correlated to the rate of polymer hydrate and its erosional properties.

Taking a different approach, Fyfe and Blazek-Welsh [57] used ^{19}F-NMR to illustrate the effect of drug solubility on rate of drug (triflupromazine/5-fluorouracil) diffusion in the gel layer, and correlated this information with rates of drug release from the matrix tablet.

A relatively recent paper by Chen et al. [58] has continued the application of more sophisticated MRI methods to pharmaceutical research. They describe Rapid Acquisition with Relaxation Enhancement (RARE)—a fast imaging technique which permitted the quantification of water concentration and self-diffusion

coefficients in less than 3 min. This had short acquisition times compared to other NMR imaging allowed for the rapid assessment of HPMC tablet hydration, and importantly, assessment during the initial stages of tablet hydration. They demonstrated that the evolution of the gel layer and, in particular, the gradient in water concentration across it is significantly different when comparing the quantitative RARE sequence with a standard (non-quantitative) implementation of RARE. The total gel thickness was found to grow faster in the axial direction than that in the radial direction and the dry core was observed to initially expand anisotropically.

The development of equipment that combined MRI with compendial dissolution testing has been a significant advance. Most commonly this has been achieved by locating the flow cell of a USP Apparatus 4 within an NMR magnet [50].

Researchers are currently focusing on the in situ study of matrix hydration and simultaneous drug release assessment under dynamic conditions. For example, Kulinowski et al. [59] studied the dissolution process of commercial quetiapine fumarate HPMC tablets in a USP 4 (flow-through cell) dissolution apparatus with simultaneous MRI imaging. The images revealed the progressive change in overall tablet size, the gel layer, and glassy/non-glassy regions of the dry core with respect to hydration time. Zhang et al. [60] used a quantitative ultra-fast MRI technique together with ^{19}F NMR spectroscopy and ^{19}F 1D imaging method to study the dissolution process of a commercial hydrophilic matrix tablet in situ. Dissolution and MRI imaging were undertaken in a combination of biorelevant media within a standard USP-Apparatus 4 flow-through cell. The results provide detailed information on the water concentration and structural evolution of the HPMC matrix (Fig. 7.7) together with the hydrodynamics inside the flow through cell. The drug mobilisation process inside the gel matrix (Fig. 7.8) was correlated with the ^{1}H MRI and drug release results. The authors suggested that these experimental conditions may better reflect in vivo dissolution processes. They also suggested that the technique could be used to investigate the drug release mechanisms and facilitate the establishment of in vitro–in vivo correlations.

Low field MRI, which on the magnetic field is generated by permanent magnets rather than superconducting magnets, has been used in extensively many industrial sectors such as petrochemicals and foods but has found use in pharmaceutical applications only relatively recently. Low field MRI instruments are small-scale, benchtop pieces of apparatus which, at typically 0.5 T, do not have the theoretical resolution of larger instruments and therefore may lack sensitivity. Nonetheless, these systems still map the ^{1}H nuclei associated with ‘mobile’ water albeit at a lower resolution than high field instruments, and can be very useful in providing information on the behaviour of HPMC matrices during hydration [61]. One such system was the MARAN-i™, formerly MARAN-iP™ (Oxford Instruments Biotools Ltd, UK). It consisted of a 20 MHz bench-top MRI with an integrated USP Apparatus 4 flow cell, therefore affording researchers the opportunity to visualise the hydration of an HPMC matrix within a compendial dissolution test on the bench [50] (Fig. 7.9). The MARAN-iP™ has been employed to show the hydration performance and physical interaction of HPMC matrices during USP-4 dissolution testing in milk and high-fat emulsions commonly used in ‘biorelevant’ media [63]. It has also been

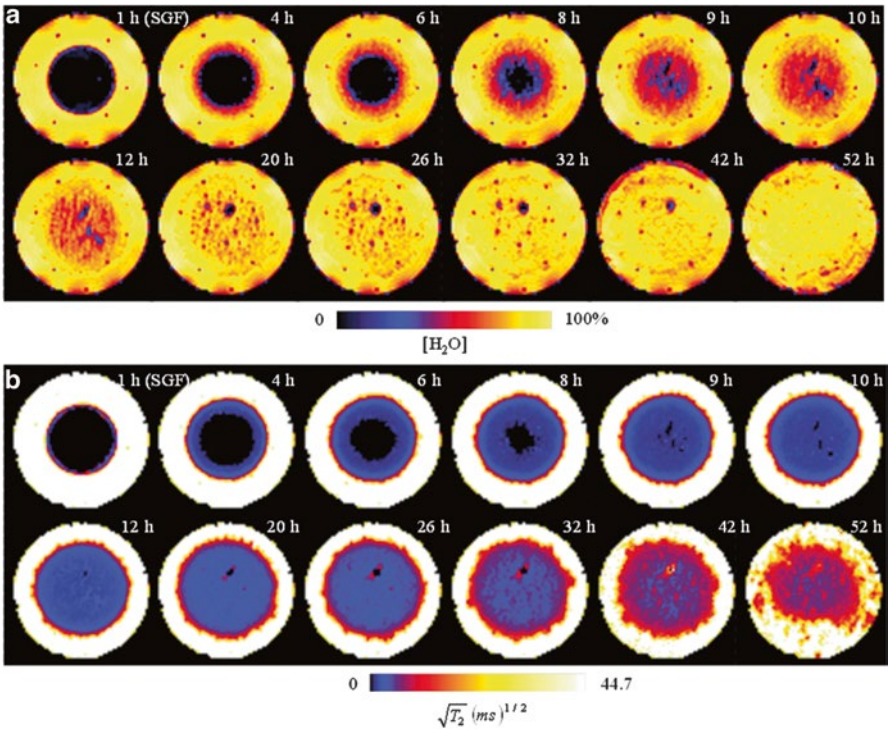

Fig. 7.7 (**a**) Typical water concentration maps of hydrating matrix, (**b**) the corresponding T_2 relaxation maps. FOV: 24 mm × 24 mm; resolution: 375 μm; slice thickness: 1.0 mm. Dissolution media: SGF: 0–1 h; FaSSIF: after 1 h (from Zhang et al. [60])

used to characterise the effects of manufacturing process and formulation variations, in addition to the effect of dissolution medium pH, on the drug release mechanism from HPMC matrix tablets [64]. The transformation in the structure of the gel layer during hydration within both low and neutral pH dissolution media was compared using two dosage forms containing the same active compound and processed by dry and wet granulation (Fig. 7.8). In both cases a prolonged exposure to low pH resulted in the drug slowly precipitating to its free acid form, which the MARAN-i characterised clearly, despite the system's relatively low resolution.

7.4.4 Confocal Laser Scanning Microscopy

With its capacity for generating high-resolution images confocal laser scanning microscopy (CLSM) has provided some unique insights into the behaviour of HPMC matrix tablets. It has been used to study the early stages of hydration and, in particular, the processes involved in the formation of the gel layer. An early study demonstrated how CLSM using a cellulose-active fluorophore in the hydration

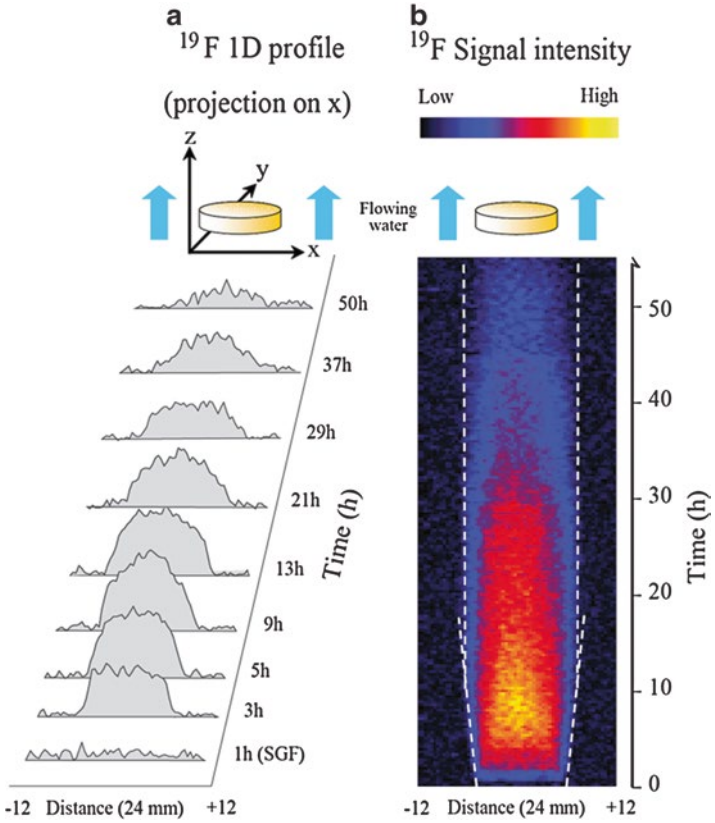

Fig. 7.8 1D-MRI profiles of ^{19}F MRI signal as a function of time. (**a**) Typical 1D profiles of ^{19}F MRI signal acquired during the experiment; (**b**) full experiment results using colours to represent the signal intensity. The physical boundary of the (outer) gel layer is shown by the *white dashed line* (from Zhang et al. [60])

medium could be used to highlight the growth of the gel layer in matrix formulations containing HPMC [65]. Only radial swelling was observed through the limitations of the cell geometry.

The technique was advanced by the development of a high-resolution CLSM method combining Congo red, a fluorophore which allows mapping of hydrated polymer regions within the gel layer with the adoption of a continuous grayscale for displaying pixel intensity within the image [62]. This has provided so far unparalleled views of the critical early stages of gel layer formation, at resolutions that reveal the hydration behaviour of single polymer particles. It showed that matrix hydration starts with liquid ingress into the surface capillary network at the tablet surface with columnar swelling of individual HPMC particles which coalesce with adjacent particles to form the coherent gel layer (Fig. 7.10). As these critical events manifest within 10 min of initial matrix hydration, the capability of CLSM for fast image acquisition makes this technique well suited to analyse the fast processes

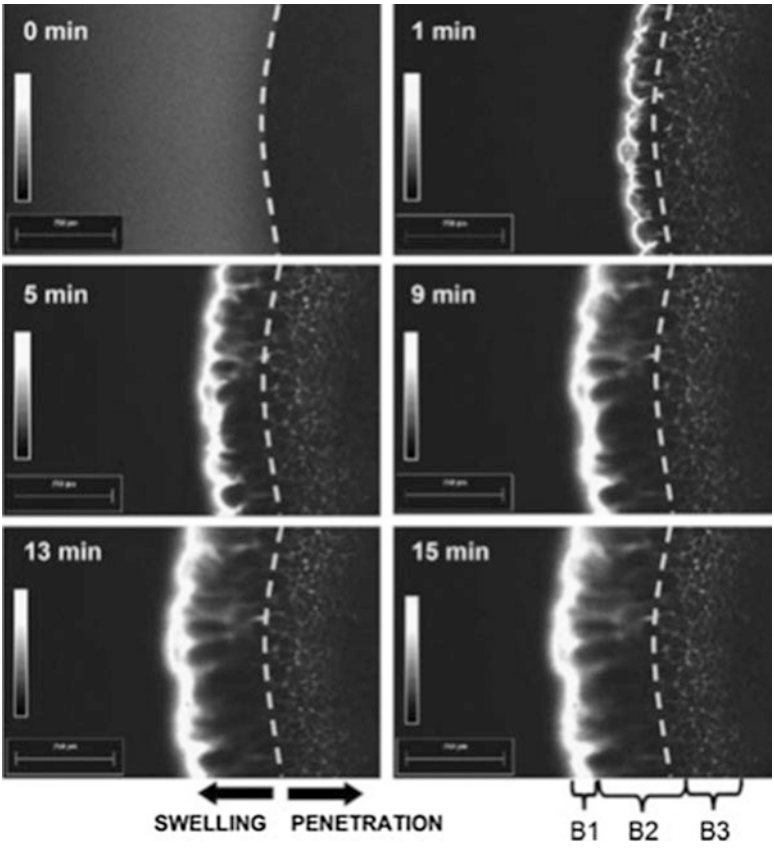

Fig. 7.9 Time series of fluorescence images taking under a Confocal laser scanning microscope of a pure HPMC matrix hydrating in situ in aqueous 0.008 % w/v Congo Red. The images show the microstructural features during formation of the gel layer (B1, B2) which occurs through columnar growth of polymer particles. Note the capillary ingress in region B3 corresponding to the penetration front in Fig. 7.1. Images are coded for fluorescence intensity from *white* (highest) to *black* (lowest) as indicated by the wedge. The bright regions indicate areas of high fluorescence, and highlight regions of polymer hydration where the fluorophore has penetrated. Hydration medium maintained at 37 °C. Ex 488/E >510 nm. Scale bar = 750 μm (from Bajwa et al. [62])

involved in gel layer formation. This was further demonstrated by the time-resolved images of surface disintegration in HPMC matrices, which occurred in high salt concentrations sufficient to prevent formation of a continuous gel layer. The mechanisms appeared to be HPMC swelling but without particle coalescence [62].

Whilst the early CLSM work investigated model matrices of pure polymer, subsequent studies have utilised matrices with more realistic formulation compositions, and studied in particular the influence of different hydrating media and co-formulated excipients on gel behaviour. These have included citrate buffers [66], dietary and excipients sugars [67], and oil in water emulsions including milk, Intralipid®, and Ensure® Plus [63].

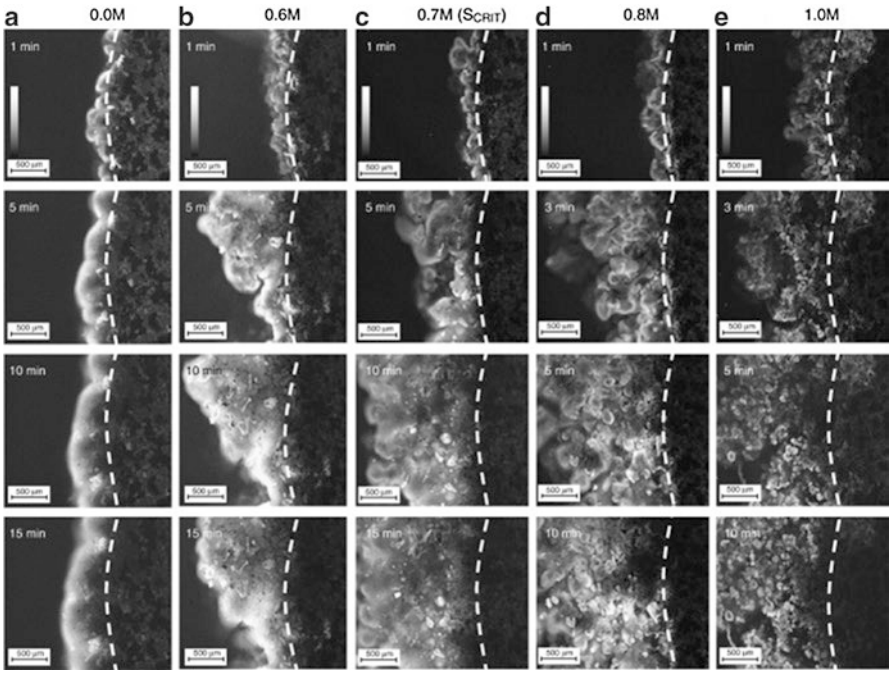

Fig. 7.10 Confocal microscope images showing disrupted gel layer formation at high sugar concentrations (from Williams et al. [7]). 0.2 M sucrose—normal gel layer development, 0.7 M limited particle swelling leading to water penetration 0.1 M no polymer swelling. 0.008 % w/v Congo Red. Hydration medium maintained at 37 °C. Ex 488/E >510 nm. Scale bar = 750 μm

Analysis of early gel layer formation in complex hydration environments has provided mechanistic insights into extended drug release performance. For example, Fig. 7.10 shows the initial 15 min of hydration of a HPMC matrix tablet in sucrose-enriched hydration media. The acquired images reveal the capacity for dissolved sugar to suppress HPMC particle swelling and coalescence, and, at very high concentrations (e.g. 1.0 M sucrose), suppress any signs of particle hydration. Critically, these observations at microscopic level could be correlated with drug release performance. In fact, it was shown that HPMC tablet sensitivity to dissolution test hydrodynamics was increased dramatically in the presence of >0.6 M sucrose. This led to immediate drug release in response to the disrupted gel layer formation caused by the presence of sugars.

A similar pattern emerged when a trivalent buffer, sodium citrate, was used to internally buffer pH within and HPMC matrix formulation [66]. CLSM studies have also been undertaken in fat emulsions used as 'biorelevant' dissolution media. It suggested that HPMC particle swelling may induce emulsion coalescence at the tablet surface, as CLSM images using differential fluorescent staining showed the hydrated gel layer was overlaid with an layer of fat [63]. This correlated lower resolution NMR images at later times, and could explain the slower release of drug into these emulsion media. Other aspects of HPMC matrix behaviour have been

investigated using CLSM imaging. These included using non-diffusing fluorescent beads within the gel layer to map the localised internal expansion within the gel layer [68] and the use of Rhodol Green, an pH-sensitive dye, as a single fluorophore to map ratiometrically changes in internal pH and the action of weak acid pH modifiers within the gel layer [68].

7.4.5 Infrared Imaging

Infrared imaging provides a capability for obtaining spatially resolved chemical images, and in its simplest application, it can provide maps of composition. For example, Fourier Transform Infrared (FTIR) imaging has allowed the mixing homogeneity of active and excipient components at the matrix surface to be investigated [69, 70]. In this technique a focal plane array infrared detector provides the capability to measure thousands of IR spectra from different locations within the sample, thereby allowing collection of spatially resolved chemical information [71].

The near-infrared (NIR) region (800–2,500 nm) has also been a considerable focus as many drugs exhibit an identifiable spectrum in this region and Hardy et al. [72] have used this region to map the components in the core and gel layer of a hydrating hydrophilic matrix tablet. Hydrated matrices were frozen immediately after removal from the dissolution bath, and problems of water interference were removed by sublimation and tablet drying. This permitted the detection of drug (caffeine), hydrophilic polymer (Methocel™ K4M) and binder (PVP). Freezing the gel however is not an ideal preparation method, as components can be displacedin highly hydrated regions and produce artefacts within the presented gel layer.

More recently, Li et al. [73] have used NIR in combination with chemometric analysis to map the distribution of water and API within an HPMC matrix. Principal component analysis of the IR spectra revealed three regions in the 1,230–1,500 nm region accounting for 99 % of the spectral variation within a 1.05 mm × 9.85 mm tablet slice. Spectral variation in the band observed at 1,460 nm was attributed to the hydroxyl groups on HPMC and their interaction with water molecules: frequency changes of this band across the tablet cross section were used to identify the region in which HPMC underwent the glassy-to-rubbery phase transition. A partial least squares method was used to quantify solid undissolved drug within the dry matrix core and gel layer. The 2,000–2,350 nm range was used to avoid interference from strong water overtones at 1,400 nm and 1,900 nm.

These studies provided some good examples of the potential for IR spectroscopy in analysing HPMC matrix performance, although the techniques described were destructive and did not permit the in situ analysis of the tablets.

Avalle et al. [74] have demonstrated how NIR microscopy could be applied to monitor in real time the hydration of a controlled-release matrix and the drug release time course. In a customised flow-through cell, a series of NIR maps were acquired and, from PLS maps of the hydrating HPMC and drug depletion, the time course and behaviour of these matrices could be followed with respect to

the drug release profile. The amount of dissolved drug was estimated from the drug-depletion profile and in the case of a diffusion-based mechanism, the method was found comparable to a USP-I dissolution up to 3 h. In a subsequent paper, Avalle et al. [75] demonstrated the migration of poorly soluble drug particles through the gel layer, thus showing further evidence of drug release controlled by erosion for low soluble drugs.

As described above, mid-IR spectroscopy has also been utilised in the form of FTIR and FTIR-ATR. The appealing factor of mid-IR stems from its ability to clearly identify functional groups and, for example, discriminate between different polymorphic forms, while for NIR this is not always the case. In addition, by looking at direct vibration modes (not overtones), mid-IR techniques in general provide sharper bands which can translate, in principle, to higher specificity and easier interpretation of the spectroscopic data. However, conventional FTIR microscopy may require lengthy measurement times, rendering it unsuitable for the study of dynamic processes, such as tablet dissolution and gel layer formation [71]. Attenuated total reflectance (ATR)-IR uses a diamond ATR accessory with high refractive index and has a relatively short acquisition time, allowing a number of images to be compiled, and is therefore better suited to analyse drug release from tablets [76].

The images produced have relatively high spatial resolution providing increased possibility of accurate quantification. The ATR acquisition times are relatively short, allowing a time resolution in the order of minutes and the technique has the potential to produce more chemically detailed images than MRI and can image changes in the gel layer [76, 77].

Another major drawback of conventional FTIR stems from the fact that useful measurements can only be made if the sample is very thin. Otherwise, the incoming infrared light is completely absorbed due to the high absorption of water and other components combined with the long path length of the infrared light in the sample. Consequently, dissolution of ordinary tablets cannot be analysed. However, using ATR spectroscopy any table size can be analysed, as infrared detection is less dependent on sample thickness.

Raman microscopy shows high potential for imaging and recent advances in technology enable really fast acquisition of larger area of the tablets. However there seems to be limited data related to in situ hydration monitoring, perhaps due to the fact that the laser has very little penetration beneath the surface of the sample and a confined arrangement whereby the tablet is placed underneath a glass window would make the spectrum of the glass competing with the scattering intensity of the sample.

7.4.6 Tomography

X ray tomography imaging has seen only recent application to pharmaceutical dosage forms, and there is little literature to date on hydrophilic matrices. However, of note is the recent work of Laity and co-workers [78, 79] which describes the

application of X-ray microtomography (XμT) in monitoring dimensional changes of a HPMC matrix during hydration. In these experiments, the axial movement of embedded glass microspheres (which are denser than water or HPMC, and thus shows stronger X-ray absorbance) revealed "bubble zones" within the areas of expansion, which might be important to the diffusional path for water ingress into the dry core and drug egress. While this method perhaps reveals a new factor which might affect drug release, synchrotron-derived X-rays were necessary to shorten acquisition times (compared with bench-top XμT apparatus) to permit the imaging of events rapidly occurring during hydration.

7.5 Future Directions

The techniques overviewed here highlight the power of physical characterisation and imaging techniques in affording an improved understanding of the underlying mechanisms of drug release from hydrophilic matrices. In the case of imaging methods this is through a direct visualisation of their hydration behaviour which can complement information from more established characterisation tools such as dissolution testing. The fact that so many studies involving these new techniques have been published in the last 5 years is testament to the increasing accessibility, reduced cost, and increased emphasis on gaining a detailed understanding as a measurable output relevant to both academic and industrial scientists. Future advances in physical and spectral microscopy (and inevitable commercialisation) will allow higher resolution, more discriminatory information to be obtained, and a more detailed understanding of the complex processes underpinning the performance of these popular dosage forms. The future prospect is that a more detailed understanding of HPMC systems will allow design of new formulations, more robust to in vivo challenge, from a position of knowledge.

7.6 Conclusions

This chapter has provided an introduction of how modern imaging and more established in vitro techniques have been applied to the characterisation of hydrophilic matrices. The rapid advances in instrumentation and characterisation technology have increasingly provided pharmaceutical scientists with new opportunities to gain unrivalled information in many aspects of the behaviour of hydrophilic matrices and their related performance characteristics. The benefits have included a better understanding of the physical and chemical attributes of dosage forms and materials, their composition, structure, and complexity of behaviour, and an ability to assess in far greater detail the consequences of formulation, environmental, and manufacturing process variables.

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Chapter 8
Physiologically Based Pharmacokinetic Modeling in the Development and Evaluation of Hydrophilic Matrix Tablets

John R. Crison

8.1 Introduction

The use of physiologically based pharmacokinetic (PBPK) models has evolved over the years from a toxicology-peripheral tissues based approach to the present biopharmaceutics-based design that includes a highly detailed representation of the gastrointestinal tract with the purpose of providing a tool for the pharmaceutical scientist for assessing the pharmacokinetic impact of a formulation or formulations changes [1–4]. As with all orally administered drug products, it is important to understand the mechanism of release of the drug into the gastrointestinal tract and the fate of the formulation, and it is extremely valuable to have a tool that describes the relationships between the physical design(s) of the drug product prior to administration and the desired pharmacokinetic results. The physiologically based pharmacokinetic model is the tool that describes these relationships.

When developing a hydrophilic matrix-based solid oral dosage form, two key objectives are (1) to improve patient compliance and (2) achieve a target plasma profile. These objectives are both drug and formulation dependent, and the PBPK model has direct application to the design and evaluation of extended released dosage forms, specifically, hydrophilic matrix-based formulations and the potential impact the formulation has on drug plasma concentrations.

This chapter will present the model and input data requirements for the application of PBPK models that simulate in vivo performance in hydrophilic matrices. Also described is information on the role of PBPK modeling in drug product development, utilizing both preclinical and post-clinical data, and a prospective view of

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how these tools can be used to design formulations. The potential application as a method for requesting biowaivers from regulatory agencies is also noted. This chapter will also discuss the limitations of using PBPK model simulations when making decisions on formulation design and in vivo fate. The chapter will not discuss specific models or modeling software products but instead will describe the importance of specific components of the model, e.g., fasted/fed conditions, gastric retention of dosage form, in vivo dissolution, pH variations in the GI tract, site-specific permeability, regional enzymes, and transporters, that are necessary to accurately simulate the plasma concentrations of drugs formulated as sustained released products in hydrophilic matrices administration.

8.2 Physiologically Based Pharmacokinetic Modeling and the Gastrointestinal Tract

Early PBPK models for simulating drug absorption and distribution in humans focused primarily on the tissue distribution aspects, with the principal application being toxicology screening [1]. In recent years, these models have been adapted to include a detailed gastrointestinal (GI) tract, e.g., the effects of gastric emptying, nonlinear absorption, and metabolism in the gut wall, pH changes, solubilization by bile salts, and, critical to modeling extended release formulations, variable drug release rates [2–4]. It is these additional compartments and physiological functions that have enhanced the capabilities of the models to provide a very thorough and mechanistic understanding of drug dissolution and absorption in the GI tract. The parameters that relate to the in vivo performance of the modified release formulations can be used as input to the PBPK to provide the formulator with an in silico tool for evaluating the formulation under different gastrointestinal conditions prior to in vitro and in vivo testing.

When utilizing a PBPK model for the evaluation of extended release formulations, it is helpful to consult the regulatory guidances to understand the conditions of the GI tract that can impact drug dissolution, absorption, metabolism, and disposition [5–12]. For example, the FDA guidance on designing in vitro dissolution methods for modified release dosage forms provides the scientific rationale for the use of surfactants, pH changes, and alternative hydrodynamics to mimic the in vivo conditions of the GI tract to achieve a “biorelevant” dissolution method. It is desirable to have a PBPK model that has mathematical representation of these different conditions in order to accurately simulate the in vivo conditions of the GI tract. This can then be used to aid in the design of the biorelevant dissolution method.

From a formulation and pharmacokinetic risk perspective, PBPK models provide value in evaluating formulation strategies to understand how changes in the release of drug from extended release formulations can impact plasma concentrations [13–24]. While there can be multiple ways to visualize these relationships, one approach is to create biopharmaceutic design spaces to show how changes in the formulation and GI physiology affect the key pharmacokinetic metrics that are being

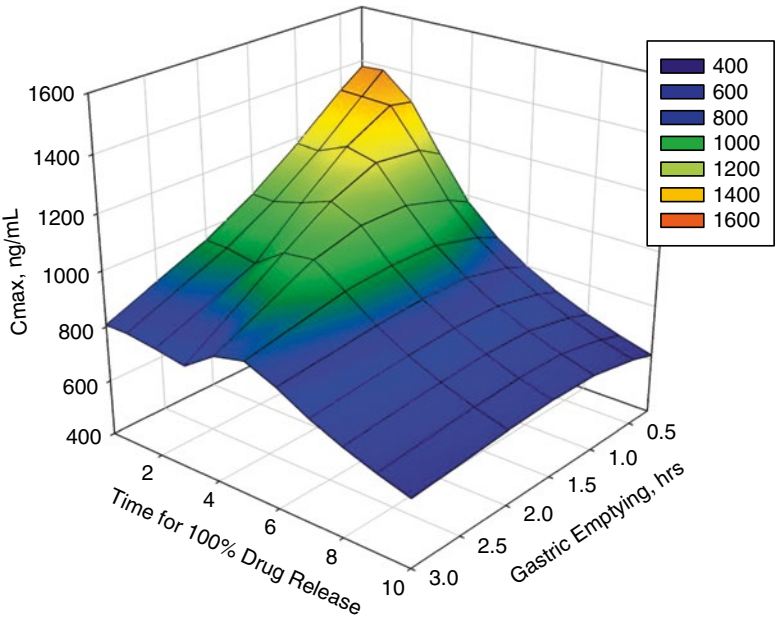

Fig. 8.1 Simulations of the C_{max} of extended release formulations as a function of the time to release and gastric emptying (PBPK model developed based on metformin ADME properties in humans)

studies. Figure 8.1 illustrates this approach as a way to link both formulation changes and physiological variability to key pharmacokinetic metrics, and also to create a "biopharmaceutics design space" for the formulator and clinical pharmacologist to use in their product development efforts.

8.2.1 Gastric Emptying

The majority of drugs administered orally, with a few exceptions, are absorbed in the intestines and so are completely dependent on the drug leaving the stomach. This can be, in the case of extended release formulations, drug in solution either already released from the dosage form during its residence in the stomach but also that retained in the dosage form or still to be released for subsequent absorption. Therefore, an accurate mathematical representation of the physiology of the stomach is important in the design of the PBPK model.

The stomach is not an organ directly involved in absorption, because its primary function is to grind food into small particles (via enzymes and physical agitation) that can be further digested and dissolved in the small for absorption and emptying from the stomach occurs when food has been sufficiently reduced in size (typically less than one millimeter in diameter) such that they empty with the liquid phase of the

stomach contents [25]. The stomach contents that do not break up into smaller fragments will stay in the stomach until the housekeeping phase, where waves of muscle movement in the stomach wall and opening of the pylorus cause emptying of stomach contents into the small intestine. This might be important with respect to the fate of hydrophilic matrix tablets that can be subjected to grinding forces when dosed in the fed state. Such forces may cause changes in release rate associated with increased rate of erosion of the dosage form which would need to be considered in building a PBPK model to predict food effects. Gastric emptying is therefore an important physiological process that can have a significant impact on the plasma concentration versus time curve for orally administered drugs and is an important feature of PBPK modeling. Gastric emptying under a variety of conditions has been studied for humans and other relevant animal models, with much data available for input into PBPK models [26–35]. In addition to the impact of physical size of hydrophilic matrix tablets, as non-disintegrating systems, on gastric emptying, the caloric value of the meal also plays an important role. These studies either incorporate radiolabeled markers into the nutrients to be studied and then utilize gamma cameras or simply use magnetic residence imaging (MRI) to follow the passage of the nutrients from the stomach to the small intestine. One study using MRI techniques showed that meals of different contents, i.e., rice versus bran, but same caloric value and volume had different emptying rates of the solid and liquid phases, but the total contents of the stomach emptied in the same amount of time [32]. A second study that incorporated a technetium-99m marker in the solid phase of the meal and showed that the number of calories emptying per minute increased for meals of different caloric value. However, the total volume of the meals also increased proportionally to the total caloric amount; therefore it is not certain whether or not this influenced the results [33]. A third study incorporated both technetium-99m and indium-111-diethylenetriamine-pentaacetic acid to mark the solid and liquid phases. This study also showed that the number of calories emptied per minute of the solid phase increased as the total caloric content increased, but in this study the mass of the meal also increased. The liquid phase of the different meals all emptied at the same rates [34].

These changes in gastric emptying times due to fed and fasted condition will play an important role in gastric emptying of and absorption of drug released from for large dosage forms that do not disintegrate, such as certain modified release formulations, since they can remain in the stomach if fed state conditions are sustained [36]. Dosage forms that do not break up into smaller fragments will have a greater probability of being retained in the stomach until the housekeeping phase or as dictated by the caloric value of the stomach contents. This emphasizes the importance of gastric emptying for matrices that swell but do not disintegrate under normal gastrointestinal stresses. Hydrophilic matrices designed to swell and not disintegrate will be retained in the stomach for typically 1–4 h under fasted conditions and up to 10–12 h if the subject is in the fed state depending on the caloric values of the meal.

The physical shape, swelling and disintegration time, size, and density of the formulation are all important characteristics and can affect the rate of emptying. However most PBPK models do not provide the capability to input these specific values and gastric emptying is inputted as a “lumped” gastric residence time.

The impact of gastric emptying of an extended release formulation, and hence on drug absorption, can vary greatly. The magnitude of the effect will be determined by several factors that include the solubility of the drug throughout the range of 1–7, release rate of drug from the hydrophilic matrix, intestinal permeability, and intestinal enzymes/transporters [23, 24, 35]. For example, non-disintegrating tablets release drug from the dosage form faster than the drug empties from the stomach. This may result in a double peak in the plasma concentration which may be observed clinically (provided there is sufficient permeability in the small intestine) which may be undesirable from a therapeutic viewpoint especially if the C_{max} and T_{max} are important. Alternatively, if the formulated drug is a substrate for cytochrome P450 3A4 (CYP3A4), a slow release profile of drug from the dosage form may result in the drug being more extensively metabolized in the intestine than if the drug is release faster, due to potential for saturating the enzyme binding sites. In addition, as CYP3A4 is not highly expressed in the distal small intestine and not at all in the colon, if a drug susceptible to CYP3A4 is provided as an extended release (XR) formulation, and significant payload is delivered to and absorbed lower down the GI tract, then the bioavailability relative to same dose given as an immediate release (IR) formulation may be increased due to reduced extent of metabolism [23, 24, 35, 37]. Therefore PBPK models that include the capability of simulating variability in gastric emptying, rate of drug release for the dosage form, and the nonlinear absorption characteristics due to metabolic and transporter properties of the small and large intestine all at the same time illustrate the immense value of this tool to understanding and designing clinical trials and product development.

While there are numerous literature sources that can be used to provide input for gastric emptying times, experimental methods for measuring gastric emptying times are also available. These include site-specific intubation and electronic devices that are radiolabeled combined with gamma scintigraphy for detection [38, 39].

8.2.2 Permeability, Transit Time, Metabolism, Transporters

To accommodate the many possible drug concentration profiles in the gastrointestinal tract that may be possible from a hydrophilic polymer matrix, the intestinal compartment, both small and large, of the physiologically based pharmacokinetic model must be complete with respect to processes that control drug concentration, absorption, metabolism (gut wall), and transit time [32]. The following section along with Eqs. (8.1)–(8.4) will provide some background as to how PBPK models include these critical parameters.

A simple mathematical expression based on Fick's Law can be written that include the important permeability and concentration parameters as well as the temporal dependence of the amount of drug absorbed from a hydrophilic matrix releasing drug as it moves through the intestine.

$$M_{(t)} = \int_0^t \iint_A P_w C_w \, dA \, dt \tag{8.1}$$

Where $M_{(t)}$ is the mass absorbed at time t, P_w is the drug permeability at the intestine wall, C_w is the drug concentration and the intestinal wall, and A is the intestinal surface area [40]. While this equation includes the relevant parameters for permeability, concentration, and time and is the initial step to predicting absorption of drugs in the GI tract, a time-dependent release of the drug from the drug product is also needed. The macroscopic mass balance approach described in Eqs. (8.2) and (8.3) includes both drug release from the drug product and absorption of the solution, both as a function of residence time in the GI tract [41, 42].

$$\frac{d\left(\dot{M}_s\right)}{dz} = j_s \cdot S_p \cdot \pi R \tag{8.2}$$

$$\frac{d\left(\dot{M}_l\right)}{dz} = j_s \cdot \pi R^2 - j_w \cdot \left(2\pi R\right) \tag{8.3}$$

where $\dot{M}_l$ the rate of mass changing as a function of intestinal length, j_{df} is the change in mass as a function of time for the drug release from the dosage form, j_w is the change in mass across the intestinal wall, and πR^2 and $2\pi R$ are the surface area of a circle with radius R and the circumference of a circle with radius R. This approach is illustrated in Fig. 8.2.

The next step in defining a mathematical model that is physiologically based is to include the variability in GI transit time throughout the small and large intestine. This was done with the following equations that now describe the differences in transit time in the GI tract by dividing it up into segments [43].

$$\frac{dM_n}{dt} = K_t M_{n-1} - K_t M_n \quad n = 1,2,\ldots,N \tag{8.4}$$

Where K_t is the transit rate constant, n is the number of compartments, M is the amount of the drug, and t is time. Equation (8.4) provides a basis for creating more complex physiologically based models of the GI tract that include regional permeability changes, pH differences, gut wall metabolism, transporters, etc. Complex PBPK-related expansions of Eq. (8.4) are available from the literature and commercially, e.g., SimCyp[tm] and GastroPlus[tm] [2–4].

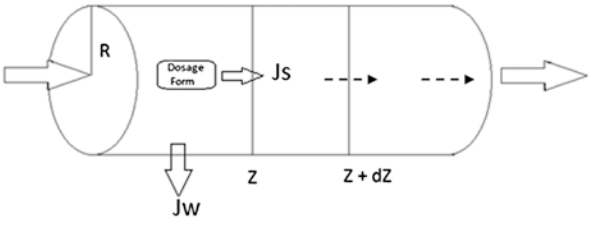

Fig. 8.2 The release rate of extended release formulations as well as intestinal transit time are equally important in determining the absorption profile (Z = intestinal length, R = intestinal radius, J_s = release of drug from solid, J_w = transit of drug through intestinal wall)

8.2.3 Determination of Intestinal Permeability in Humans

One of the more important, and often most difficult to measure, parameters used in modeling the absorption of drug from sustained release hydrophilic matrices is intestinal permeability. The challenge is that while permeability in the proximal small intestine can be estimated based on in vitro or in situ measurements, it is much more difficult to estimate the permeability of the drug in the distal small intestine and colon primarily due to the physical inability to maneuver the tubing of a dispense and collection device, as is used for proximal intestinal measurements, throughout the curves of the small intestine to reach into the distal intestine [44]. Since extended release formulations are by definition, designed to release drug over extended time periods in vivo such that there is an expectation of delivery of drug in the distal small intestine and colon, accurate modeling and simulations will require experimentally measured permeabilities in these regions. In addition to the permeability measurements, gut wall metabolism and transporter information will be critical input to the model so that the predictions can capture nonlinear effects [23, 24, 35]. These intestinal parameters, when combined with different release rates from the extended release hydrophilic matrix, can potentially impact the plasma concentration versus time profile by one or all of the following;

- Absorption as a function of regional permeability characteristics
- Degree of metabolism in the lumen or intestinal epithelia
- Rate and/or extent of absorption due to active or carrier mediated influx and efflux

While numerous papers have been published that relate how the permeability, metabolic, and transport characteristics of the intestine may impact the absorption of immediate release compounds, little has been presented that combine the above with the rate of drug released from extended release dosage form [35].

The most common method for measuring the regional intestinal permeability in humans is to use an indigestible miniature remote mechanical device that uses radio signals to operate a valve system to release drug into specific regions of the gastrointestinal tract. The valves of the device which release the drug are controlled by an external transmitter and the device contains a radiolabeled marker, usually a gamma emitter such as samarium-153, so that the transit of the device through the stomach and small and large intestine can be followed in the study subjects externally via scintigraphic cameras. Plasma concentrations of the released drug are measured as the device moves through different regions of the GI tract and the permeability is then calculated from drug concentrations [38, 39].

As discussed above, measuring intestinal permeability directly in humans is a complicated task; therefore much work has been done look to use animal or cell culture data as surrogates that include indirect and direct measurements [44–57].

From a cell culture perspective, most commonly used are either the Caco-2 or MDCK cell lines [45–48]. Cell cultures are a direct form of measuring permeability as the initial drug solution is placed on the apical side of the cells and then the drug

concentration is measured as a function of time on the basal side. This method is useful in providing a mechanistic understanding of the absorption process and is used widely throughout the industry.

The indirect approach, or single pass perfusion model, measures the loss of drug from a solution that is perfused through excised, i.e., everted, small intestinal sacs, or a living intestinal segment in the rat [48, 49]. The amount of drug absorbed is then calculated based on the difference between the input and out concentrations of drug. A more complex model was developed where drug was measured directly from the hepatic vasculature going from the intestine to the liver as the drug is simultaneously perfused through the intestinal segment [50].

While correlations of cell culture and animal permeability measurements have been made to humans, caution must be taken in freely using these correlations in human PBPK models. These methods may not have the complete array of physiological or metabolic and transports features for a direct application to human models; however they can provide an initial estimate of the permeability until more accurate data is available. Several labs have studied and compared the relevant gastrointestinal properties between cell and animal models and human and have reported these findings so that the best decisions regarding input data for the PBPK model can be made [51–58].

8.3 In Vitro Dissolution Data as Input to Represent In Vivo Dissolution

One important component critical to the success of the PBPK model is an accurate understanding of the in vivo release of the drug from the hydrophilic matrix [59, 60]. There are two approaches that commercial software products typically use to represent the dissolution of drug in vivo in the model simulations: (1) mechanistic calculation of the drug dissolution based on physical chemical properties of the drug, the available surface area of the solid, solubility, and assumptions pertaining to the convective component of the mass transport equation, and (2) using an in vitro dissolution profile that the software directly uses as input for the absorption calculations and assumes to represent the in vivo release. The calculation of release of an embedded drug from a non-disintegrating single unit dosage form such as a hydrophilic matrix tablet is complex and not included in most commercial software packages. Equations used to calculate the drug release profile from a hydrophilic matrix are numerous, but most are essentially diffusion-based with additional complexities, such as reactions, polymer interactions, etc., included to adequately describe the dosage form characteristics [61–63]. These calculations are usually performed off-line and then the percent released versus time is inputted into the software. Experimentally determined dissolution profiles for an extended release hydrophilic matrix can be labor intensive since the dosage form is typically mechanically intact and liberating drug for a period of time throughout the intestine. Therefore the in vitro test must be designed to mimic the various phases of the gastrointestinal tract over a sufficient amount of

time to capture the key dissolution times. If it is subsequently found that the model does not adequately predict the drug plasma concentrations, then the dissolution profile needs to be investigated to determine if it is physiologically relevant. Solving this problem can be iterative and time-consuming.

8.4 Use of PBPK Modeling to Establish an IVIVC

One of the more novel applications of PBPK models is in establishing in vitro–in vivo correlations. The classical method for establishing an IVIVC is to deconvolute a plasma concentration versus time profile to determine the in vivo release, and then plot this against the in vitro dissolution profile to establish a correlation. This method was originally published in the 1960s and since then several variations have been proposed [64]. However, recently PBPK models are being considered as a mechanistic approach for establishing an IVIVC [16, 65]. For a predictive PBPK model that has been developed to accurately predict plasma concentrations, the in vitro dissolution profile essentially has been shown to correlate to the drug plasma concentrations [66]. This model can then be used to compare different formulations to determine if the changes to the formulation will affect key pharmacokinetic metrics using the in vitro dissolution profiles for the different formulations as input to the model and provided that all other input parameters remain constant. Based on this reasoning, the PBPK has become a mechanistic in vitro–(in silico)–in vivo correlative tool. This method requires further investigation, but if successful, it will provide a very useful tool for screening formulations and will have a potential use in requesting biowaivers for scale-up and post approval (SUPAC) changes [8].

8.5 Limitations of a Model and Potential Sources of Error

As with all mathematical models, the quality of the simulations is highly dependent on (1) how accurately the model mathematically represents the "real world", in this case the human body and gastrointestinal tract, and (2) the quality source of the input data. When using commercial software, the user must review in detail the approach that the software vendor is using to represent the human body and, specifically, the gastrointestinal tract. Often the vendor clearly states the equations that are incorporated into the model, the source references, and the assumptions, and the user should review this material in detail to make certain that they agree with the vendor's utilization of this material in the model. For example, in the specific case of extended release hydrophilic matrices, the way in which the software incorporates gastric emptying can have a significant impact on the C_{max} and T_{max} of the simulated plasma concentrations. As stated earlier in this chapter, non-disintegrating extended release dosage forms can reside in the stomach for a period from a few minutes to many hours, depending on when the dosage form is ingested relative to

the phase of gastric emptying and how the normal cycle of gastric emptying might be modified by the caloric value of the stomach contents. In order to accurately simulate this scenario, the model must be able to include the dosage form retention time in the stomach which is likely to be very different from typical gastric emptying of particles and solutions.

While PBPK models are mechanistic, it is not unusual for a very detailed and complex model to include approximations for individual components either due to the lack of knowledge or the lack of experimental data. This is not "wrong" provided the assumptions that were made for such non-mechanistic approximations are transparent and understood by the user. However, it is the responsibility of the user of commercial PBPK software products to critically review the default parameters that are often supplied by the vendor to ensure that they are accurate and that the assumptions underlying these parameters apply to the model being developed.

Finally, it is important for the user to understand the source of the data that is being inputted into the model. As is most often the case during the early stages of model development, much of the data used to build the model are taken from preclinical studies or are in situ based. For example, as in the case of sustained release hydrophilic matrices, if the data does not reflect the temporal conditions of the GI tract that are relevant to humans, then the simulations can be erroneous.

8.6 Conclusions

PBPK models are useful for understanding the mechanistic complexities of the parameters that dictate the absorption of drugs from the GI tract, and equally important, PBPK modeling has the potential application as supplementary information for requesting biowaivers from regulatory agencies. Furthermore, these models can also be used to create a biopharmaceutics design space to better understand the risk associated with a particular formulation approach ultimately leading to a more robust, extended release product.

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Chapter 9
Approaches to Rapid In Vivo Optimization of Hydrophilic Matrix Tablets

John McDermott, Peter Scholes, Wu Lin, and Alyson Connor

9.1 Introduction

An effective hydrophilic matrix tablet must deliver a stable stream of active compound at an optimal rate to the gastrointestinal (GI) tract in order to achieve a beneficial therapeutic effect. It must do this whilst moving through the GI tract, passing through a range of different environments, and experiencing environmental changes in pH, fluid volume, fluid composition, and physical forces, whilst also accounting for regional changes in drug absorption.

In addition to this variable environment, the physico-chemical and biopharmaceutical properties of new drugs (or NCE, "new chemical entities") emerging from the industry R&D pipeline increasingly possess suboptimal solubility [1] and and/or permeability characteristics which have an influence on the drug delivery. When tasked with developing a hydrophilic matrix tablet formulation, the development team must therefore rationalise these many parameters in order to meet the target product profile (TPP).

Traditional formulation development studies involve expensive and time-consuming screening of multiple prototypes in preclinical species, in order to identify a limited number of "lead" systems to then take forward into human clinical pharmacokinetic (PK) studies (Fig. 9.1). This process can cost over $1.5M and take 12–15 months [2].

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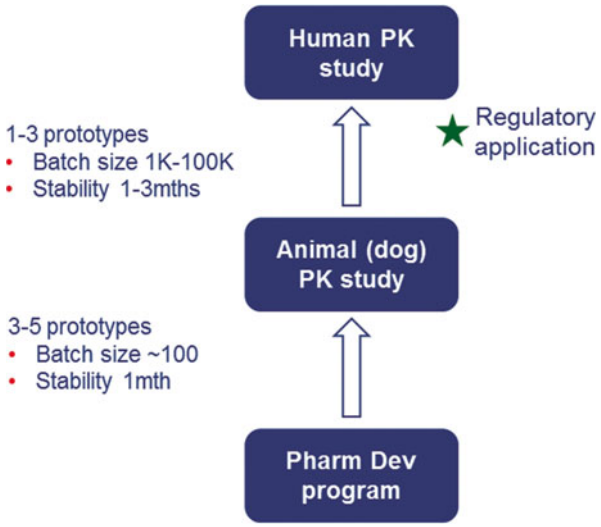

Fig. 9.1 Traditional formulation development process

Published data have previously indicated the lack of predictability between animal bioavailability and human bioavailability as a result of the substantial differences in inter-species physiology, which affects the dissolution, absorption, and metabolism of the drug molecule [3]. As a result of this lack of predictability, a frequent outcome from traditional development approaches is that the TPP is not achieved "first time" and further cycles of in vitro and in vivo studies are needed.

In order to move away from this paradigm, alternative approaches are required to reduce the reliance on in vitro and preclinical methodology and to allow the rapid in vivo optimisation of hydrophilic matrix tablets.

9.2 The Role of Biopharmaceutics in Successful Development of Modified Release Products

9.2.1 Physico-chemical and Formulation Factors that Affect Tablet Performance

The mechanism of drug release from hydrophilic matrix tablets depends on both the nature of the hydrophilic polymer and the physico-chemical properties of the drug loaded. Release can be either diffusion controlled through the hydrated polymer layer, via direct erosion of the matrix, or, in most cases, a combination of the two [4].

In order to achieve a desired drug release profile, such as zero or first order, it is important to understand how the drug, polymer, and the wider formulation will affect the drug release profile of a hydrophilic matrix tablet.

9.2.2 The Influence of Drug on Tablet Performance

Drug factors affecting the tablet performance include drug solubility, loading, and molecular weight [4–7]. Highly soluble drugs generally show relatively fast drug release, primarily via a diffusion mechanism. In this case, the molecular weight of the drug is an important consideration as drugs with low molecular weight will tend to diffuse through the gel layer of the hydrophilic matrix more easily than those of high molecular weight leading to a relatively fast drug release rate [6]. As drug solubility decreases, the release mechanism takes on an increasing erosion component and, ultimately, for poor solubility drugs, tablet erosion will become the driving force for release [8]. In these cases molecular weight may become less influential. In addition, drugs that ionise in the physiological pH range can have variable solubility properties in different regions of the GI tract. This can change the drug release mechanism and have an impact upon the overall release profile.

9.2.3 Influence of the Rate-Controlling Polymer on Tablet Performance

For the rate-controlling polymer, the two primary factors affecting drug release in vitro and in vivo are the polymer molecular weight (or viscosity), and the polymer content within the matrix tablet [4, 5].

A significant characteristic of the hydrophilic matrix tablet in controlling drug release is the rate of hydration of the tablet matrix and the strength of the matrix when hydrated, both of which are directly related to the molecular weight of the polymer [4]. Low molecular weight hydrophilic polymers have low viscosity and gel strength and hence will show relatively fast and erosion-controlled drug release mechanisms. As the molecular weight of the polymer increases, the gel becomes stronger and more resistant to erosion. The gel layer around the hydrated tablet also becomes more difficult to penetrate, and therefore drug diffusion and the drug release rate is slowed. However, the effect of polymer viscosity on the drug release is not linear, and once polymer viscosity reaches a certain threshold, the impact on drug release rate will plateau [9].

The polymer content in the matrix also contributes to the strength of the hydrated matrix, and this can be one of the primary routes for optimising drug release. The content of a hydrophilic polymer in a matrix tablet is typically in the range 20–50 % w/w. Higher polymer levels reduce the space for drug loading and lead to high cost of goods, whereas lower polymer levels can lead to reduced strength of the gel layer and increase the risk of premature disintegration and undesirable dose “dumping” effects [10]. For this reason it is not recommended to formulate hydrophilic matrix tablets using low contents of a high molecular weight polymer, despite sometimes being able to achieve desirable in vitro dissolution profiles.

9.2.4 *Influence of Wider Formulation Factors on Tablet Performance*

A number of other formulation factors can affect matrix tablet performance and are described in detail elsewhere in this volume. These include the properties of other excipients, for example those used as fillers and pH modifiers, the tablet size, and the tablet surface area-to-volume ratio (SAVR) [11–13].

Tablet shape or SAVR can affect the rate of drug release from a hydrophilic matrix tablet. Missaghi et al. [13] have investigated freely soluble and practically insoluble drugs and found that although the mechanisms for drug release are different, changing the tablet geometry did not change the release profile when SAVR was constant. It was also found that when the same blend was used for tableting, an increase in tablet weight could achieve an increased drug dose with a reduced drug release rate due to the decrease in SAVR values. As such, the amount of drug released as a function of time was not affected, but the release duration was extended.

9.2.5 *Summary of Physico-chemical and Formulation Factors that Affect Tablet Performance*

As described above, drug release from hydrophilic matrix tablets can be affected by numerous factors. Depending upon the drug–polymer combination used, and the formulation approach selected, the formulation scientist may therefore develop in vitro a range of suitable candidate formulations with the required in vitro drug release kinetics, which may then be used for further assessment. However, once developed, these formulations must contend with the in vivo environment to truly deliver the designed performance.

9.3 Gastrointestinal Physiology and Transit Rates

The development of successful Modified Release (MR) formulations not only depends on formulation factors. No matter how good the formulation development process and the in vitro performance, it is also necessary to take into account the environment factors to which the formulation will be exposed on dosing the patient. An array of factors can promote or impede drug absorption and must be considered [14]. These include the gastrointestinal (GI) transit time, the available surface area for absorption, drug permeability, GI fluid volumes, and their composition, pH, and enzyme and transporter expression (Table 9.1).

Table 9.1 Properties of human regional gastrointestinal fluids (adapted from data in [15])

		Stomach	Small intestine			Large intestine	
			Duodenum	Jejunum	Ileum	Proximal colon	Distal colon
Total fluid volume (ml)	PM	118 ± 82	212 ± 110[a, c]			187[b]	
Free fluid volume (ml) [3]	Fed	NR	54 ± 41[a]			11 ± 26[b]	
	Fasted	45 ± 18	105 ± 72[a]			13 ± 12[b]	
Bile salt concentration (mM)	Fed	0.06	11.2	8 ± 0.1	2–10	NR	NR
	Fasted	0.2 ± 0.2	0.57–5.1	0.8–5.5	NR	NR	NR
pH		1.0–2.5	NR	6.6 ± 0.5	7.5 ± 0.5	6.4 ± 0.6	7.0 ± 0.7
Bicarbonate (mM)		NR	6.7	6; 8.2	30; 40	NR	30
Potassium (mM)		13.4 ± 3	NR	5.4 ± 2.1	4.9 ± 1.5	NR	4.7 ± 1.0
Sodium (mM)		68 ± 29	NR	142 ± 13	140 ± 6	NR	0.6 ± 0.3
Chloride (mM)		102 ± 28	NR	126 ± 19	125 ± 12	NR	0.3 ± 0.1
Calcium (mM)		0.6 ± 0.2	NR	0.5 ± 0.3	4.2	NR	21 ± 5.2
Magnesium (mM)		NR	NR	NR	2.8	NR	7 ± 1.1
Short chain fatty acids (mmol)	PM	NR	NR	NR	13 ± 6	131 ± 9	80 ± 11

PM post-mortem, *NR* data not reported

[a]Indicates that the stated value represents the whole small intestine, or no differentiation was reported

[b]Indicates that the value is for the whole colon

[c]Recalculated value based on originally reported data

9.3.1 Anatomy

The GI tract extends to over 7 m in length and can be divided into a number of regions and sub-compartments. The stomach is perhaps the simplest region and it comprises four regions: the fundus, body, antrum, and pylorus. Its function is to store and grind food, mix it with gastric secretions, and empty the resultant chyme at a controlled rate into the duodenum. Consistent with this function, the stomach is primarily a secretory rather than an absorptive organ and it has a relatively small surface area. In theory, drug absorption from the stomach can occur, but it is a very small percentage of the total systemic exposure, even for an immediate release formulation. Consequently, the rate of gastric emptying is a primary driver of systemic exposure to the drug.

The small intestine is around 6 m long, and stretches from the pyloric sphincter to the ileo-caecal junction (ICJ). It can be divided into three main regions: the duodenum (~30 cm long), the jejunum (~2.4 m long), and the ileum (~3.6 m long). In contrast to the stomach, the key function of the small intestine is the absorption of nutrients, and to facilitate this, the epithelial surface is covered with villi and microvilli. This results in a very large surface area of over 450 m^2.

The large intestine, or colon, is approximately 1.25 m long and is commonly divided into eight regions: the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. In comparison with the small intestine, the colon has a much reduced surface area (~1.5 m^2), and in approximate terms, the function of the first half of the colon is to absorb water, whereas the second half is the storage of solid matter. The colon has a much reduced fluid content, with volumes between 1 and 44 mL reported in the fasted state [15]. Depending on the quantity of drug administered, and its unique physico-chemical properties, this represents a challenge for drug dissolution in this region.

9.3.2 Regional Variations

In addition to the anatomical changes, the physiology of the GI tract varies from region to region. Perhaps the best understood is the change in luminal pH along the length of the GI tract. Changes in pH are significant, ranging from pH 1 to 2 in the fasted stomach, through to pH 7 to 8 in the distal regions of the GI tract. Characteristic changes in pH are observed, including a reduction in pH, generally of at least 1 pH unit [16], in the caecum as a result of microbial activity. However, in the small intestine, inter-subject variability is low, with variation (CV%) typically less than 10 % [17, 18] (Fig. 9.2).

As described in the previous section, in the case of an ionisable compound, the pH of the local environment will impact on drug solubility, and hence the amount of drug available for absorption. Weakly basic molecules have higher solubility in the

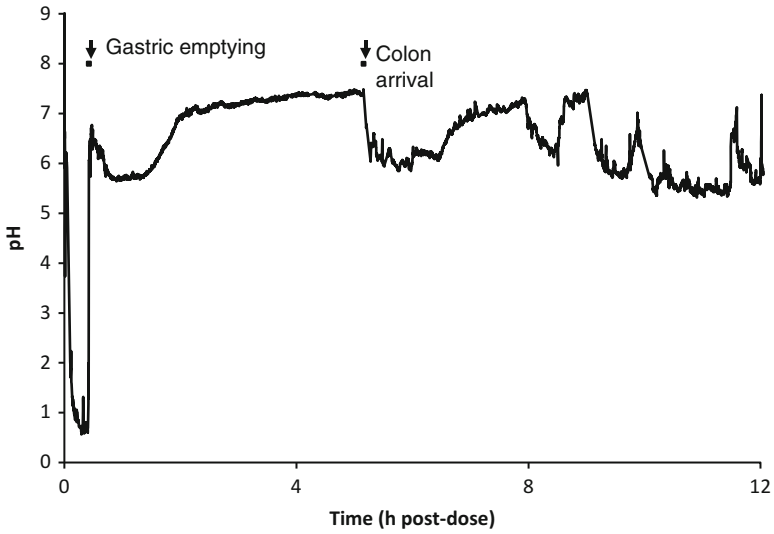

Fig. 9.2 Gastrointestinal pH profile from a single subject using the SmartPill pH capsule

stomach than the small intestine, which may result in a "burst release" effect in the stomach but with the potential to precipitate out in the small intestine. Conversely, weakly acidic drugs will have limited solubility in the stomach and better dissolution in the small intestine. It is also worth noting that these molecules will be subject to variations in pH in vivo and may require formulation strategies to mitigate that in order to assure reliable drug delivery. This is discussed further in Chap. 11.

Another aspect that has received significant attention is the occurrence of the many transporters and enzymes within the GI tract. Some are ubiquitous and others are expressed preferentially in the certain regions. Expression gradients have been documented for a number of enzymes and transporters and their relevance is molecule specific. One common example is that of the enzyme CYP3A4, which is expressed in higher concentrations in the upper small intestine but has limited expression in the colon [19]. Delivery of a drug that is metabolised by CYP3A to the colon could bypass this pre-systemic metabolism and increase bioavailability. This phenomenon has been reported for a small molecule, anti-infective compound which exhibited a 50 % increase in bioavailability when delivered to the colon, and for simvastatin, which exhibited a threefold increase in bioavailability following delivery to the lower GI tract [20, 21]. In general, however, the presence of saturable metabolism or transporter processes in the GI tract needs careful consideration when designing modified release formulations, given there is the potential for drug release rates and local concentrations in the GI tract, to be below the saturation thresholds. This can result in suboptimal pharmacokinetics.

9.3.3 Regional Drug Absorption

Investigation of the regional absorption of drugs reveals how the different regions of the GI tract influence systemic exposure. As might be predicted from the function and physiology of each region, the general trend is for drugs to have reduced rates and extents of absorption when delivered to the colon. Examples include M100240 [thioester of MDL 100,173; a dual angiotensin-converting enzyme (ACE)/neutral endopeptidase (NEP) inhibitor], which has 41 % bioavailability from the colon relative to an immediate release reference, and bevirimat (an HIV maturation inhibitor), which has 28 % bioavailability from the colon relative to an immediate release reference [22, 23]. However, it is not uncommon for drugs to be well absorbed from the colon, despite their suboptimal characteristics. Examples include fasudil (a kinase inhibitor for the treatment of stable angina), which has a mean systemic availability from the colon which is 1.14 times that of the oral solution, and ATHX-105 phosphate (a 5-HT_{2c} receptor agonist for the treatment of obesity), which has a bioavailability of 121 % from the colon relative to the immediate release formulation [24, 25].

9.3.4 Transit Times

Since the different regions of the GI tract have the potential to affect the systemic exposure of a drug, when developing a hydrophilic matrix formulation it is important to understand what proportion of the drug dose might be delivered to each region. Release rate is controlled by the formulation, but the length of time that formulation resides in each region and the location to which the drug is delivered are controlled by GI transit times.

Early clinical development studies are typically performed in healthy subjects in the fasted state. Analysis of GI transit data from over 350 clinical studies performed by Quotient Clinical provides a comprehensive understanding of human in vivo GI transit times via scintigraphic imaging [2].

In the fasted state, gastric emptying on average occurs about 30 min after dosing, and transit through the small intestine (measured as the time from gastric emptying through to arrival at the ICJ) occurs with a mean time of around 3 h. Transit through the large intestine generally takes a further 20 h of which about 2 h, and often much longer, can be attributed to transit through the ascending colon.

Transit through the small intestine is known to be less variable than gastric emptying or colon arrival. Factors that can have a substantial impact on gastric emptying such as dosage form type and size (e.g. single unit versus multi-particulate) and prandial state do not influence small intestinal transit to the same extent. However, intra- and inter-subject variability in small intestinal transit times does exist. Transit through the jejunum and ileum can range from 1 to 4.5 h and residence at the ICJ can be anything from 0 to 12 h. Commonly, small intestinal transit is quoted as ranging from 1 to 6 h [26].

A key metric that can be derived from these data is that, on average, a dosage form will arrive in the colon about 4 h after dosing. Consequently, there is limited time for delivery to and absorption from the small intestine. In contrast, transit through the colon is extended, and this has the potential to allow prolonged uptake provided that the drug is sufficiently well absorbed.

The impact of GI transit time can be seen in the data obtained from a study performed by our group. A prototype HPMC matrix formulation was developed to release drug over 4 h. In vivo erosion was quantified using scintigraphic imaging. The time taken to completely erode was reproducible, ranging from 2.5 to 3.1 h after dosing. However, despite administering the dosage form in the same controlled conditions to the healthy volunteers, the location of the dosage form on completion of erosion ranged from the stomach to the colon. The impact of variable colon transit times is exemplified by an investigation with oxprenolol, which correlated plasma concentration time profiles and extent of absorption, with GI transit time and particularly with colonic transit [27].

9.3.5 Effect of Food

Understanding potential food effects is an important aspect of hydrophilic matrix product development. As generally measured via systemic exposure, food effects can be positive (i.e. increasing exposure to drug) or negative (i.e. decreasing exposure to drug), and these effects result from changes in transit rates, impact on the performance of the formulation, or interaction with the drug itself.

The effects of food include an altering of GI physiology (e.g. increased pH, slower gastric emptying, presence of contractile forces, induction of bile), which in turn can result in interactions with the dose form (e.g. premature loss of integrity due to increased contractile forces) or with the drug substance (improved solubilisation due to the lipid content of meal, or chelation with cations such as calcium).

The slowing of gastric emptying caused by food is a result of the physiological response to the ingestion of food, because the stomach requires time to grind the food and mix it with gastric secretions to create chyme. The extent of this effect is dependent on the meal provided, with high fat, high calorie meals resulting in a much slower delivery of the stomach contents into the duodenum. Whilst solid dosage forms are able to empty from the stomach in the fed state, this tends to be serendipitous. In the majority of cases, the dosage form remains in the stomach for a prolonged period of time and, consequently, the hydrophilic matrix must be able to withstand the process of digestion within the stomach in order to maintain control over drug release rate. If this is achieved, drug is then released into the duodenum for much longer than would occur in the fasted state. This was illustrated by the work presented by Davis and colleagues [28], in which the combined effect of more rapid erosion and altered anatomical site of drug delivery was observed to result in an increase in the extent of drug absorption.

9.3.6 Summary

Hydrophilic matrix formulations are designed to deliver drug over a sustained period of time. During the delivery period, the dosage form will transit through the GI tract and be exposed to a variety of factors. Understanding how the formulation performs in vivo, to which regions the drug is delivered, and the extent of absorption from each region is key to the informed design and optimisation of this formulation type.

9.4 Limitations of Established Characterisation Techniques

Established techniques for matrix tablet characterisation include in vitro methods such as dissolution, in silico simulation methods such as GastroPlus™ (Simulations Plus, Lancaster, CA, USA), and preclinical assessments in different animal species. These techniques are used as they are simpler and cheaper than clinical evaluations, and when operating within a conventional organisational structure, they are also quicker. However, in order to utilise these techniques it is important to understand the biorelevance of each methodology, so that data can be interpreted appropriately.

An increasing amount of work is being undertaken to improve the predictive capability of in silico models. However, as discussed in Chap. 8 the predictive ability of any model is dependent upon the quality of the data input, the way it is developed, and the results of model validation [29].

The predictability of preclinical models is widely reported within the literature and numerous papers contrast parameters such as intestinal pH, transit time, and fluid compositions that would affect the dissolution and absorption processes in preclinical species and humans [30, 31] (Table 9.2).

The use of animal models in predicting human bioavailability has been studied [3] but has been shown to be poorly representative, because of substantial interspecies physiological differences, including the dissolution of the dosage form. Therefore, the product performance observed in preclinical testing may not be reflected in human studies, and a further cycle of in vitro and in vivo studies is required, causing additional delays to the development programme.

One example of this has been reported by Reddy et al [32] studying an NS3 protease inhibitor which suffered from poor solubility and permeability. The objective of the work was to investigate the potential to develop a drug product that was appropriate for once-a-day dosing using an in silico model (GastroPlus™). The model predicted colonic bioavailability to be between 4 and 28 %, indicating once-a-day dosing would be feasible for this drug. This result was confirmed by preclinical experiments in the monkey (relative bioavailability 30 %). However, in order to validate the model, a human regional drug absorption study was performed which demonstrated for a particulate formulation that the actual drug absorption from the colon was just 0.6 %. Therefore, human colonic absorption was overestimated by

Table 9.2 Comparison of dog and human gastrointestinal systems

	Human	Dog
Intestinal pH	5.5–6.8	6.5–8
Small intestine transit	Mean 238 min (mean 180–300 min)	Mean 111 min (15–206 min)
Bile acid concentration (fasted state)	2 mM	6 mM
Phospholipid concentration (fasted state)	0.2 mM	2 mM
Neutral lipid concentration	0.1 mM	3 mM

both the preclinical and in silico models of human absorption. This indicated that an important mechanism impacting on human colonic absorption was not fully understood, and limited the usefulness of the models.

9.5 Clinical Tools to Understand MR Design and Performance In Vivo

9.5.1 Regional Absorption Studies and Case Studies

Clinical investigations of regional drug absorption have been undertaken principally through intubation, or by using remote controlled capsules [33–36]. Intubation involves the insertion of an oro- or naso-gastric tube through which the drug molecule in a solution formulation is delivered to different sites within the GI tract [34]. Absorption is then assessed through the appearance of the drug molecule in the systemic circulation by standard pharmacokinetic analysis. Although ethically acceptable, intubation is disadvantaged by having to be performed by a specialist gastroenterologist and is restricted to the use of solution formulations.

The Enterion™ capsule is the most commonly used remote controlled capsule to investigate regional drug absorption [35]. It has been used in over 120 clinical investigations, which have involved the administration of over 4,000 capsules. The capsule is similar in size to a 000 hard gelatin capsule, and is capable of delivering a wide range of formulations including solutions, suspensions, particulates, pellets, and mini-tablets. A typical regional absorption clinical study will be based upon a crossover design in which test formulations are delivered to different regions of the GI tract to enable the compilation of a regional drug absorption map for the drug molecule. Extension of the study to include both solution and particulate formulations can also enable the challenges of poor solubility versus poor permeability to be teased apart—providing a further piece of pivotal information to support the project [32]. The driver for performing this type of investigation may stem from a desire to understand regional bioavailability in order to set expectations prior to the development of a matrix formulation. Alternatively, they can be performed in response to suboptimal pharmacokinetic profiles which have been obtained from the clinical testing of a prototype formulation. The study will then aim to diagnose whether the poor performance is a result of regional differences in absorption [37].

9.5.2 Scintigraphic Imaging and Pharmacokinetic Case Studies

The technique of gamma scintigraphy was first used to investigate the in vivo release properties of drug formulations in 1976 and since then it has become an increasingly useful tool for evaluating the GI performance of pharmaceutical dosage forms [36, 38].

Gamma scintigraphy has been used in the development and evaluation of pharmaceutical drug delivery systems, including enteric-coated tablets and complex modified release formulations [39–41]. The technique provides information on the deposition, dispersion, and movement of a formulation. Typically, such scintigraphic imaging is combined with assays of drug concentrations in blood or urine, to provide information on the sites of release and absorption within the body [38]. This is termed pharmacoscintigraphy.

Appropriately designed oral formulations can also be used to provide an insight into the changes in the absorption profile across the regions of the GI tract [42]. However, the use of coated formulations to delay drug release and to obtain precise data by accurate targeting of regions of the small intestine or colon is fraught with challenges, such as ensuring consistent and accurate intra- and inter-subject performance. However, the correlation of data obtained by gamma scintigraphy (and other drug product imaging techniques) when combined with key PK parameters for hydrophilic matrix drug products can provide valuable data and define the factors that influence a variable exposure profile, including changes in the absorption profile with site of drug molecule delivery.

In a study performed by Nicholson and colleagues [43], three hydrophilic matrix extended release formulations of 6-hydroxybuspirone were prepared and tested in healthy volunteers. In vitro testing indicated a predominantly diffusion controlled release mechanism. A gamma emitting radionuclide (samarium-153) was incorporated into the dosage forms to monitor performance in vivo. The scintigraphic results confirmed that transit through the GI tract was as expected. The time taken for release of the radiolabel from the dosage form matched the rank order of release observed in vitro. Correlation of scintigraphic and PK data confirmed that the initial process of drug release was predominantly diffusion as the appearance of drug in the systemic circulation occurred prior to the observed physical release of radiolabelled marker. Furthermore, a good correlation with in vitro data was obtained. Correlation with dosage form location in the GI tract confirmed that that plasma–concentration time profiles were controlled by the formulation and that absorption was not affected by location (e.g. arrival in the colon).

An alternative mechanism that contributes to the process of drug release from the hydrophilic matrix tablet is erosion of the hydrated matrix, which can be very different in vivo from what is observed in vitro. In the investigation reported by Lobo and colleagues, three prototype hydrophilic matrix formulations (containing LY545694 tosylate) with drug release ranging from 3.5 to 8 h were compared with a reference controlled release formulation [44]. In vitro, the formulation with a 6 h

release profile (prototype 1) was observed to release more quickly than the reference controlled release formulation. However, scintigraphic data confirmed that prototype 1 eroded more slowly in vivo, as was indicated by the rate of liberation of the radiolabel. The data were used to clarify the underlying reasons for this. This showed that in 9 of the 16 subjects, a complete loss of integrity of the remaining tablet core occurred when only $\leq$60 % erosion had occurred. This indicates that the matrix was no longer able to withstand the peristaltic contractions of the GI tract—a phenomenon that was not observed during dissolution testing. LY545694 was suspected to be poorly absorbed from the colon, resulting in a fraction of the dose being "lost" if release occurred over too long a period. The data from this investigation confirmed this and, as a result of this feature of the drug, a key driver of variability in exposure was gastric residence time. The longer the dosage form remained in the stomach, the more opportunity there was for absorption from the small intestine.

9.6 Flexible In Vivo Methodologies to Screen and Optimise MR Formulations

9.6.1 Drivers for New Clinical Testing Paradigms

Designing and developing an extended release formulation capable of delivering drug at the right time at the right rate and to the right region of the GI tract can present a significant challenge for the formulation scientist with regard to achieving the required accuracy and precision, to ensure an optimal therapeutic outcome. Whilst the anatomical location for treating local disease will be known, or the target plasma–time concentration profiles for systemically acting drugs will be defined, fundamental questions remain in the selection of the formulation technology and composition, in order to ensure the desired in vivo performance and therapeutic outcome. Elsewhere in this chapter the risks of relying solely on a priori knowledge from in silico, in vitro, or preclinical studies to determine formulation compositions for human evaluation have been highlighted. Whilst industry and academia continue to invest in developing enhanced predictive in silico or in vitro models, the ability to reliably and routinely define specific formulation compositions with a guarantee of "right-first-time" success in humans can arguably be viewed as one of the "holy grails" of drug development that may always remain out of reach. Until actual clinical data on the new MR formulation prototype are available, its performance within the complex physiological environment of the GI tract will never be truly understood.

The challenge then becomes one of maximising the probability of success within the clinical study, and of identifying a formulation prototype to deliver the drug in line with requirements of the TPP. In an attempt to minimise the risk of a poor outcome, the pharmaceutical industry has therefore typically manufactured and had available for clinical dosing a number of MR formulations (usually three), which differ in their release rate. This ensures some contingencies in case of unpredicted, suboptimal in vivo performance of the target formulation.

Table 9.3 Disadvantages and challenges of conventional drug product development approaches

Generation of unnecessary drug product stability data (e.g. 3–6 months) for unproven NCEs
Delayed initiation of clinical studies due to CMC critical path
Predetermination of unit dose strengths
Inflexibility in formulation composition of functional excipients
Inability to respond to "within protocols" to emerging clinical data
Wastage of undosed product
Increase demand on API consumption

There remains however one fundamental restriction : the inability of the project team to respond in real time to arising clinical safety, PK, or PD data and actually adjust the levels of critical-to-performance components in the formulation in real time, manufacture and then dose. This limitation is a result of the structural evolution of the pharmaceutical industry whereby alignment and infrastructure have been based around functional disciplines rather than focused on study or programme delivery. This polarisation into two vertical channels focused on making and testing of products has imposed on industry a rigidity with regard to the determinant of what is dosed. This is what was manufactured (often months beforehand) rather than what the arising clinical response dictates or requires. Additional disadvantages and limitations of this model are summarised in Table 9.3.

A new paradigm, Translational Pharmaceutics [45], has recently emerged based on horizontal integration of chemistry, manufacturing, and control functions (CMC) and clinical capabilities to address these restrictions.

9.6.2 Translational Pharmaceutics

The focus of Translational Pharmaceutics is to enable human clinical data to inform real-time rapid formulation selection to ensure efficient and effective identification of optimum systems, meeting desired in vivo performance criteria (Fig. 9.3). The development of the concept was discussed at a recent AAPS workshop [46]. This approach can benefit early clinical pharmacology studies, where the focus is on accelerating key Proof-of-Concept (PoC) milestones (e.g. mechanism, delivery, and concept), as well as studies where the primary objectives and end points of the study are linked to identification of an optimum drug product formulation composition. For example, it could be used prior to initiation of pivotal Phase II/III studies or as part of a life-cycle management (LCM) programme.

There are several key elements required to realise the benefits:

- An operational capability to manufacture, test, release, and dose products rapidly in "real time" (within a 7 day cycle time), to ensure viability of crossover clinical study designs
- Clinical protocol flexibility based upon up-front assessments of "what-if" outcomes, describing appropriate decision algorithms for formulation selection and modification

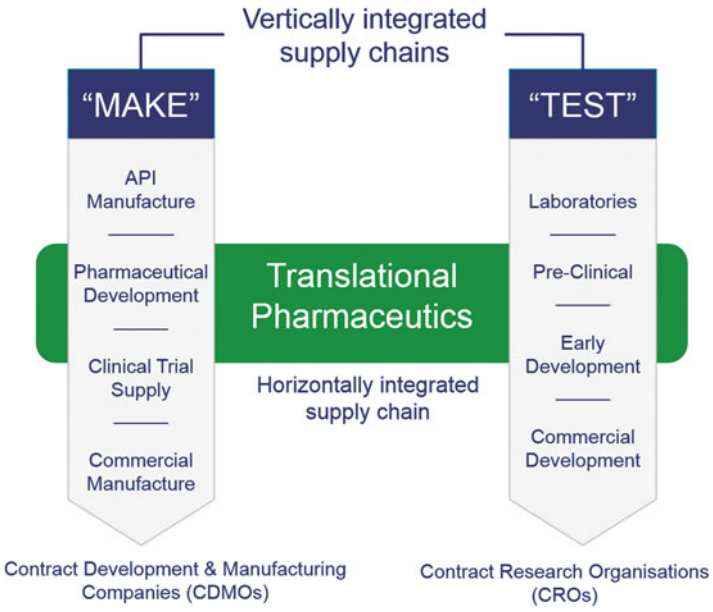

Fig. 9.3 Integration of supply chains through translational pharmaceutics

- A regulatory framework that following initial approvals empowers organisations to be accountable for real-time decision making without the need for further agency interactions

9.6.3 RapidFACT Clinical Studies and Formulation Design Space

Rapid Formulation development and Clinical Testing (RapidFACT) programmes utilise the principles of Translational Pharmaceutics and are ideally suited to the development of MR matrix-based dosage forms.

Benefits are maximised by the adapted utilisation of the concept of "design space" as originally described in ICH Q8 [47] documentation. In this legacy context, design space is linked to a Quality-by-Design (QbD) development paradigm, where the intention is that a formulation or processing space will be defined within which in vivo product performance will not be affected. In this new application however a formulation space is defined and characterised by the pharmaceutical development team within which it is fully expected that in vivo product performance *will* vary as compositions are changed. This allows critical-to-performance formulation components to be utilised as continuous variables during the conduct of the clinical study, enabling enhanced precision in selection of the formulations to manufacture for

Table 9.4 Critical-to-performance parameters amenable to design space approaches

Drug loading per tablet
Level of release-controlling polymer in monolithic tablet
Ratio of two or more release-controlling polymers in monolithic tablet
Bilayer flexibility if immediate release or gastroretentive components required
Coating compositions and thicknesses for delayed or additional MR control

dosing. Examples of extended release matrix formulation parameters where a design space would de-risk to predefined levels are shown in Table 9.4. More than one variable can be accommodated within studies.

9.6.3.1 Programme Design

The building blocks of a RapidFACT study are illustrated in Fig. 9.4.

Pharmaceutical Development

In essence, the starting point for the formulation scientist remains the same, utilising all available a priori knowledge to design the required MR formulation. However, with the potential for design space utilisation there is no longer a need for predetermination and pre-manufacture of fixed quantitative drug product compositions prior to the onset of clinical dosing. This avoids the absolute reliance on in silico, in vitro, and preclinical datasets which can be used for guidance only.

Drug Product Regulatory Data Package

In the UK environment, the expectations of the Medicines and Healthcare products Regulatory Agency (MHRA) are that drug product data representative of the clinical batches need only be included in the Investigational Medicinal Product Dossier (IMPD). This is submitted with the Clinical Trial Application, not quality control analytical data from the clinical batches themselves. The role of the Qualified Person (QP) negates the need to provide subsequent clinical batch data to the agency. Data should be generated from product manufactured at the intended site clinical manufacture. Given the intent of dosing product quickly following manufacture then appropriate risk-based release specifications can be justified.

In addition only short-term stability data are required given the rapid cycle time between the onset of manufacture, product release, and completion of dosing. Typically 7-day data are sufficient. Development teams may still choose to conduct longer-term ICH stability studies to support shelf-life assignment for next-stage clinical studies. However this can be managed off the critical path.

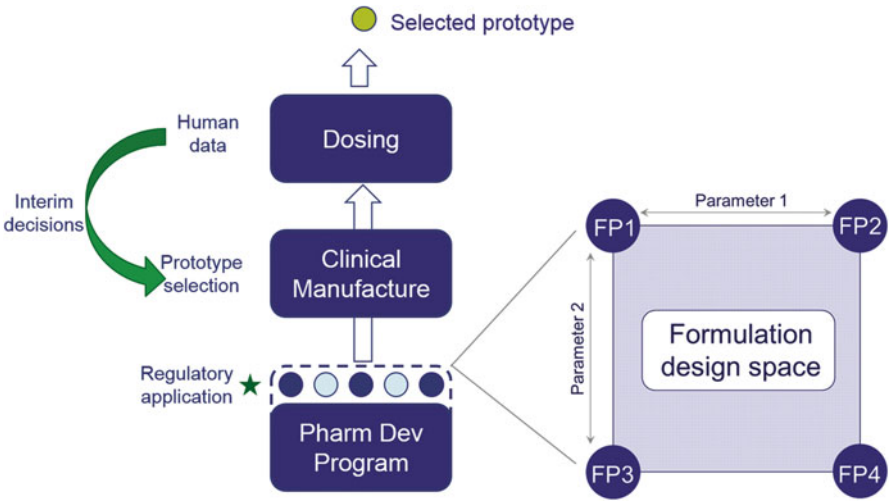

Fig. 9.4 RapidFACT process

For studies that include a formulation design space as described in Sect. 9.6.3, then batch data from the extreme compositions are included in submissions, analogous to standard bracketing approaches used in stability testing [48].

Clinical Study Design and Interim Decision Making

Clinical studies to evaluate and optimise extended release formulations are exploratory, non-randomised crossover designs, with subject numbers which are determined by known pharmacokinetic variability and number of completing datasets required. An illustrative example for a 5-way crossover study is shown in Fig. 9.5.

Decision-making algorithms are described up front in the clinical protocol, in the context of desired performance criteria. Rapid generation and analysis of clinical data is performed to inform the interim decision-making process. Safety, pharmacokinetic, biomarker, pharmacodynamic, and scintigraphic data can all be used to determine selection of formulation compositions for the next dosing period.

9.6.3.2 Case Studies and Applications

Product Optimisation Using a Two Dimensional Design Space

SLx-2101, a novel phosphodiesterase type 5 (PDE-5) inhibitor for hypertension, had previously been assessed in Phase I/II studies using an Immediate Release (IR) tablet formulation which failed to meet the target PK profile due to C_{max}-related

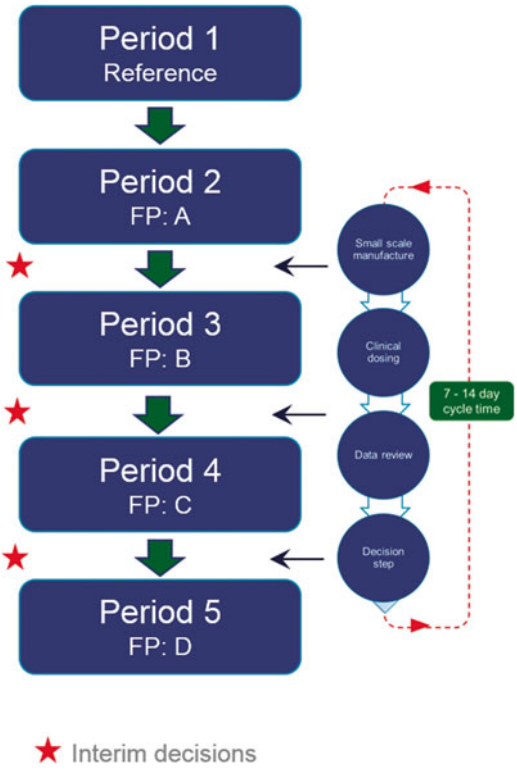

Fig. 9.5 Example RapidFACT clinical study design

adverse events, and C_{24} falling below the efficacious plasma concentration threshold [49]. In order to reduce the peak-trough ratio and thereby improve the safety profile and ensure once-daily dosing, an MR tablet was required to deliver a PK profile within the therapeutic window.

The drug molecule had demonstrated good biopharmaceutical and bulk properties, and hence was amenable to the development of an HPMC-based matrix tablet prepared by direct compression. To exploit the "design space" approach, a fixed mass tablet composition was developed with the potential to vary both the dose at a defined release profile and release profile at a defined dose [50]. Anticipated dose range and release duration for the MR tablet were based upon analysis and simulations from the available (IR) clinical PK data. A formulation design space was defined, which provided flexibility for a unit dose of between 10 and 20 mg SLx-2101, and an (in vitro) release duration of between 8 and 14 h (for 80 % drug release). Two different types of HPMC were used to control drug release rate and duration: variable levels of Methocel K4M Premium DC (8–16 % w/w) and a fixed level of Methocel K100LV Premium (12 % w/w). In vitro dissolution data are shown in Fig. 9.6, illustrating the flexibility in the drug delivery functionality which was available during the clinical programme.

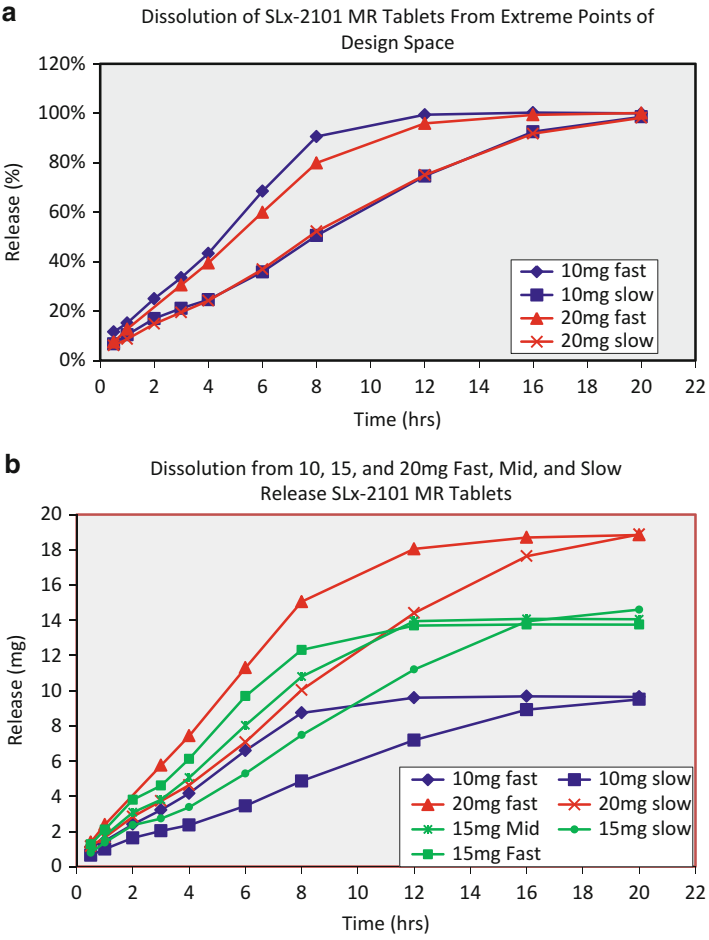

Fig. 9.6 In vitro drug release profiles for SLx-2101 MR tablets from extreme points of design space (**a**) % released; (**b**) mass released

A flexible 5-period clinical study was performed in 12 healthy volunteer subjects. Different MR formulation compositions were manufactured and dosed, with quantitative levels of SLX-2101 and HPMC determined based on interim PK data. The formulations dosed and key PK data are summarised in Table 9.5. As expected all MR formulations demonstrated lower C_{max} values and prolonged T_{max} in comparison with the IR tablet formulation. The mean C_{24} values were higher for the MR formulations than the IR tablet, with the highest mean C_{24} value observed for the 20 mg slow release formulation. There was an expected decrease in AUC_{last} values across the 20, 15, and 10 mg MR formulations. However the dose-normalised data were comparable. This indicated dose proportionality across the range studied. Terminal half-life was similar for all MR formulations and the IR tablet.

Table 9.5 Pharmacokinetics summary of SLx-2101 MR formulations. Based on information reported in [21]

Product	1	2	3	4	5
Dose	15 mg	15 mg	20 mg	10 mg	20 mg
IR or MR	IR	MR fast	MR slow	MR slow	MR slow
Fed/fast	Fast	Fast	Fast	Fast	Fed
C_{max} (ng/mL)	94.6 (40.1)	35.2 (13.2)	36.0 (12.6)	18.2 (5.78)	69.7 (14.8)
T_{max} (h)	1.42 (0.95)	5.83 (3.01)	6.17 (5.77)	6.53 (4.94)	5.91 (1.76)
C_{24} (ng/mL)	6.34 (3.98)	10.5 (5.77)	15.7 (7.24)	9.03 (3.54)	14.0 (7.87)
AUC_{last} (ng h/mL)	726 (250)	582 (205)	697 (214)	386 (102)	918 (289)
AUC_{inf} (ng h/mL)	743 (264)	605 (229)	711 (236)	424 (128)	962 (323)
Terminal half-life (h)	9.01 (1.65)	9.67 (3.13)	8.45 (1.88)	10.5 (3.55)	9.89 (2.83)
C_{max} (DN)	6.3	2.3	1.8	1.8	3.5
AUC_{last} (DN)	48.4	38.8	34.9	38.6	45.9

Bracketed number after pharmacokinetic parameter is standard deviation
DN dose-normalised data

Through the iterative selection of prototype compositions during the study it became apparent that a high-dose/slow release profiles were needed to achieve required target PK criteria. The 20 mg slow formulation was therefore identified as giving the desired performance attributes, maintaining AUC but blunting C_{max} and extending C_{24} compared to the reference product. When the formulation was evaluated in the fed state C_{max} and AUC_{last} values were higher, and although T_{max} was similar, there was a delay in the absorption of SLx-2101 in the fed state compared with the fasted state (T_{lag} 0.68 compared to 0.08 h). Data confirmed the continued MR input function in the fed state.

Design Space Augmentation with Gamma Scintigraphy

As described in Sect. 9.5.2, radiolabelling of MR dosage forms for scintigraphic imaging allows direct in vivo visualisation of dosage form performance. A recent publication has described how the combined use of a formulation design space coupled with PK and scintigraphic end points enabled the effective optimisation of a second-generation MR formulation for LY545694 Tosylate, a prodrug for compound 645838 [44]. To overcome dose-limiting adverse events from immediate release dosage forms, an initial 35mg MR formulation (Methocel® K4M Premium CR, 80 % targeted release over 8–10 h) had been developed. De-convolution techniques had shown however that the preferred site of absorption for LY545694 was in the small intestine, and hence based on expected GI transit times, significant quantities of LY545694 were being delivered to a non-absorptive region. The requirement was therefore to identify a revised MR formulation capable of achieving the same exposure and plasma concentration–time profile, but with a lower dose

Table 9.6 Study design and formulations for the investigation of LY545694 MR drug product. From [44], with kind permission of Springer Science and Business Media

Period	Formulation	Radiolabelled?	MR polymer	Dose (mg)
1	Oral solution reference	N	n/a	25
2	New MR	Y	K100LV (30% w/w)	25
3	MR reference	Y	K4M	35
4	New MR	Y	K100LV (24% w/w)	25
5	New MR	Y	K100LV (20% w/w)	25
6	MR reference	N	K4M	35

(25 mg), by a precise, optimal targeting of drug delivery to the small intestine. The authors described how a formulation design space was established with Methocel® K100LV Premium CR as the release controlling polymer (composition range 20–50 % w/w per tablet) to enable flexible, real-time targeting of drug release within the small intestine. Based on in vitro dissolution data, the K100LV polymer was expected to give a faster in vivo release than the K4M formulation. Tablets were radiolabelled with ≤1 MBq In resin to allow scintigraphy as well as PK to be used for interim decision making. A six-arm flexible RapidFACT study in 16 healthy volunteer subjects, dosed in the fasted state, was conducted to identify an optimum composition of Methocel K100LV from within the formulation design space (Table 9.6).

Results are shown in Table 9.7 (pharmacokinetics) and Fig. 9.7. Based on in vitro dissolution data (Fig. 9.8) Prototype 1 (30 % w/w K100LV) should have given a faster release profile in vivo than the reference MR formulation, resulting in the desired improvement in relative bioavailability. However the scintigraphic and PK data actually confirmed a slower completion of erosion and only comparable dose-normalised exposure. This was attributed to a higher mechanical strength in vivo than otherwise predicted from dissolution testing.

Given the within-protocol flexibility, however, Prototypes 2 and 3 were subsequently selected and dosed (24 % and 20 % w/w K100LV respectively), in response to the emerging data, with the 20 % polymer level successfully giving the desired exposure profile at 25 mg tablet strength. AUC ratios relative to the reference were 1.25 for the prodrug and 1.31 for the active moiety. Scintigraphic data supported this observation, and showed that in all subjects, erosion was largely complete in the small intestine. The authors concluded how the outcome would have taken multiple iterative clinical studies to achieve using a more traditional development approach.

Implications for In Vitro: In Vivo Correlations

A key goal for development teams working on extended release formulations will at some stage be to assess if an in vitro–in vivo relationship or correlation (IVIVR or IVIVC) can be established between in vitro dissolution data and PK parameters. If possible, significant benefits can be gained in regard to justification of Quality

Table 9.7 Summary PK data for LY545694 and compound 645838 after dosing different MR formulations to human subjects. From [44], with kind permission of Springer Science and Business Media

	Regimen	Solution	Unlabelled reference	Labelled reference	Prototype 1	Prototype 2	Prototype 3
LY545694	C_{max} (ng/mL)	134 (27)	65.6 (57)	71.6 (39)	47.2 (39)	60.6 (42)	70.3 (40)
	Median T_{max} (h)	0.51	3.00	3.16	3.00	3.00	3.00
	AUC (ng h/mL)	173 (44)	280 (46)	300 (47)	205 (36)	230 (38)	249 (29)
	C_{max}/C_{12}	465 (79.4)	23.8 (52.2)	24.8 (67)	25.2 (59)	32.8 (51)	49.9 (90.6)
	AUC ratio[a] (90 % CI)	–	–	0.93 (0.73, 1.20)	1.02 (0.82, 1.29)	1.15 (0.92, 1.45)	1.25 (0.99, 1.56)
645838	C_{max} (ng/mL)	130 (19)	70.5 (28)	68.7 (50)	47.1 (50)	52.9 (43)	71.3 (37)
	Median T_{max} (h)	1.75	4.00	4.00	4.00	4.00	4.00
	AUC (ng h/mL)	687 (22)	521 (29)	556 (45)	356 (44)	395 (44)	488 (35)
	C_{max}/C_{12}	16.9 (30.2)	6.07 (31)	4.87 (39)	5.72 (32)	6.12 (30.3)	7.23 (44)
	AUC ratio[a] (90 % CI)	–	–	0.94 (0.76, 1.16)	0.96 (0.78, 1.18)	1.06 (0.86, 1.31)	1.31 (1.06, 1.62)

[a]Dose-normalised AUC ratios versus unlabelled reference; geometric mean values (%CV) reported for C_{max}, AUC and C_{max}/C_{12}

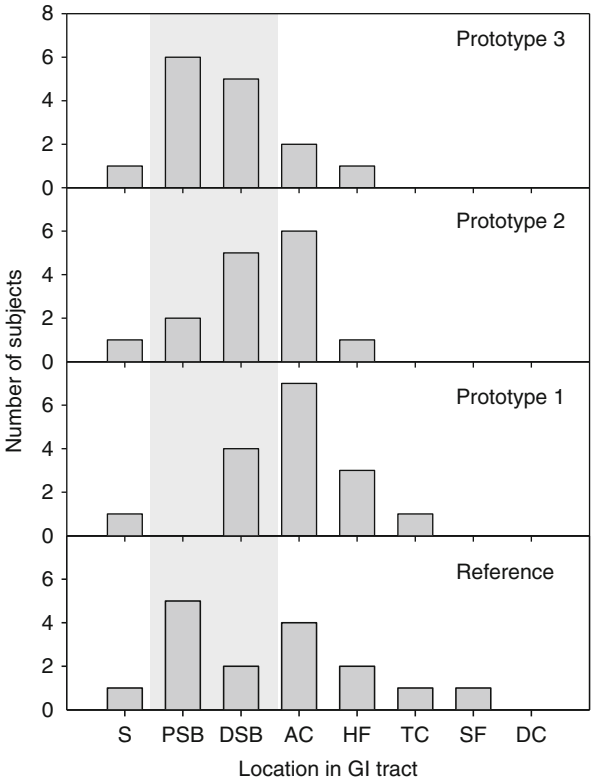

Fig. 9.7 Anatomical location of complete erosion for radiolabelled reference and prototype LY545694 formulations. Shaded area indicates apparent regions for absorption. From [43], reproduced with kind permission from Springer Science and Business Media

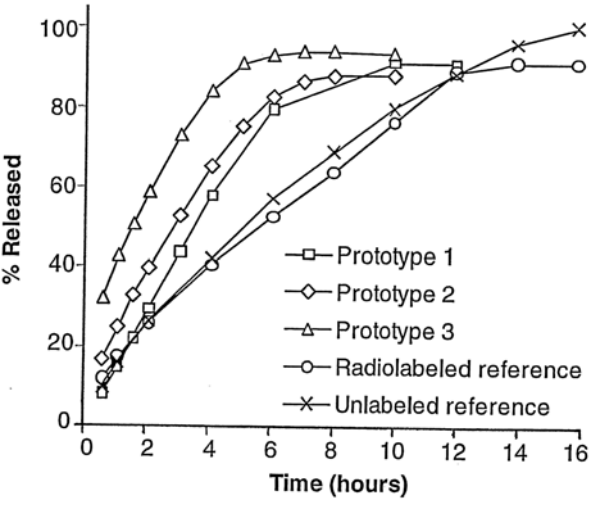

Fig. 9.8 In vitro drug release profiles for extended release LY545694 formulations employed in the clinical study. Labelled and unlabelled reference, $n=12$; Prototypes 1, 2, 3, $n=6$. From [43], reproduced with kind permission from Springer Science and Business Media

Control dissolution specifications, and managing the impact of CMC changes during development and post-commercialisation via biowaivers in lieu of performing clinical bioequivalence studies [51, 52]. Clinical studies will therefore be conducted with this specific objective at some stage during the development cycle.

Based on the above case studies, it can be seen that a natural outcome from clinical studies that exploit the real-time capability for adjustments in MR drug product compositions with the intent of identifying an *optimal* formulation prototype. In addition, this approach will also be a rich output of corresponding in vitro dissolution and in vivo PK data amenable for IVIVR/C analysis. It has recently been reported [53] that a numerical-based IVIVC assessment using WiNonlin (Pharsight Corp) was able to establish a Level A correlation between de-convoluted fraction absorbed data and in vitro dissolution fraction released results from a RapidFACT study. The clinical study had evaluated an MR matrix tablet composition with a two-dimensional design space with capability to vary drug and HPMC polymer loading. The pharmacokinetics data could be dose normalised (in the linear range) and dissolution profiles were varied by at least 10 % as per the guidance requirements. The clinical study had been a 6-way crossover which therefore generated datasets for both internal and external model validation. Such approaches offer further opportunities to drive development efficiencies.

Quality-by-Design

Over the past decade there have been strong industry and regulatory drivers for companies to be able to demonstrate a full and complete understanding of the impact of product or process change on product quality and performance through QBD [47]. Risk-based assessments are made of formulation compositions and manufacturing processes in order to identify potential critical-to-quality attributes. Typically however the impact of variability in these parameters is then characterised by in vitro studies only (e.g. dissolution testing) which, in the absence of an IVIVC/R, may not provide assurance of in vivo performance. As such identification of "safe space" control strategies via process settings or product specifications carries risk. Rapid, flexible clinical studies also offer the potential to generate clinical PK data to underpin a QbD strategy.

For an MR matrix tablet it can be critical to understand the relationship, for example, between SAVR from a product design perspective. To accommodate different tablet strengths it may be preferred to have a common blend and vary dose via tablet weight. The impact of subsequent changes in SAVR therefore needs to be understood to ensure comparable drug release (and PK profiles) in terms of dose proportionality. Recent studies have included the development of a two-dimensional design space for a hypromellose K100M-based tablet, and to evaluate the clinical impact of varying SAVR as well as the drug: polymer ratio. This is illustrated in Fig. 9.9 (unpublished data). Real-time flexibility then allows a more accurate definition of the "safe space", based on human PK data, and concomitant definition of product and process controls.

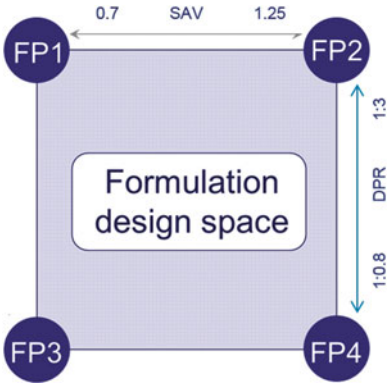

Fig. 9.9 Quality by design formulation space for a hydrophilic matrix tablet

9.7 Conclusions

An effective hydrophilic matrix tablet must deliver a stable stream of active compound at the right rate to the gastrointestinal (GI) tract in order to express a beneficial therapeutic effect. It must do this whilst moving through the GI tract, passing through a range of different environments, experiencing changes in environmental parameters such as pH, fluid volume, fluid composition, and physical forces, whilst also accounting for regional changes in drug absorption. This requirement, when coupled with the physico-chemical and biopharmaceutical properties of molecules in development, presents a considerable challenge to the development team in identifying a drug product formulation capable of achieving the TPP. Traditional formulation development strategies have proven to be suboptimal and time-consuming for the development of matrix-based tablet formulations, and carry the "accepted risk" that in silico, in vitro, and preclinical testing methods are as yet unable to provide categorical insights into the predicted in vivo performance in humans. New development paradigms have emerged based upon a Translational Pharmaceutics platform and flexible regulatory strategies which provide the development team the ability to optimise formulation compositions and production processes in real time based on arising human data.

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Chapter 10
Extrusion: An Enabling Technology for Controlled-Release Hydrophilic Matrix Systems

Divya Tewari and Thomas Dürig

10.1 Introduction

The use of hydrophilic polymers in controlled-release matrix tablets dates back to the 1960s. An early example is the work of Lapidus and Lordi who reviewed factors affecting the release of water-soluble drugs from a hydrophilic matrix system [1]. However, the widespread commercial implementation of polymers like high molecular weight HPMC type 2208 for controlled release did not occur until the mid-1980s and can be said to have reached a peak in 1990s when a large number of hydrophilic matrix-based blockbuster drugs were launched in the United States and in Europe. Some examples include metformin HCl 500 and 750 mg extended-release tablets (Glucophage XR, Bristol-Myers Squibb), amoxicillin/clavulanic acid 1,000/62.5 mg extended-release tablets (Augmentin XR, GlaxoSmithkline), clarithromycin 500 mg extended-release tablets (Biaxin XL, AbbVie), divalproex sodium 250 and 500 mg tablets (Depakote ER, AbbVie), buproprion HCl 150 and 300 mg tablets (Wellbutrin SR, GlaxoSmithkline), zileuton 600 mg extended-release tablets (Zyflo CR, Cornestone), paroxetine HCl 12.5 and 25 mg extended-release tablets (Paxil CR, GlaxoSmithkline), and zolpidem tartrate 6.25 and 12.5 mg extended-release tablets (Ambien CR, Sanofi-Aventis). While other technology platforms such as coated multi-particulates (membrane-reservoir systems) and oral osmotic pump systems have also found commercial implementation, hydrophilic

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matrix systems are today a dominant controlled-release technology platform. This is largely due to their decades-long proven safety and efficacy record and being amenable to commercial processing and manufacturing unit processes. In recent years, advances have been made in hydrophilic matrix polymers to provide directly compressible HPMC 2208 grades such as Benecel™ HPMC PH DC and a broad range of viscosity grades such as Benecel™ HPMC K250 PH PRM, K750 PH PRM, and K1500 PH PRM.

Due to the changing needs of new compounds and therapeutic regimes the drug delivery limitations of conventional controlled-release dosage forms are becoming increasingly common. This has required the development and introduction of new approaches to hydrophilic matrix formulation and processing to enable the delivery and commercialization of new compounds. In this chapter, we describe how the use of twin-screw extrusion combined with new hydrophilic matrix formulation approaches can provide for the controlled delivery of challenging compounds.

10.2 Limitations of Hydrophilic Matrix Systems and Approaches to Overcome the Limitations

Although widely used commercially, hydrophilic matrix systems have some well-known limitations. Amongst them is the ability to accommodate and control the release of large doses of highly soluble drugs.

Typical drug loads for wet granulated, dry granulated, or directly compressed tablets are usually 50 % or less. At drug loads of 75 % or higher, the drug mechanical properties may dominate and also polymer choice when using typical amounts of around 25–30 % w/w increasingly has little impact on modulation of release profiles for highly soluble drugs. One thus faces the challenges of inadequate tablet compaction properties coupled with inadequate control of drug release kinetics. Additionally, the acceptable upper tablet size limit and mass limit for swallowing by a patient and to assure compliance ranges from 800 to 1,400 mg, therefore requiring the amount of added excipients to be minimized [2]. Commercial examples of tablets approaching this limit include metformin 750 mg extended-release tablets (Glucophage XL, Bristol-Myers Squibb), niacin extended release with lovastatin immediate release (Advicor, various strengths, AbbVie), ranolazine 1,000 mg extended-release tablets (Ranexa, Gilead), and metformin/sitagliptin (Janumet XR, Merck).

Approaches to overcome these limitations have included simple crystal and particle coating and preparation of microbeads with insoluble polymers such as ethylcellulose and methacrylic acid copolymer, thus maximizing surface area to volume coverage of the rate controlling excipients. Examples of these approaches include potassium chloride 10 mEq extended-release tablets (Klor-Con, Upsher Smith) and metoprolol succincate 25, 50, 100, and 200 mg extended-release tablets (Toprol XL, AstraZeneca). However, these processes require the use of organic solvents and

fluid bed coating with long cycle times. Alternatively, instead of coating with hydrophobic polymers, excipients such as waxes and magnesium stearate can be incorporated *into* a controlled-release dosage form to provide physical diffusion barriers while minimizing overall excipient volumes [2, 3]. However, such approaches have found limited applications due to lack of robustness at commercial manufacturing scale and variability due to food-dependent in vivo results.

A further approach to overcome these limitations has been the use of matrix tablets combined with additional release controlling film coatings (matrix-reservoir combination systems) [4]. However, such an approach adds cost and manufacturing complexity as compared to simple matrix systems.

In addition the opposite challenge, i.e., the extended delivery of low soluble drugs, is also encountered with increasing frequency. In this case, hydrophilic erodible systems using intermediate molecular weight grades of polymers such as HPMC or hydroxypropyl cellulose, HPC may be well suited; however additional means of solubilization such as inclusion of large amounts of cyclodextrins or surfactants have to be attempted. This again can push the limits of dosage form size.

For both these scenarios where limited or no feasible technical options exist, twin-screw extrusion processing may offer a commercially viable and practical solution. This is further discussed in this chapter.

10.3 Hot-Melt Twin-Screw Extrusion: An Enabling Technology for Controlled Release

10.3.1 General Background

Extrusion can be generally described as a process by which an extrudate with new or composite properties is formed by forcing one or more components through an orifice under controlled conditions of temperature, shear, and pressure [5]. Extrusion is widely applied in many industries and is generally regarded as a mature technology, having been largely developed and refined during the nineteenth and twentieth centuries. However, extrusion remains highly relevant in food and plastics manufacturing and is now a significant emerging technology for solid dosage form manufacturing.

A major advantage of twin-screw extrusion over conventional unit processes such as mixing, powder blending, high shear granulating, and roller compacting is that these unit processes can be combined into essentially a single operation within the extruder. Moreover, the extent of these individual aspects of the overall process can be readily controlled and manipulated by the extruder design. In particular screw configurations and die designs offer large flexibility as does the option of employing various temperature profiles and shear rates. Finally, while extruders are suitable for a batch mode of manufacturing in the case of smaller volume, but high value pharmaceutical products, the process is inherently a continuous one. This also makes it of utility in the manufacturing of large volume products as it allows for a smaller, more efficient footprint with discrete manufacturing unit operations validation

and quality control. Additionally, due to the small footprint and contained nature of the feeding mechanism and the extruder barrel, the process can be readily isolated in the case of highly potent compounds.

10.3.2 Basic Process Description

A basic twin-screw extruder consists of a drive system, a series of independently controlled modular barrel blocks, two screws with an individual screw element arranged on a screw shaft, a die, and connections to utilities and controls. Additional downstream equipment such as conveyor belt, calendering rolls, and pelletizers and mills are common. An illustration of a pilot-scale 18 mm extruder suitable for formulation development and scale-up is shown in Fig. 10.1. The equivalent model in GMP configuration is shown in Fig. 10.2. A schematic layout for a typical extruder is given in Fig. 10.3 and typical screw designs are shown in Figs. 10.4 and 10.5. Several excellent reference texts have been written on pharmaceutical extrusion technology and the reader is referred to these for more detailed process descriptions [6, 7].

Fig. 10.1 Pilot-scale 18 mm Leistritz ZSE extruder as used in some of the work highlighted in this chapter (picture courtesy of Leistritz Extrusionstechnik/Germany)

Fig. 10.2 Leistritz ZSE 18 PH extruder, 18 mm barrel diameter, suitable for GMP manufacturing (picture courtesy of Leistritz Extrusionstechnik/Germany)

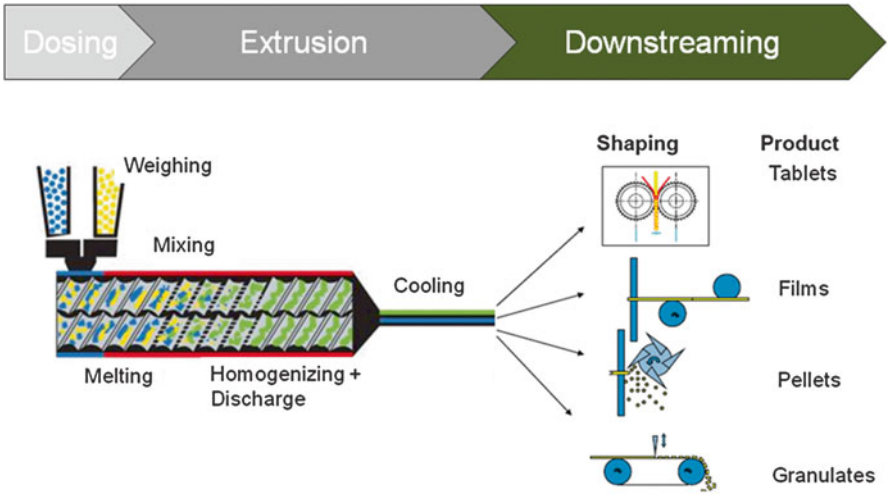

Fig. 10.3 Schematic of the extrusion process

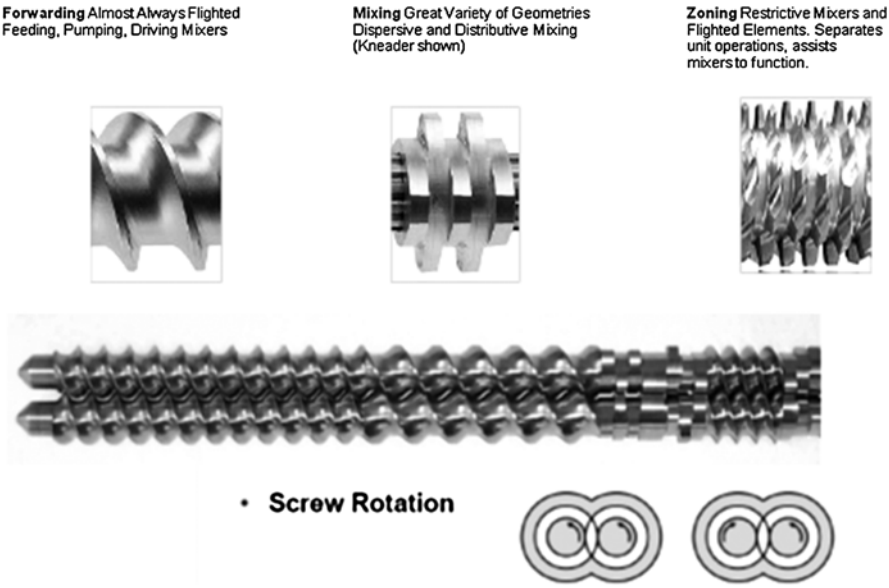

Fig. 10.4 Typical extruder screw element design options (picture courtesy of Leistritz Extrusionstechnik/Germany)

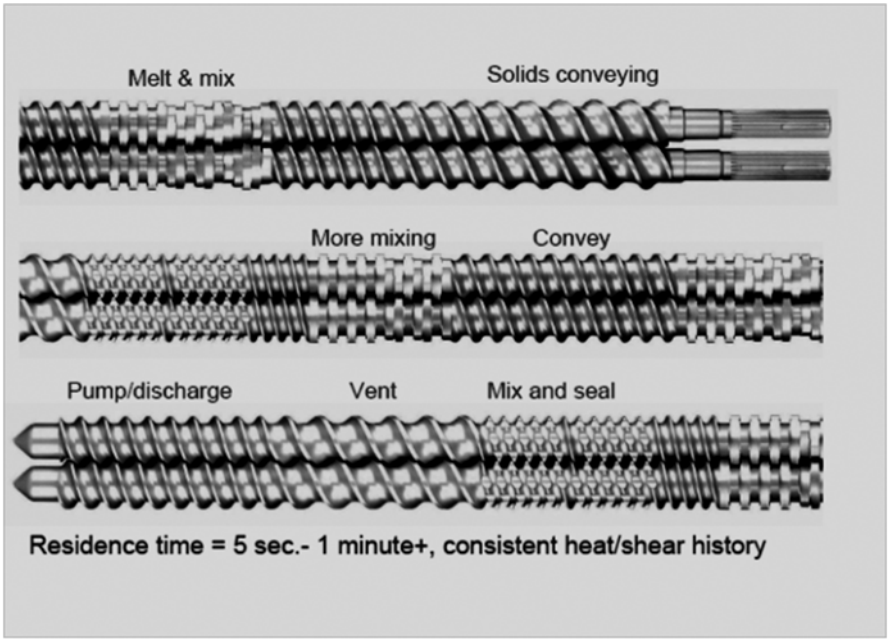

Fig. 10.5 Various co-rotating screw configurations based on different assemblies of elements (picture courtesy of Leistritz Extrusionstechnik/Germany)

10.3.3 Polymers Used for Extrusion

The selection of the polymers for hot-melt extrusion mainly depends on factors such as the thermoplasticity of the polymer, drug–polymer miscibility, polymer stability, and the desired drug release kinetics. Thermoplastic polymers are typically preferred as they can be processed with the extruder at suitable temperatures without affecting the stability of volatile or heat-sensitive drugs. Plasticizers are often added to the polymer if the processing temperature is not suitable for the drug. In some cases, the drug itself can be an effective plasticizer. Polymers used in hot-melt extruded dosage form range from water-soluble ones used to achieve diffusion-dependent drug release kinetics to water-insoluble polymers which can be employed to achieve diffusion- and erosion-dependent drug release mechanisms.

Commonly used, pharmaceutically approved polymers include the cellulose derivatives (hydroxypropylcellulose [HPC], hypromellose [HPMC], ethylcellulose [EC], hypromellose acetate succinate [HPMCAS], cellulose acetate [CA], CA phthalate [CAP]), vinyl polymers (polyvinylpyrrolidones [PVP], copovidone [PVP-VA]), polyethylene oxide (PEO), polyethylene glycol (PEG), and methacrylates (Eudragit™ series) [8]. Hydrophilic polymers such as cellulose ethers (HPC and HPMC) and vinyl lactam polymers (PVP and PVP-VA) are most frequently used as release modifiers and solubilizing carriers. McGinity et al. [9] have also demonstrated the use of natural polymers such as chitosan and xanthan gums as hydrophilic release retardants in hot-melt extrusion applications.

10.3.3.1 Cellulose Derivatives

Cellulose ethers are chemically modified versions of a naturally occurring polysaccharide. Each glucose unit in the polysaccharide, linked to its neighbor by β-1-4 glycoside bonds, has three hydroxyl groups that can be derivatized by alkalization to have hydroxypropyl, hydroxypropyl methyl, and many other semisynthetic cellulosics (Fig. 10.6).

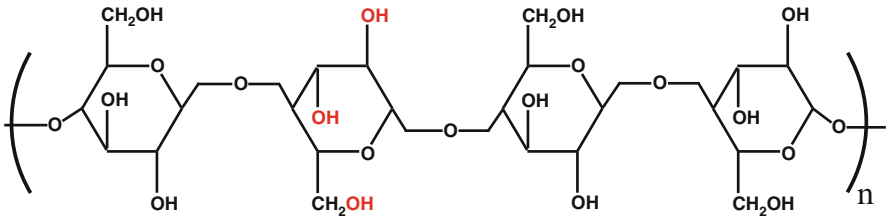

Fig. 10.6 Representative structure of cellulose

Table 10.1 Thermal, physical, and mechanical properties of hydroxypropylcellulose (HPC) (based on manufacturer's data for Klucel™, adapted from data from [8])

Property	HPC	Method
Solid State—particle size (μm)	Mean diameter-50–80 μm for fine grind and 250–300 μm for regular grind	Sympatec Helos laser diffraction
Molecular Weight range (Da)	40,000–80,000	
Glass transition temperature range (°C)	−4.0 to −4.5	DSC: TA instruments DSC Q2000 software
Melting temperature range depending on the molecular weight (°C)	182–191	TA instruments
Melting temperature range (°C)	150–210	
Processing temperature (°C)	100–130	Based on Leistritz ZSE 18HP
Processing temperature (°C) maximum	270–285	DSC: TA instruments DSC Q2000 software
True density (g/cm^3)	1.200–1.214	Mirometrics AccyPyc 1300 Pycnometer
Amorphous density (g/cm^3)	1.088	Instron Capillary Rheometer
Crystalline density (g/cm^3)	2.054	X ray diffraction
Bulk density (g/cm^3)	0.28–0.39	
Crystallinity (%)	14.9	Water-cast film/instron capillary rheometer/X ray diffraction

10.3.4 Hydroxypropylcellulose

The thermal and mechanical properties of hydroxypropylcellulose (available commercially from Ashland Inc. as Klucel™ HPC and Nippon Soda, Nisso™ HPC) (Table 10.1), make it pliable and easy to extrude. HPC has a low glass transition temperature, T_g, of approximately −4.5 °C which provides for a low-melt viscosity and fast-melt flow properties, depending upon the molecular weight of the polymer used (Fig. 10.7). Low molecular weight grades of HPC are often utilized as carriers to attain solid dispersions of poorly soluble drugs [10] and typically do not require plasticizers to melt extrude. The hydroxyl groups of the cellulose backbone and the incorporated substituent hydroxypropoxyl groups are capable of donating hydrogen bonds to active pharmaceutical ingredients (APIs) with hydrogen bond accepting groups. HPC is most capable of stabilizing amorphous dispersions of APIs with hydrogen bond accepting groups. One of the limitations of HPC for use as solid dispersion carrier is its low T_g. This tends to impart a lower T_g to the drug–polymer dispersion which predisposes the dispersion to recrystallization. As a rule of thumb, the T_g of the resultant dispersion should be 50 °C above the highest anticipated storage temperature, e.g., 50–70 °C higher than the accelerated stability temperature of 40 °C. Higher molecular weight grades of HPC (commercially available from Ashland, Klucel HPC HXF and Klucel HPC MXF) are typically recommended for controlled-release applications [11, 12].

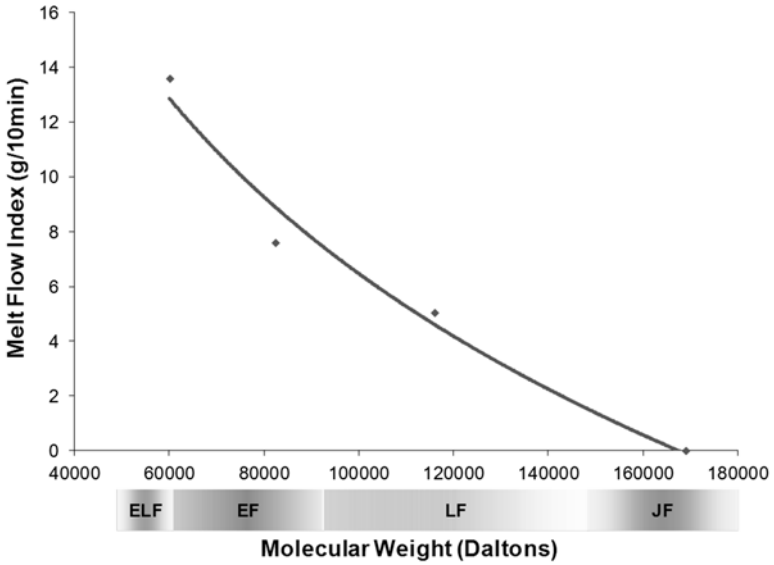

Fig. 10.7 Effect of molecular weight on the melt flow of Klucel™ hydroxypropylcellulsoe (HPC) at 150 °C using ASTM D1238

10.3.4.1 Hypromellose and Hypromellose Acetate Succinate

HPMC is available in several grades that vary in viscosity and extent of substitution (commercially available from Ashland Inc. as Benecel™ HPMC and from Dow Chemical Co. as Methocel™ HPMC grades). The T_g of these polymers varies from 178 to 202 °C depending upon the molecular weight. Due to this high T_g it may therefore require the addition of plasticizers, up to 30 % w/w, to enable melt extrusion. The methoxyl groups are comparably very weak hydrogen bond acceptors, relative to the hydroxypropoxyl groups but, like HPC, HPMC is most able to interact with APIs with hydrogen bond accepting groups. Associated with these hydrogen bonding propensities is recrystallization inhibition which is useful in stabilizing amorphous drugs and thereby enhancing the bioavailability of poorly soluble drugs. The supersaturated levels generated by dissolution of the amorphous solid dispersion can arise from the stabilizing effects of the polymers [13] or the complexation of the crystalline drugs in the polymer matrix, hence reducing the degree of supersaturation and lower thermodynamic tendency toward recrystallization [14]. Higher molecular weight grades of HPMC have been used successfully as release modulators and stabilization enhancers for controlled release of poorly soluble drugs [15].

HPMCAS was originally developed as an enteric polymer for aqueous dispersion coating. The enteric coating prevents drug dissolution in the acidic pH environment of the stomach in order to reduce drug degradation or ameliorate stomach irritation. HPMCAS has a cellulose backbone with hydroxypropoxy, methoxy, acetyl, and

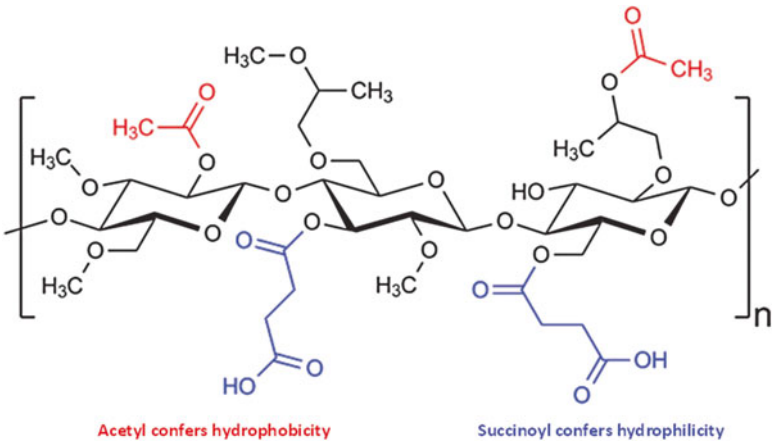

Fig. 10.8 Representative structure of hypromellose acetate succinate (HPMCAS)

succinoyl substituent groups (Fig. 10.8). There are six grades available commercially (AquaSolve™ HPMCAS from Ashland Inc.; Aqoat™ HPMCAS from Shin-Etsu Chemical Co. Ltd) based on the physicochemical properties of the polymer. The F (fine) and G (granular) grades differ only in their particle size, whereas L, M, and H grades are chemically different and vary in their pH solubility. The L, M, and H grades dissolve at pH ≥ 5.5, 6.0, and 6.8, respectively. Thus, the release of the drug in the gastrointestinal tract from a tablet dosage form containing these polymers can be controlled as required by using a suitable grade of the polymer. HPMCAS is an amorphous polymer and has a T_g of about 120–125 °C. The hydroxyl groups of the cellulose backbone and the 2-hydroxypropoxyl substituent groups are capable of donating hydrogen bond to APIs with hydrogen bond accepting groups. The acetyl and succinoyl groups are capable of accepting hydrogen bonds from APIs which is important in stabilizing solid dispersions by inhibiting recrystallization. The overall stabilization effect is attributed to the interaction between API and the polymer functional groups, including specific hydrophobic interactions between the drug and the acetyl groups. Due to the relatively poor thermal plasticity of HPMC and HPMCAS, plasticizers or co-formulation with another more thermoplastic polymer as an extrusion aid may be necessary for melt extrusion of HPMC and HPMCAS.

10.3.4.2 Polyethylene Oxide

Polyethylene oxides (PEOs) are nonionic homopolymers of ethylene oxide represented by the formula $(OCH_2CH_2)_n$. These high molecular weight hydrophilic polymers are available as white, free-flowing powders and are manufactured by Dow Chemical Company under the trade name of POLYOX™. The pharmaceutical grades of POLYOX are available in molecular weight ranges of 100,000–7,000,000 Da

Table 10.2 Commercial grades of polyethylene oxide used in the pharmaceutical industry (based on manufacturer's data for POLYOX™)

POLYOX resins	Molecular weight (Da)	Aqueous viscosity range at 25 °C (m Pa s)
WSR N-10 NF	100,000	12–50 (at 5 % w/v)
WSR N-80 NF	200,000	65–115 (at 5 % w/v)
WSR N-750 NF	300,000	600–1000 (at 5 % w/v)
WSR 205 NF	600,000	4,500–8,800 (at 5 % w/v)
WSR 1105 NF	900,000	8,800–17,600 (at 5 % w/v)
WSR N-12 K NF	1,000,000	400–800 (at 2 % w/v)
WSR N-60 K NF	2,000,000	2,000–4,000 (at 2 % w/v)
WSR 301 NF	4,000,000	1,650–5,500 (at 1 % w/v)
WSR coagulant NF	5,000,000	5,500–7,500 (at 1 % w/v)
WSR 303 NF	7,000,000	7,500–10,000 (at 1 % w/v)

(Table 10.2). Despite its high molecular weight, POLYOX is highly crystalline and has a melting point around 65 °C, above which the polymer becomes thermoplastic. Due to its low melting point and good melt flow index it's considered as a suitable polymer for use in hot-melt extruded formulations. The high molecular weight grades require plasticizer addition in order to enable melt extrusion at moderate temperatures [16]. Zhang and McGinity [17] described a novel method to prepare POLYOX sustained-release matrix tablets using a single screw extruder employing chlorpheniramine maleate as a model drug. The influence of PEO properties on drug release was investigated. PEG 3350 was included as the plasticizer to assist the extrusion processing and 4.5 mm diameter rods were extruded and cut across the diameter of the rod to yield tablets. The stability of PEO was studied as a function of polymer type, temperature, and residence time in the extruder. They demonstrated that excellent mixing of the components occurred in the barrel of the extruder, since the content uniformity of the extruded tablets was within 99.0–101.0 %. An increase in the amount of plasticizer was found to increase the drug release, whereas increasing drug concentration in the matrix only slightly affected drug release up to drug loading levels around 20 % w/w. Combinations of different grades of POLYOX with other polymers may enable formulators to tailor release profiles of the drugs as well as enhance the melt-extrusion processing.

10.3.5 Polyvinyl Lactam Polymers

Polyvinyl lactam polymers available as homopolymers, such as polyvinylpyrrolidone (povidone, commercially available from Ashland Inc. as Plasdone™ and BASF SE as Kollidon™ grades), or as copolymers, polyvinylpyrrolidone-vinyl acetates (copovidones, commercially available from Ashland Inc. as Plasdone™ and BASF SE as Kollidon™), have been widely used in the pharmaceutical industry

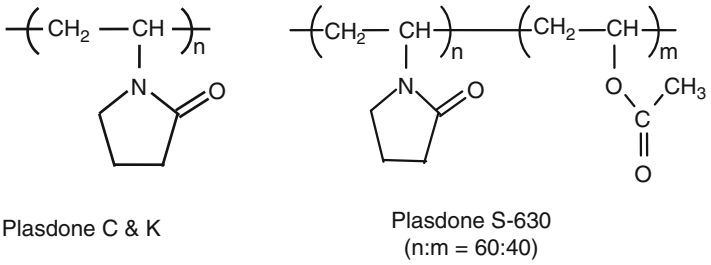

Fig. 10.9 Representative structure of povidone (Plasdone C and K) and copovidone (Plasdone S-630)

for more than 40 years (Fig. 10.9). These polymers are synthesized by radical polymerization of the corresponding monomers and depending upon the reaction conditions different polymer properties can be obtained.

Povidones (Plasdone™ *K* grades) are commonly used as solubilization carriers. The T_g ranges from 120 to 174 °C depending upon the *K* value. They are compatible with most plasticizers and may require the addition of plasticizers for melt extrusion. The monomer units are capable of accepting hydrogen bonds. Copovidone PVP-VA copolymers (Plasdone™ S630) have a T_g around 106 °C that makes it ideal for melt-extrusion applications. It is both aqueous and organosoluble and both monomer units are capable of accepting hydrogen bonds. Its limitation in HME application is its hygroscopicity. Both povidones and copovidones are water soluble which limits its applicability in controlled-release applications. They are most frequently used to enhance solubility of poorly soluble drugs [18] and in combination with cellulose ethers in controlled-release applications [15].

Graft copolymers can also be obtained by grafting monomers onto other polymers. These polymers differ significantly in their hydrophilicity/lipophilicity properties which are derived from the graft components and grafted side chains. One such graft polymer, Soluplus®, was developed by BASF in 2009. It was produced by grafting vinylcaprolactam and vinyl acetate onto polyethylene glycol in a copolymerization reaction. As a result, it has a backbone of polyethylene glycol and side chains comprising the two vinyl monomers. This gives the product an amphiphilic character and it is mostly utilized for solubility enhancement. It has a low T_g and dense particle structure that enables melt extrusion to be carried out at extremely high-throughput rates as the polymer can be fed into the extruder rapidly [18].

BASF's Kollidon® SR, which is a formulated mixture of the two polymers polyvinyl acetate and povidone in the ratio of 8:2, is designed to be used in sustained-release applications. The insoluble polyvinyl acetate provides for an extremely high degree of plasticity and also presents a diffusion barrier that slows down the release of the drug. The water-soluble povidone creates micropores in the framework of the polyvinyl acetate through which water can penetrate the entire system, thereby dissolving the active drug and allowing the diffusion of the drug. Özgüney et al. [19] recently demonstrated the utility of Kollidon SR in melt-extrusion applications.

10.3.6 Use of Twin-Screw Extrusion in Controlled-Release Matrix Applications

10.3.6.1 Recent Advances for Controlled Release of Highly Soluble Drugs

The limitations of conventionally manufactured hydrophilic matrix high doses of highly soluble drugs have been described in Sect. 10.2. Hot-melt extrusion offers an elegant means to overcome many of these limitations.

Recently melt extrusion has been utilized for various controlled-release applications in which extrudates are milled to produce granules and compressed into final tablet dosage forms. These formulations are not necessarily based on water-soluble polymers alone but may also require water-insoluble polymers in order to optimize release profiles and modulate release of extremely highly soluble drugs. In 2010, Pinto and coworkers [20, 21] investigated the feasibility of using hot-melt extrusion as an alternative to wet granulation or direct compression for the preparation of highly soluble drugs at high loads (75 % w/w drug load). Higher molecular weight grades of HPC, Klucel™ HF hydroxypropylcellylose and Aqualon™ ethylcellulose, were used as hydrophilic and hydrophobic controlled-release polymer, respectively, using metformin as a model high-dose, high solubility drug. The metformin tablets made by employing hot-melt extrusion were twice as strong and also smaller and consequently less porous when compared to the analogous tablets made by wet granulation or direct compression (Table 10.3, Fig. 10.10). The improved mechanical properties and smaller tablet size for the same weight of unit dose can be attributed to the intimate mixing of drug with polymer in the molten state and the substantial elimination of air in the extrudate. In addition, the extrusion process also resulted in improved compactibility and reduced elastic recovery as evidenced by the enhanced tablet strength and reduced friability. The reduced porosity of the metformin tablets prepared using hot-melt extrusion resulted in a dramatic improvement in the release retardation of metformin as compared to wet granulated and direct compression tablets (Fig. 10.11). These differences can be attributed to the lower porosity of the hot-melt extruded tablets which resulted in slower ingress of media into the tablet (Fig. 10.12) and slower diffusion of dissolved drug out of the tablet, notably in the early time phase (first 30 min). After this initial period a sufficiently strong gel layer envelops the tablet to control the further ingress of water into the system. Higher

Table 10.3 Physical characteristics of extended-release tablets prepared using different manufacturing processes

Unit process	Granule density (g/ml)	Tablet volume (ml)	Porosity (%)	Tablet strength (kp) 3 kN pre-compression 15 kN main compression
Extrusion	1.30	0.8	3.4	14.2
Wet granulation	1.35	0.9	12.7	4.0
Direct compression	1.35	0.9	15.3	5.0

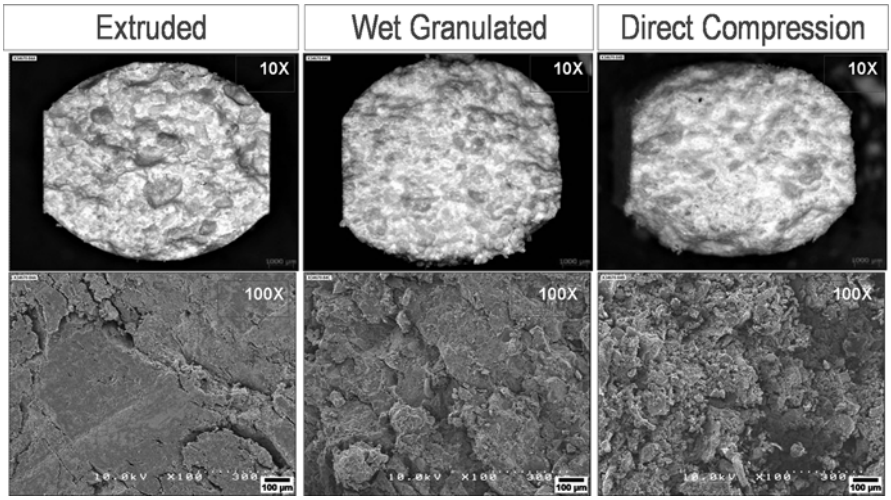

Fig. 10.10 Porosity of metformin hydrochloride tablets prepared by different processes. Scanning electron microscopy pictures of the cross section of the tablets indicates that tablets made by the extrusion process were denser and less porous relative to tablets made by the alternate processes

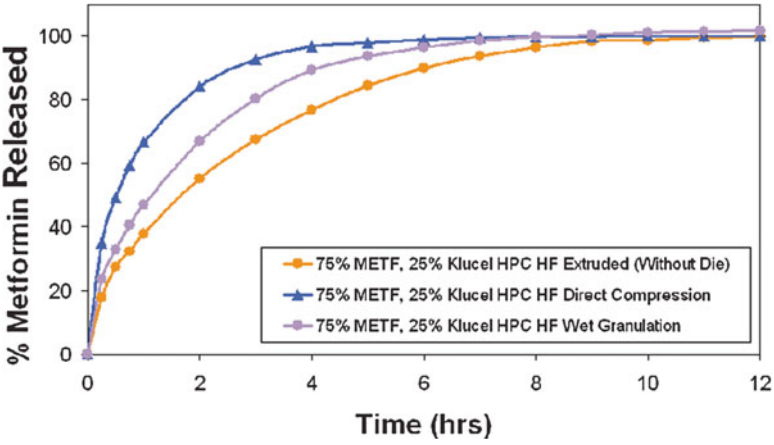

Fig. 10.11 Dissolution profiles of metformin tablets. Tablets made by the extrusion process exhibited a reduced rate of drug release relative to tablets made by other processes (USP apparatus 1; 6.8 phosphate buffer; 100 rpm)

MW hydroxypropylcellulose grades formed stronger gel layers as evidenced by the slower tablet erosion rates and slower drug release profiles.

Successful application of hot-melt extrusion for modified-release dosage form was also reported by Serajuddin et al. [22]. They were also able to develop controlled-release formulations using the higher molecular weight grade of Klucel™ HPC HF. Additionally, they were able to demonstrate the in vivo performance of the formulation in a clinical study, where the matrix tablet demonstrated a plasma t_{max}

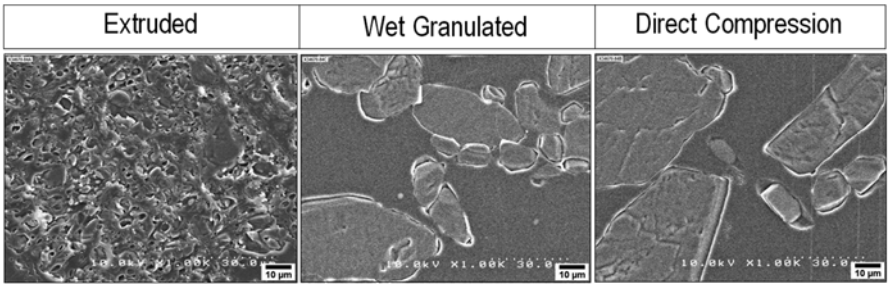

Fig. 10.12 Porosity of metformin hydrochloride extruded granules. Scanning electron microscopy pictures of the cross section of granules embedded in epoxy resin indicate that granules made by the extrusion process had more internal voids relative to granules made by alternate processes. This may explain the lower granule density for those made by extrusion relative to those made by alternate process

of 4–8 h, thus providing proof of concept for hot-melt extrusion processing as an enabling controlled-release technology. Using this technology a high-dose, highly soluble drug was delivered in a smaller tablet than what could be manufactured by conventional granulation techniques.

In 2000, Zhang and McGinity [23] conducted a study to investigate the properties of polyvinyl acetate (PVA) as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion. They found the release rate of the drug to be dependent on the granule size, drug particle size, and drug loading in the tablets. As the size of hot-melt extruded theophyllline/PVAc granules was increased, there was a significant decrease in the release rate of the drug. Higher drug loading in the hot-melt granules also showed higher release rates of drug. Water-soluble materials such as PEG 400 and lactose were demonstrated to be efficient release rate modifiers for this system.

Fukuda et al. [9] prepared tablets utilizing a hot-melt extrusion process containing chlopheniramine, chitosan, and xanthan gum. Drug release from tablets containing either chitosan or xanthan gum was dependent on media pH and buffer species and the release mechanisms were controlled by the solubility and ionic properties of the polymers. Tablets which contained both chitosan and xanthan gum exhibited extended release which was pH and buffer species independent. In 0.1 N HCl, the dual polymer tablets formed a gel layer that retarded drug release even after switching to pH 6.8 and 7.4 phosphate buffers, and when media contained high ionic strength. As the tablets without chitosan did not form a gel-like structure in 0.1 N HCL, loss of drug release retardation was seen on switching media pH for these single polymer tablets.

From the research described in this section, it can be seen that hot-melt extrusion provides a robust manufacturing process to provide for tablets with higher compactibility and lower friability compared with equivalent formulations made by conventional processes. The process can result in tablets of reduced size for high-dose drugs and combination products, relative to conventional approaches by decreasing the need for relatively large amounts of excipients.

10.4 Recent Advances for Controlled Release of Low Soluble Drugs

Increasingly drug candidates emerging from discovery programs suffer from poor water solubility. This can lead to a variety of problems such as rate-limiting dissolution, slow absorption, and limited bioavailability [24]. Extended release of poorly water-soluble drugs is one of the most challenging issues for the formulators. Solid dispersion formulation is a commonly used approach to improve bioavailability by enhancing drug solubility. The solid dispersion approach usually produces immediate-release forms. The combined and synergistic approaches of solid dispersion and extended release for dosage forms containing poorly water-soluble drugs have become a valuable technique for achieving optimal drug bioavailability in a controlled manner and thereby providing the predictability and reproducibility of the drug release kinetics.

In recent years, significant work has been done in the application of hot-melt extrusion process for the preparation of solid dispersions [25, 26]. The utility of hot-melt extrusion for the controlled release of drugs has been discussed in the previous section. Ozawa et al. [27], Nakamichi [28], Miyagawa [29], and Sato [30] developed the twin-screw extruder method for the preparation of solid dispersions of water-insoluble and soluble drugs by controlling both kneading and heating at the same time under the fusion point of each drug as well as feed rate, screw speed, and barrel temperature. Their results showed they could achieve increased solubility of poorly soluble drugs and decreased solubility of water-soluble drugs.

Lian et al. [31] investigated the feasibility of combining hot-melt extrusion with thermoplastic water-soluble polymers, a technique to simultaneously enhance the solubility of poorly soluble compounds and to facilitate the production of nifedipine extended-release hydrophilic mini tablets that deliver the drug payload over a period of 8 h. A 75 mg dose (representing 20 % drug load) was selected to achieve a fivefold supersaturation concentration in FaSSIF (fasted simulated intestinal fluid). Table 10.4 and Fig. 10.13 show the process conditions and twin-screw extruder setup for a blend consisting of 20 % nifedipine, 40 % Benecel™ HPMC K15M, and 40 % copovidone Plasdone™ S-630. They found that several formulation variables such as drug loading (Fig. 10.14), level and ratio of HPMC and copovidone (Fig. 10.15), molecular weight of HPMC (Fig. 10.16), and processing variables such as pelletizer feed speed and die orifice diameter had profound impact on degree and sustainment of supersaturation achieved and drug release rate.

Pure copovidone without HPMC did not show sufficient release retardation. When a 1:1 ratio of copovidone and HPMC (750 cps instead of 15,000 cps) is used, extended release over 4 h was produced and a fourfold supersaturation concentration equivalent to 60 mg was achieved.

HPMC is a known recrystallization inhibitor [10, 32] and higher molecular weight polymer grades inhibit the molecular mobility of the drug in a solid dispersion. Therefore, the higher molecular weight HPMC might not only slow drug release but also maintain higher degree of supersaturation. Effect of molecular

Table 10.4 Typical process conditions for the preparation of nifedipine extended-release mini tablets by extrusion

Extruder process temperature								Extruder process condition				Pelletizer process condition	
Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8	Feeder speed (RPM)	Extruder speeder (RPM)	% Load	Melt pressure (PSI)	Feedroll speed (RPM)	Cutter speed (RPM)
50 °C	100 °C	120 °C	140 °C	140 °C	140 °C	140 °C	137 °C	100	100	30	350	55	65

Fig. 10.13 Extruder and pelletizer setup for nifedipine mini tablet extrusion

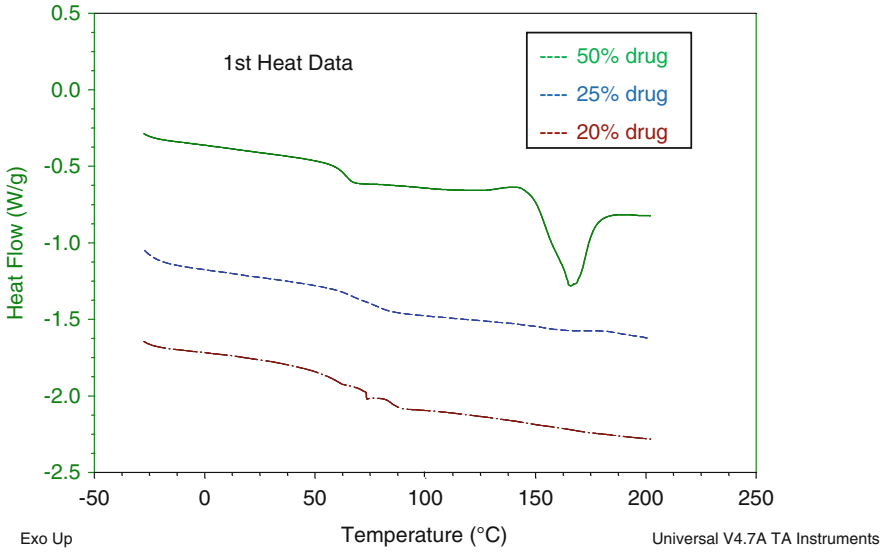

Fig. 10.14 DSC thermograms illustrating the effect of nifedipine loading. Amorphous dispersions could be obtained at 20 and 25 % w/w drug loading but not at 50 % w/w drug loading as evidenced by the melting endotherm for nifedipine at 170–180 °C

weight of HPMC on drug release and supersaturation is shown in Fig. 10.16. Combining HPMC and copovidone in the formulations (40 % Benecel™ K15M HPMC, 40 % Plasdone™ S-630 copovidone, 20 % drug) maintained supersaturation at 0.70 mg/ml for up to 8 h in contrast to the formulation where 750 cps HPMC was used and with extended release of only 4 h. In addition, release profiles reaching 100 % drug released in 8 h could be achieved under non-sink conditions.

The effect of surface area/volume ratio (SA/V) of the hydrophilic matrix mini tablets was studied by varying the die orifice diameter and pelletizer feed speed.

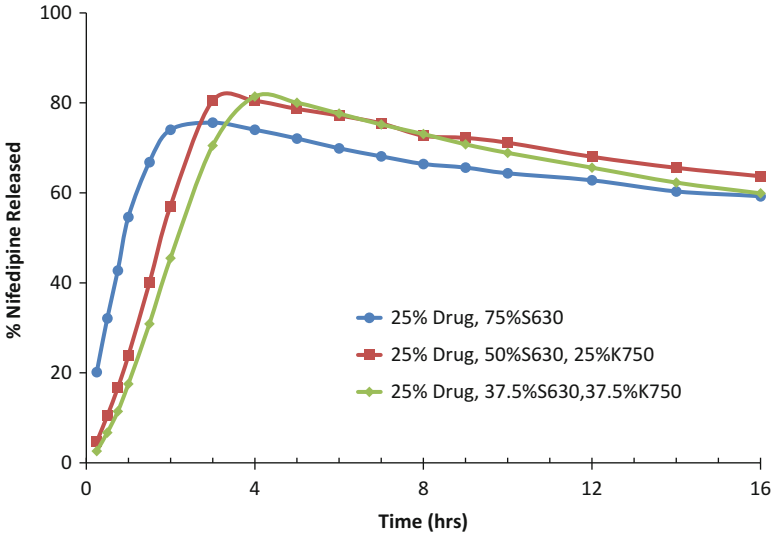

Fig. 10.15 Effect of HPMC (750 cps grade) to copovidone ratio on the release of nifedipine from mini tablets made by extrusion

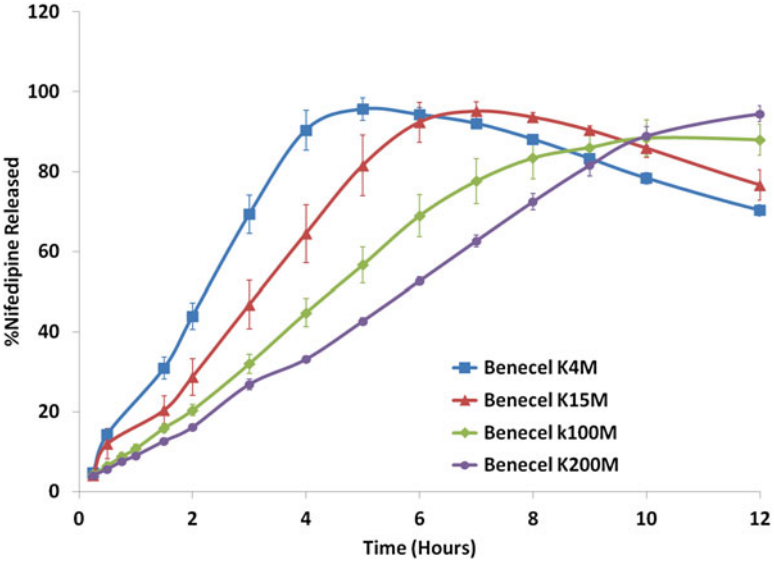

Fig. 10.16 Effect of HPMC molecular weight on release of nifedipine from mini tablets made by extrusion (tablets were 25 % w/w nifedipine, 37.5 % w/w/copovidone, and 37.5 % w/w HPMC of varying molecular weight)

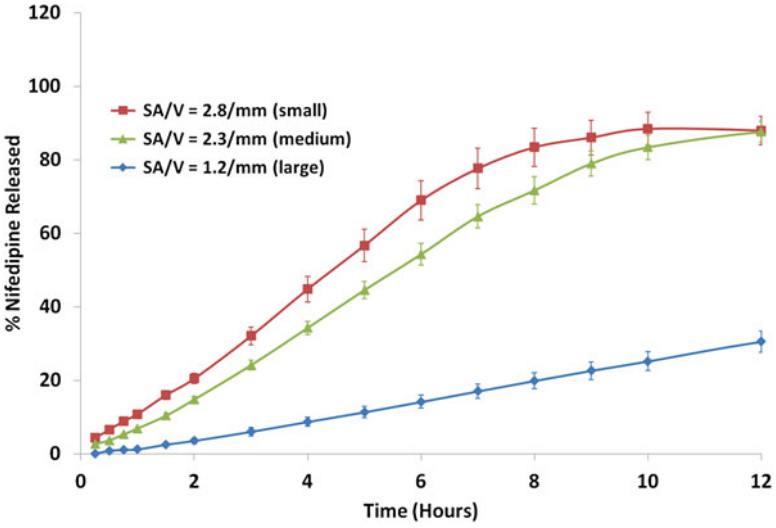

Fig. 10.17 Effect of tablet size expressed as surface area-to-volume ratio (SA/V) on release of nifedipine from mini tablets made by extrusion. Tablet size is inversely proportional to SA/V

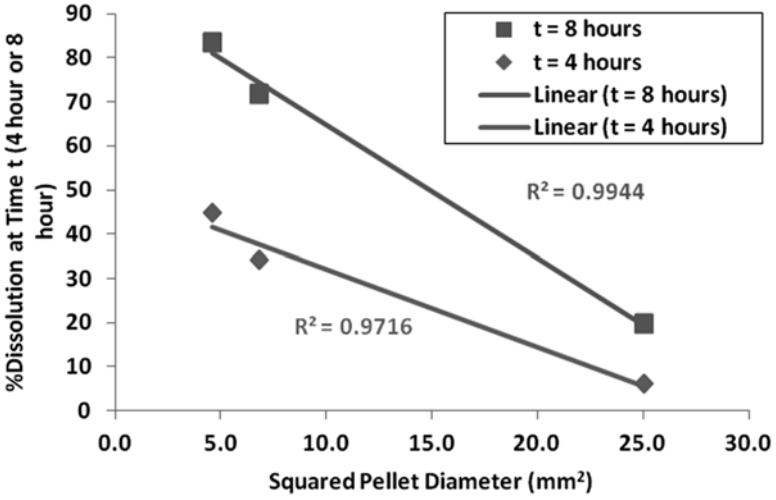

Fig. 10.18 Relationship between mini tablet surface area and drug release

The larger mini tablets have a significantly slower drug release as illustrated in Fig. 10.17. It should be noted that tablet size is inversely proportional to SA/V; thus the larger the SA/V, the smaller the tablet size. Conversely the release rate was found to be directly proportional to mini tablet surface area (Fig. 10.18). Hot-melt extrusion processing facilitated the formation of a solid solution with a continuous

hydrophilic matrix structure that was shown to control the drug diffusivity; simultaneously the extruded strand was conveniently cut into mini tablets without the need for further processing and tablet compaction.

10.5 Conclusion

Over the last 40 years hydrophilic matrix systems have emerged as a major technology platform for the oral controlled delivery of drugs. Major advances have been made in the understanding of drug release mechanisms, in modeling of drug delivery systems, and in the rational design and manufacturing of controlled-release matrix systems and polymers for hydrophilic matrix dosage forms.

Twin-screw extrusion represents an enabling technology and step change to further enhance the value of hydrophilic matrix systems. Specifically as highlighted in this chapter, hot-melt extrusion enables the design of formulations and delivery of highly soluble as well as insoluble drugs and in a manner not possible with traditional manufacturing unit processes. In addition, twin-screw extrusion represents an opportunity to replace traditional batch unit processes such as fluid bed, high shear granulations, and batch blending with a more robust and economical continuous manufacturing process. Added advantages which accrue involve the ease of scale-up from pilot to manufacturing scale. In this regard, work is ongoing on the development of continuous manufacturing systems involving extrusion as a key enabler not only in hot-melt modes but also as a means of more efficient wet granulation process. An example of this is GEA's new Consigma, continuous manufacturing concept [33]. We therefore expect that the industry will continue to embrace twin-screw extrusion processing and related technologies as a source of innovation in controlled release as well as other applications.

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Chapter 11
Microenvironmental pH Control and Mixed Polymer Approaches to Optimise Drug Delivery with Hydrophilic Matrix Tablets

Peter Timmins and Samuel R. Pygall

11.1 Introduction

Many drug substances are either weak bases, acids or their salts, often with dissociation constants within the physiological pH range. Consequently, they exhibit pH-dependent solubility within the biorelevant pH range. For hydrophilic matrix tablets, where diffusional drug release is often the primary or significant contributing element to the overall drug liberation process, this may translate to pH-dependent drug release from the dosage form. Drug dissolves in the hydrated gel layer of the tablet formed after fluid immersion and diffuses through the gel layer before being released into the surrounding fluid environment. This can occur in vivo, when the drug subsequently becomes available for absorption, or in vitro, when drug is amenable to analysis. The pH of the hydrating fluid influences the resulting gel layer pH, subject to attenuation by dissolved drug and excipients. For example, a strongly acidic drug might lower gel layer pH if the hydrating medium possesses a low buffer capacity. The concentration of dissolved drug in the gel layer is then the driving force that defines the rate of release, except in instances where drug release is primarily controlled by erosion of the hydrated gel layer, i.e. where drug solubility is very low.

As a consequence, the environment of the gastrointestinal (GI) tract, which shows inter-individual and intra-individual variation and can be affected by disease, diet and medication [1–6], presents significant challenges for the reliable and

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consistent delivery of a drug from a hydrophilic matrix tablet. The variation in pH as the dosage form transits the GI tract, as well as inherent variability between subjects and day-to-day or within day variations for individual subjects, may result in changes in release rate owing to the environmental change. An optimised dosage form will have in-built elements of control to minimise performance variation associated with these environmental challenges. To attempt to provide control of the gel layer pH against challenge from the hydrating medium, the inclusion of pH-modifying excipients, such as (1) organic acids, (2) bases or (3) anionic or cationic polymers, has been pursued in attempts to control microenvironmental pH within the dosage form during the drug release process. These formulation modifications and their impact on the in vitro and in vivo performance of hydrophilic matrices will be reviewed in this chapter.

11.2 The Concept of Microenvironmental Control in Oral Dosage Forms

Although the concept of pH in the strictest scientific definition does not apply to solids, the terms "microenvironmental pH" or "surface pH" have been used in conjunction with solid oral drug product formulations. An early utilisation of the term with respect to the microenvironmental control within a dosage form to manage drug release was its use in the case of buffered solid dispersions [7]. The expressions "microenvironmental pH" and "surface pH" have been applied to hydrogen ion activity in non-crystalline regions of solid dosage forms, such as sorbed water layers or water-plasticised amorphous domains. The microenvironmental pH has been implicated in a number of performance properties of solid dosage forms, for example, as a factor influencing (1) drug degradation, (2) disproportionation of salts, (3) drug dissolution behaviour and consequently (4) bioavailability [8, 9]. Despite this, the concept of microenvironmental pH within a solid dosage form is not well defined, with no well-established technique available to measure it.

Solid oral dosage forms have adsorbed water, which acts as a vehicle for the formation of a saturated solution of soluble components in the formulation, both drug and excipients. This provides an environment in which a "microenvironmental" pH may be defined. As drug dissolves from the dosage form surface, the microenvironment is the diffusion layer that forms around dissolving solid material. For hydrophilic matrix tablets, the initial stages of the drug release process might include dissolution of drug (and other soluble components) from the surface of the tablet. However, once the gel layer is established, the saturated solution of soluble formulation components entrained within the hydrated polymer gel layer can be considered the "microenvironment".

It has been demonstrated that pH-dissolution and pH-solubility profiles correlated only when drug solubility data determined at the pH equivalent to that of a saturated solution the dissolution medium is used to compare pH-solubility and pH-dissolution profiles [10]. Hence, the pH of the microenvironment resembles that

of the pH of a saturated solution of the drug in the dissolution medium. This is important when estimating the microenvironmental pH in hydrophilic matrix tablets and using it to explain drug release behaviour in varied pH media and in the presence and absence of microenvironmental pH-modifying additives.

11.3 Theoretical and Practical Considerations of Microenvironmental Control in Hydrophilic Matrix Tablets: Methods for the Evaluation of pH in a Solid Dosage Form

11.3.1 Determination of Microenvironmental pH Using a pH Meter

The solid dosage form pH evaluation methods described in the literature rely largely on an indirect measurement of the microenvironmental pH within a dosage form. These approaches can take one of two forms. Firstly, a pH meter can be used with a model system such as a slurry of drug and excipients. In this method, the pH of the supernatant is determined and declared the microenvironmental pH. Alternatively, direct measurement inside the gel layer itself can be carried out using a microelectrode. Secondly, a probe molecule can be incorporated into either a dosage form or a model system and a property of the probe that varies with pH is then determined. Through the monitoring of this property, a pH is indicated that is declared to be the pH of the microenvironment within the dosage form [8]. There are a number of assumptions and problems that investigators need to be aware of prior to using these published approaches to measure microenvironmental pH within a product under investigation.

The first approach involves determination of a pH value indicative of microenvironmental pH using a pH meter. In the slurry method, hydrogen ion activity is measured in a system that can possess significantly higher water-to-solids ratio, compared with that of an adsorbed moisture layer or within the hydrated gel layer of a hydrophilic matrix tablet. This evidently could bias the outcome of the determined result. In fact, the slurry pH will be dependent on the concentration of solid in the slurry, and this could be significantly different from the actual hydrogen ion activity in the solid dosage form. However, microenvironmental pH measured using the slurry method has demonstrated some success in correlating with the stability of immediate release formulations [11, 12] and identifying the level of pH-modifying agent needed to provide the required microenvironmental pH which minimises the risk of salt disproportionation [13].

However, the slurry method has a number of limitations. Attempting to use the slurry method to simulate the hydrated gel layer with realistic excipient concentrations will result in attempting to measure pH of a very viscous, concentrated hydrated polymer gel with drug and excipients dispersed and dissolved in it and

with a concomitant low water activity. This may challenge the practicality of the approach, both from the perspective of slurry preparation and in making the pH measurement of the gelled slurry. An additional problem is that the slurry approach provides only a fixed representation of the hydrating dosage form. This is an issue since the hydrating dosage form is a dynamic system, with release of drug and soluble excipients occurring at the outer edge of the dosage form into the bulk medium. It also has a gradient of drug and excipient concentrations down to where the dry core is being hydrated as a consequence of the release process and so perhaps best equates to the layer in the hydrated gel layer immediately outside of the dry core.

An alternate approach to determining hydrated gel microenvironmental pH has been to fabricate the actual dosage form, initiate hydration by immersing it in the relevant aqueous medium for a defined period of time and insert a micro-pH probe (from 100 μm up to 1.3 mm diameter) into the hydrated gel layer [14–17]. With the larger diameter probe [14], it was necessary to hydrate the matrix tablets sufficiently and, for a fixed time, to facilitate penetration of the electrode into the gel. This ensures that measurements are taken at essentially the same depth from sample to sample, so this approach was only able to offer microenvironmental pH data at a fixed location within the dosage form and at a fixed elapsed time in the drug release process. It was unable to illustrate dynamic information on the temporal variations in microenvironmental pH that occur as drug and presumably pH modifier are continually released from the hydrated matrix and it cannot provide a depth profile of microenvironmental pH within the gel layer [14].

Using a 100 μm diameter electrode, it was possible to monitor dynamic changes in the gel layer of a hydrophilic matrix tablet containing tromethamine or sodium citrate as a pH modifier [15, 16]. In another study, a special microelectrode (diameter 10 μm) was utilised to follow the pH gradient in an extended-release hydrophilic matrix tablet containing the active ingredient vincamine hydrochloride and succinic acid as pH modifier. Tablets were hydrated in pH 7.5 buffer for 3 h, and it was determined that at the surface of the tablet, pH was 7.5; just below the surface, pH 6.8; and within the gel, its layer was between pH 3.5 and pH 4.5 [17].

By removing tablets from the dissolution vessel at different time points during the course of drug release, drainage of excess fluid, sectioning the now hydrated tablets and measuring the pH with a surface pH electrode, a reliable assessment of any gradient of measured pH from the outer edge of a tablet to its evolving dry core is possible. This method is not dependent on an operator's ability to place an electrode reproducibly into the gel layer at a required depth. Alternatively, it can be carried out with the hydrated tablet frozen and microtomed to provide axial slices. Measurement of each sequential slice with the surface electrode allowed the determination of any pH gradient from the outer edge of the tablet into the core [18–20].

11.3.2 Determination of Microenvironmental pH Using Indicator Dyes

The second set of approaches involves the use of probe molecules included directly in, or taken up, by the hydrated gel layer. The use of indicator dyes is a straightforward approach that can provide a direct visual indication of the pH within a hydrated gel layer of a hydrophilic matrix tablet. This technique can also allow a dynamic perspective of the evolving gel layer pH as the process of drug release occurs. One approach [21] requires the matrix tablet to be sectioned axially and the half tablet hydrated for an initial period of 2 min, held between two microscope slides (Fig. 11.1). The upper slide is removed, and this allows it to be mounted in a USP apparatus II, with the cut face of the tablet adhering to the lower slide by virtue of its hydrated gel layer. The dissolution medium includes 0.5 % v/v universal pH indicator solution which, as it swells the polymer to form the gel layer, exhibits a colour indicative of the microenvironmental pH within the hydrated gel layer. The slide can be removed at intervals to photograph the hydrated gel layer and compare its colour with a reference and so determine its pH. This approach was used to demonstrate (Fig. 11.2) the sustaining of gel layer pH in HPMC matrix tablets buffered with sodium citrate under the challenge of ingress of acidic medium and the release of the soluble buffering agent [15]. Coincident with data generated in the same system with a pH microelectrode, the pH indicator method visually demonstrated that the control of gel layer pH was sustained for only 2 h post-immersion in dissolution medium due to release of the highly water-soluble buffer from the tablet and at a rate faster than could be replenished by dissolution of buffer at the hydrated layer/dry core interface. This visual approach showed changes occurring at the outer edges of the gel as well as effects deeper within the gel layer, which a pH electrode would not easily achieve.

It is very convenient to introduce tablets into a dissolution test vessel containing medium of the required pH and universal indicator solution and then remove the tablets throughout the drug release process. The hydrated tablets can be sectioned with a sharp blade and the half tablet examined to determine pH in different regions of the gel layer, indicated by the colour of the universal indicator solution hydrating the gel. It is possible to define the time course of gel layer evolution and growth and dry core diminution during drug release by using this kind of sampling technique. In studies of this kind in a hydrophilic matrix tablet containing a free base ($pK_a = 2.8$, 4.4, 7.9) form of an investigational compound, a gradation in pH was observed from that of the dissolution medium in which the dosage form was immersed at or near the surface of the hydrated tablet, to a significantly higher pH at the hydrated layer/dry core interface. Presumably in this region, the solid drug coexists with its saturated solution in dissolution medium and as a free base acted as an alkalising agent (Fig. 11.3). The effect of adding agents to modify the microenvironmental pH across the gel layer was also demonstrated in such studies.

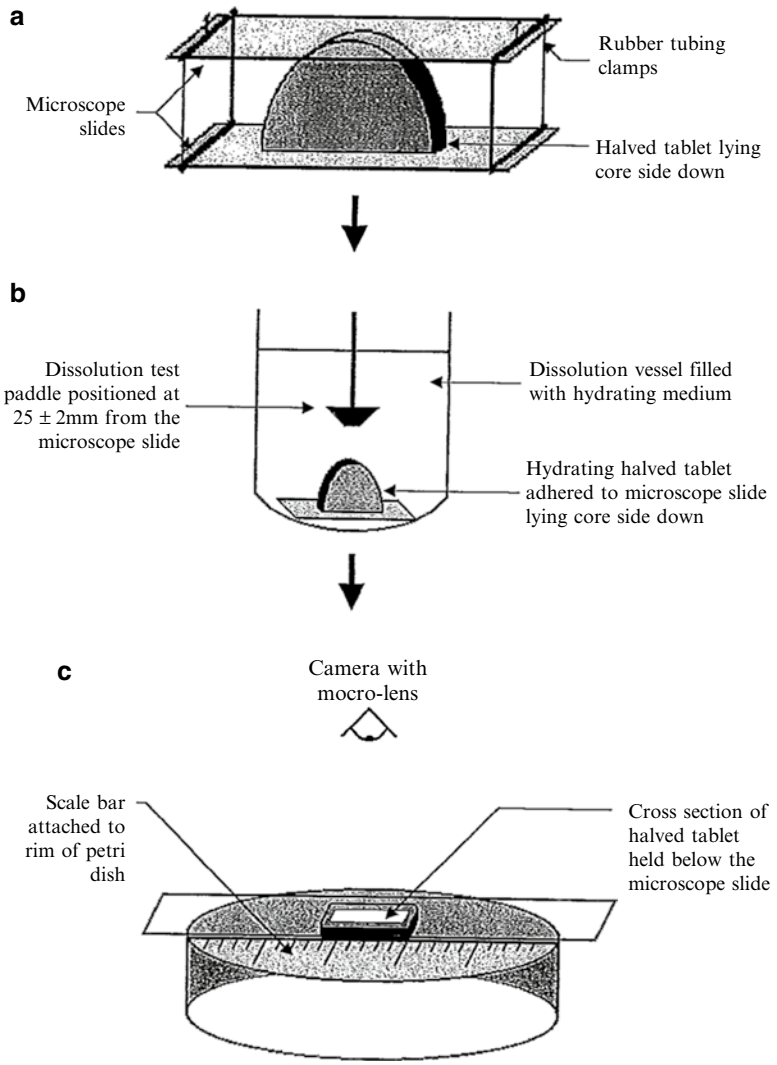

Fig. 11.1 Experimental geometry to observe gel layer development in a hydrophilic matrix tablet, including the effect of pH indicator dyes in the hydration medium (adapted from [21] by permission of copyright holder)

Colorimetric methods can also be used to compare the colour exhibited by indicator dye absorbed by a hydrated gel layer of a tablet. Such a methodology might reduce subjectivity in making the pH assessment. Diffuse reflectance UV spectrophotometry has been used to determine the surface acidity of solid pharmaceutical excipients in the presence and absence of a buffer using peak height ratios of the acid and basic forms of the indicator dye to indicate pH [22]. This approach is

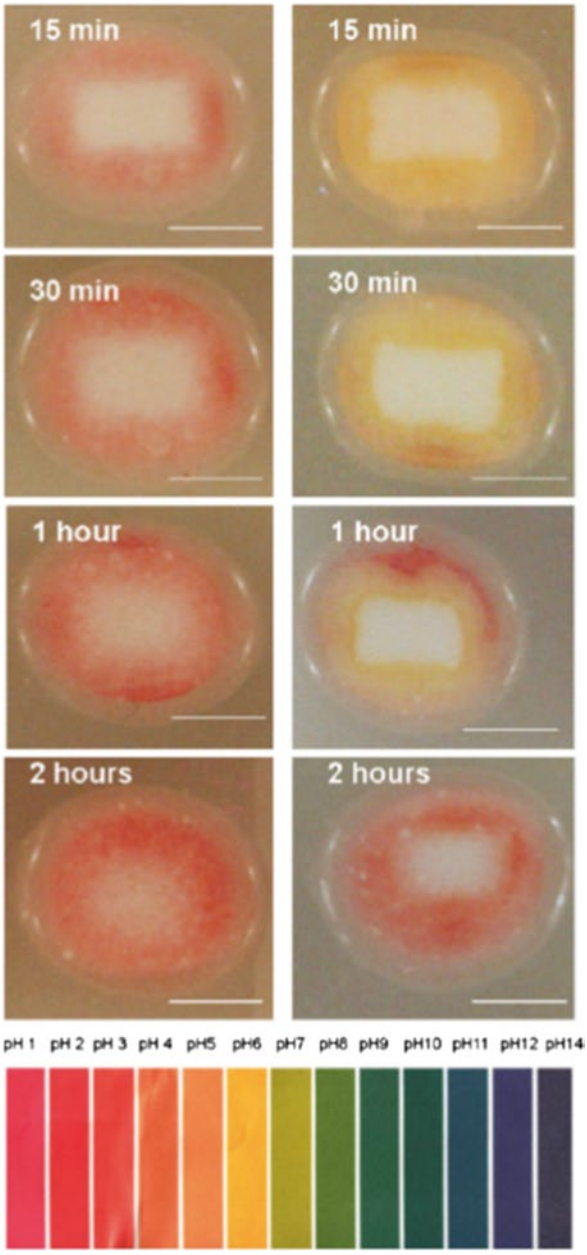

Fig. 11.2 Images of a hydrophilic matrix tablet prepared as in Fig. 11.1 based on hydroxypropyl methylcellulose and containing either 50 % sodium citrate (*right column*) or no sodium citrate (*left column*) during hydration with 0.1 M hydrochloric acid containing 0.05 % (v/v) universal indicator solution. Scale bar = 2 mm (Reproduced from [15] by permission of the copyright holder)

potentially more valid than a slurry approach. The pH scale is appropriate only to dilute aqueous solutions and for highly concentrated aqueous solutions, such as in the hydrated gel layer of a hydrophilic matrix tablet, or in the case of surface pH for excipients, where we are dealing with the adsorbed moisture layer around the excipient particles, the Hammett acidity function is more appropriate.

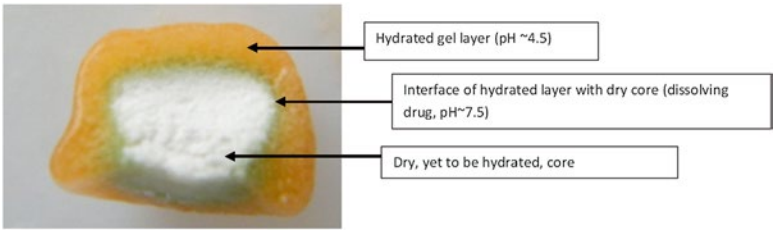

Fig. 11.3 Hydrophilic matrix tablet (sectioned to show internal structure) of a free base experimental compound. Tablets were hydrated in pH 4.5 acetate buffer containing 0.05 % (v/v) universal indicator. Note how the drug itself modulates microenvironmental pH at the interface between the dry core and the hydrated gel layer yielding a higher pH as indicated by the *blue-green* colour

This is determined by the change in ratio of unionised and ionised form of the indicator dyes as their protonation changes in accord with local proton activity [23]. The measurement of an equivalent pH by the use of indicators in this way is valid if the ratio of extinction coefficients of the dye is the same in dilute solution of a given pH and in the concentrated solution state of the surface of a pharmaceutical excipient or in the hydrated gel layer of a hydrophilic matrix tablet. Specifically, the pK_a of the dye molecule needs to be the same under these conditions, where ionic strength and polarity in the microenvironment will be different to a dilute solution [24–26]. However, it has been reported that the diffuse reflectance UV spectroscopy approach using solution state calibration curves of the indicator dye may not be applicable to the determination of microenvironmental pH where the dye is in an adsorbed state on a surface. Determining the pH of a concentrated slurry with a glass electrode and a pH meter may still therefore provide a judicious approach to determining microenvironmental pH, as it is a simple and reliable approach and the extent of the reliability of the dye method may be dependent on the compound studied and the indicator dye chosen [27].

Published studies on the use of indicator dyes for determining microenvironmental pH in the hydrated gel layer hydrophilic matrix tablets have compared hydrated gel layer colour to a standard colour chart for the dye at varied pH [15, 21]. The validity of this pragmatic approach versus spectrophotometric measurement of the two forms for the dye and determination of the Hammett acidity function as a pH equivalent of that environment has not been reported. The approach has been criticised in that it only visualises pH in regions where the dye solution has penetrated and cannot indicate the microenvironmental pH in the poorly hydrated regions of the tablet [28]. This would be valid if the concern was for the pH sensitivity and stability of the active ingredient within the dosage form, but in general, the interest in hydrophilic matrix tablets is the pH inside the hydrated gel layer and its impact on drug release. The indicator dye method would appear to be valid for this.

11.3.3 Application of Confocal Microscopy to Determine Microenvironmental pH

Confocal microscopy was developed originally for cellular and biomedical applications, and it allows imaging of fluorescent probe molecules within a dosage form that can provide information about the interior structure of the dosage form, including dynamic measurements of evolving systems. It can be applied to pharmaceutical systems to provide high-resolution images, non-invasive optical sectioning of samples and three-dimensional reconstructions [29]. It has been used to image pH-sensitive fluorescent dyes within eroding polyglycolide microspheres, where this technique has provided a spatial distribution of the pH within the system [30–32]. It has also been described as a tool for exploring the effect of acidic modifiers on the microenvironmental pH of controlled release pellets containing a weakly basic drug [33, 34]. However, there has been little research on its application to microenvironmental pH measurement in hydrophilic matrix tablets. One study has described the influence of added succinic or fumaric acid on the pH gradient within a tablet and drug release over time for hydrophilic matrix extended-release tablets based on hydroxypropyl methylcellulose and the weakly basic model drug papaverine [35]. Ratiometric measurements of the fluorescence emission of Rhodol Green were used to quantify pH. The technique provided a visual representation of the pH across the gel layer, and it was confirmed that tablets with added organic acid maintained a low pH throughout the gel layer, whereas tablets without acid had higher internal pH and a pH gradient across the gel layer. These observations correlated with the observed drug release kinetics. One constraint of this imaging method is that it requires the sample to be held between two clear Perspex discs to allow for only lateral hydration and swelling of the sample to enable the imaging. This presentation of the tablet to the drug release medium is very different to that in officially recognised dissolution methods.

11.3.4 Determination of Microenvironmental pH Using Electron Paramagnetic Resonance

Electron paramagnetic resonance (EPR) (also referred to as electron spin resonance, ESR) has found several applications in drug delivery research, including the characterisation of microenvironmental pH [36]. The technique of EPR has parallels with nuclear magnetic resonance (NMR) spectrometry in that it involves the interaction of electromagnetic radiation (microwave radiation in the case of EPR) with a magnetic moment. In the case of EPR, the magnetic moments are associated with electrons rather than nuclei as in the case of NMR. The magnetic moment arising from the spin of an electron, if not cancelled by the opposing spin of its normally paired partner electron existing in the same outer orbital of an atomic nucleus, provides for

the interactions with an electromagnetic field. Molecules with an unpaired electron, typically free radicals, carry the paramagnetic property that the EPR technique is based upon [37]. Lower-frequency spectrometers (1.5 GHz) are useful for studying hydrophilic matrix tablets, as although these are of lower sensitivity, the lower-frequency microwaves penetrate hydrated samples better than higher-frequency microwaves (e.g. spectrometers operating at 10 GHz), and there are reduced dielectric losses.

The application of EPR to the study of the microenvironmental pH within a hydrophilic matrix tablet requires the incorporation of a suitable probe molecule with paramagnetic properties. Probe molecules will be relatively stable radicals, and nitroxides are widely utilised in biomedical and pharmaceutical research [37, 38]. The unpaired electron in a nitroxide such as TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl), which gives these compounds their paramagnetic properties, is localised on the N-O bond. This allows interaction with the strong external magnetic field of the EPR instrument and the weaker influence of the magnetic moment of the nitrogen nucleus coupled with much weaker impact of nearby protons. This results in an EPR spectrum consisting of three broad lines [38]. The shape of the lines (intensity, broadening) is influenced by both the polarity and viscosity of the environment around the probe molecule. Changes in the spectra inform of changes in both properties within the microenvironment of a polymer matrix [38].

The effect of water content on the microviscosity of polysaccharide solutions has been investigated by EPR to explore the influence of the polymer on bulk water mobility [39]. The results suggested that polymer structure had little effect on bulk water mobility, but in conjunction with NMR data, it was concluded that the bound water mobility is highly influenced by polymer structure. In order to follow microenvironmental pH, it is necessary to use a probe that ionises in a way that influences the EPR spectrum (Fig. 11.4). Imidazoline-based spin labels are typically employed [38, 40, 41].

As in the case of NMR microscopy (or magnetic resonance imaging, MRI), EPR can utilise the resonance spectroscopy technique to create 2D maps of the materials under analysis. EPR imaging has been applied in the context of tracking microenvironmental pH and to spatially monitor pH and the rotational correlation time, tau(R), a parameter indicative of the surrounding microviscosity within HPMC matrix tablets [40]. In the study, fumaric, citric and succinic acids were employed as pH modifiers in a matrix tablet, with 4-(methylamino)-2-ethyl-5,5-dimethyl-4-pyridine-2-yi-2,5-dihydro-1H-imidazole-1-oxyl (MEP) as the spin label. Fumaric and citric acids were found to reduce the pH to equal extents during the initial phase of hydration. However, as hydration proceeded, the more soluble citric acid diffused out from the tablet, resulting in an increase in microenvironmental pH, originating in the outer layers. In contrast, the less soluble fumaric acid maintained a constantly reduced microenvironmental pH throughout the gel layer. Owing to its lower acidic strength, succinic acid did not reduce the microenvironmental pH as effectively as the other pH modifiers investigated. In addition, the more water-soluble acids stimulated water penetration into the matrix, thereby rapidly decreasing tau(R). Once the matrix tablets were fully hydrated however, these pH modifiers were found not to influence tau(R) significantly.

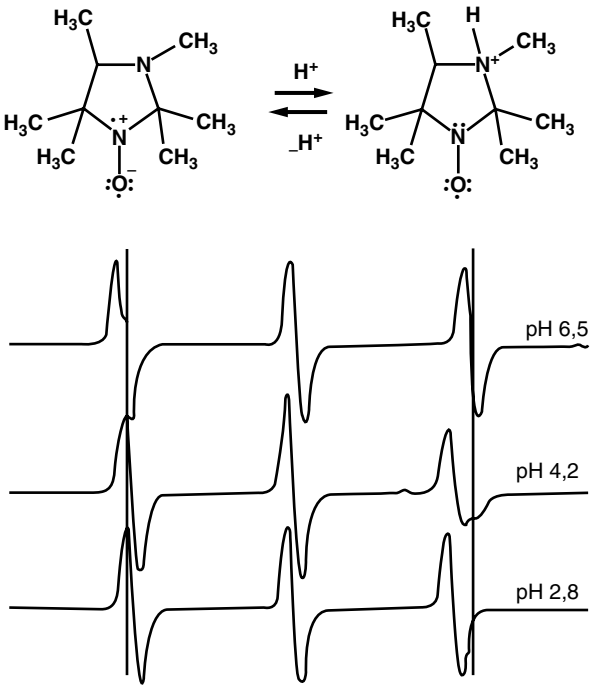

Fig. 11.4 EPR scans showing changes in the 3-line structure with pH using an imidazole-derived nitroxide as a pH-sensitive spin probe (Reproduced from [38] with permission of the copyright holder)

In multilayer hydrophilic matrix tablets formulated to contain pH modifiers, EPR spectrometry and EPR imaging was found to be better than using indicator dyes or fluorescence imaging to study microenvironmental pH. EPR could provide information on both the spatial distribution and the evolution of pH within an individual hydrating tablet, providing a data over the entire course of hydration [41]. The only disadvantage of EPR studies is that the pH range that can be studied is in a narrow window, around ±1.0 to 1.5 pH units of the pK_a of the spin probe [40, 41]. If a wider range of pH would need to be measured, this would require running parallel studies with other spin probes with different pK_as.

11.4 Selected Case Studies of Microenvironmental Control in Hydrophilic Matrices

11.4.1 Acidic pH Modifiers for Basic Drugs

The incorporation of organic acids as pH modifiers (e.g. citric, succinic, fumaric or sorbic acid) is a common approach employed with hydrophilic matrix tablets in order to achieve pH-independent in vitro release of basic drugs. The use of succinic acid to improve the pH independence of the release of the nootropic drug vincamine from a hydrophilic matrix tablet was one of the very early reported attempts at such performance improvement [17].

The incorporation of weak acids as pH modifiers theoretically enhances the release of weakly basic drugs in higher pH environments by reducing and sustaining the microenvironmental pH against the challenge of the higher pH-dissolution medium. There needs to be sufficient organic acid, and the pK_a of the chosen acid may be important, in order to lower the pH appropriately during initial hydration of the gel layer. There must be sufficient reserve in the matrix to sustain the lowered pH, as of course not only will the now more soluble ionised form of the basic drug readily diffuse from the hydrated matrix, but the organic acid modifier will also be released. Siepe et al. [40] investigated the relationship between the microenvironmental pH, drug release and pH modifier release. They sought to achieve simultaneous release of both the drug and the pH modifier over the entire 6 h dissolution time in phosphate buffer (pH 6.8). Citric acid and fumaric acid at 20 % w/w in the formulation were equally effective in producing the initial low pH required within the hydrated gel layer. However, the more soluble citric acid diffused out more readily, leading to the evolution of an increase in the microenvironmental pH in the outer layer of the gel relative to that seen with fumaric acid. They found that succinic acid, with a pK_a a little higher than citric or fumaric acid, did not reduce the microenvironmental pH as effectively. Based on the key parameters of acidity and solubility, it is important to choose an acid with a solubility low enough to avoid rapid depletion from the hydrated matrix during the parallel drug release process but high enough to assure it yields the desired low microenvironmental pH. On this basis, citric acid and fumaric acid were selected to prepare a cinnarizine extended-release hydrophilic matrix tablets exhibiting pH-independent drug release in vitro [42]. Citric acid was found to be very effective in providing for pH-independent release, but was itself rapidly released. Fumaric acid was better retained in the matrix, but was less effective than citric acid at lowering the microenvironmental pH. An optimised formulation was identified with a defined ratio of both acids, combined to produce the desired pH-independent drug release and to sustain the low microenvironmental pH for an extended period [42].

There remains the concern that the acidifier could release more rapidly than the drug from a matrix, such that the pH independence of release is of limited duration over the entire course of drug release. However, this phenomenon was not observed in a study which investigated the effect of incorporating various acids into an ethylcellulose (EC) or HPMC matrix containing verapamil hydrochloride [43]. All three acids tested (fumaric, sorbic and adipic) resulted in significant increases in drug release in both pH 6.8 and 7.4 phosphate buffers, and significant amounts of acid remained in the matrix even at the end of the 8 h release study. Fumaric acid was found to be more effective than sorbic and adipic acids in enhancing drug release, and it provided release profiles in phosphate buffer that were almost the same as those in 0.1 N HCl. It was suggested that the lower pK_a of fumaric provides a lower pH within the matrix, relative to that provided by adipic or sorbic acids. The drug release profile was shown to be independent of the amount of fumaric acid in the formulation, indicating that sufficient fumaric acid existed in the matrix to maintain a low microenvironmental pH even at the lowest fumaric acid concentration tested in this study.

Others have indicated that it is necessary to optimise the acidifier level and choice [44], with again the lower pK_a, lower solubility fumaric acid seeming to have advantages in improving the extended delivery of dipyridamole over the more soluble, but less acidic succinic acid. The slower release of fumaric acid from the hydrophilic matrix relative to succinic acid, associated with its lower solubility in the buffer, meant it could sustain the low microenvironmental pH for a longer period against the challenge of ingressing pH 6.8 buffer [44].

Although citric acid has been shown to be liberated more rapidly than fumaric acid from hydrophilic matrix tablets during in vitro release studies [40] again associated with its solubility properties, it has been successfully employed to modulate the in vitro release of several basic drugs [45–49]. These studies allowed some characterisation of the impact of the acidifier on the drug release mechanism. Generally there was the observation that the exponent n in the power law equation [50]

$$M_t/M_\infty = kt^n$$

(where M_t and $M\infty$ are the amounts of drug released at time = t and infinity, respectively, n is the release exponent and k is a constant for the dosage form) moved towards a value around 0.5, indicative of a diffusion-dominated release mechanism [46, 47, 49]. The suggestion that rapid dissolution of the citric acid may also increase the porosity of the hydrated matrix and hence increase drug release rate could be another contributing factor to the overall drug release mechanism [45, 46]. The lower microenvironmental pH provided by the acidifier in the presence of the higher pH-dissolution medium buffer was considered as increasing drug solubility in the hydrated matrix, relative to a citric acid free formulation. This led to drug release being dominated by a diffusion mechanism driven by the higher drug solubility in the hydrated matrix [47, 49].

Texture analyser studies of hydrated gel layer formation in oxybutynin hydrochloride hydrophilic matrix tablets showed how the addition of fumaric acid to deliver pH-independent drug release can modify the evolution of the gel layer. There was a delay in initial gel formation but a development of a thicker layer in the presence of the acid [51]. It has been proposed that loss of citric acid from the tablet matrix during gastric transit can be prevented by adding the acid as enteric coated crystals [52]. Only when the dosage form reaches a higher pH environment of the small intestine is the citric acid liberated to have its effect.

A range of acids have been demonstrated as useful in sustaining pH-independent drug release for swellable and poorly swellable hydrophilic matrix systems, maintaining low microenvironmental pH over an extended period against a pH 6.8 buffer challenge [53]. Adipic, glutaric and tartaric acid showed slower drug release in pH 6.8 buffer relative to fumaric acid owing to their faster leaching from the matrix. This resulted in a slightly higher microenvironmental pH when those acids were employed instead of fumaric acid.

The in vivo advantage of maintaining pH-independent drug release has been clearly indicated and demonstrated in a human study of extended-release formulations of 6-hydroxybuspirone in which the pharmacokinetics and location of the

dosage form in the gastrointestinal tract were compared. The in vivo absorption profile of the optimised drug product, with citric acid included to yield pH-independent in vitro drug release, showed no discontinuity of drug absorption wherever the dosage form was releasing its contained drug in vivo, suggesting good resistance of the drug release mechanism to variations in environmental pH within the gastrointestinal tract [49].

11.4.2 Basic pH Modifiers for Acidic Drugs

Compared with basic drugs in the preceding section, there is less published research on the buffering of hydrophilic matrix systems to achieve pH-independent release of acidic drugs. To overcome the observed pH-dependent dissolution of commercially available extended-release formulations of divalproex sodium, the excipient Fujicalin (a proprietary form of processed dibasic calcium phosphate anhydrous) was added as a non-polymeric potential alkalising agent [54]. It was shown to have some capacity for affecting the pH when added to 0.1 N hydrochloric acid, but its weak buffering effect meant it was of limited utility in providing pH-independent drug release of the compound studied. Alternate approaches using aminoalkyl methacrylate copolymers were more successful [54].

The use of trisodium citrate as a buffer to raise the microenvironmental pH in HPMC matrix formulations has been shown by use of indicator dyes, to raise gel layer pH in an acid medium. However, the duration of the effect was limited (<2 h), owing to leaching of the sodium citrate buffer during drug release testing [15]. Furthermore, the added buffer reduced HPMC particle swelling and caused disruption of early gel layer formation, which could have led to the failure of the matrix and loss of extended-release properties. However, it was observed that the gel layer formation recovered once the buffer species concentration in the matrix was depleted, but the consequence of the initial disruption followed by recovery had led to complex drug release profiles for the model drug, felbinac. The more highly methoxylated grade HPMC 2910 seemed more susceptible to this effect than HPMC 2208.

The comparison of tris(hydroxymethyl) aminomethane (tromethamine, THAM, TRIS, trometamol) with sodium citrate as internal buffering agents for HPMC (4,000 cps) 2208 and 2910 matrices containing felbinac, a weak acid drug which exhibits pH-dependent solubility was reported [16]. The study showed how drug release, in both pH 1.2 and 7.5 media, was accelerated by both buffers, but tromethamine-buffered matrices provided extended, diffusion-based release kinetics, without loss of matrix integrity, at high matrix buffer content [16]. Drug release kinetics appeared to be independent of media pH. In contrast to trisodium citrate, tromethamine did not depress the sol-gel transition temperature or suppress HPMC particle swelling and had minimal effects on gel layer formation. Sodium citrate promoted greater thickness of the early gel layer than tromethamine. Measurements of internal gel layer pH showed that both buffers produced a rapid alkalisation of the gel

layer which was progressively lost. However, as a consequence of its higher p*K*(a) and molar ratio, tromethamine provided a higher internal pH and a greater longevity of pH modification. Based on these findings, it would appear that tromethamine offers a useful buffering option for weak acid drugs in HPMC-based matrix systems.

11.4.3 Use of Ionic Polymers and Non-ionic/Ionic Polymer Mixtures

Both ionic polymers used alone or as mixed non-ionic/ionic polymer combinations have been used by a number of investigators to modulate drug release from hydrophilic matrix tablets. They have mitigated the effect of external environment pH on drug release, but not all these investigations focus on microenvironmental pH control as the mechanism by which such mitigation is achieved. For completeness in terms of a review of approaches for modifying the response of hydrophilic matrix tablets to external environment pH, these studies are reviewed here, even if the researchers did not evaluate the microenvironmental pH.

Zero order, or near-zero order, in vitro drug release has been achieved with optimised mixtures of HPMC and sodium carboxymethylcellulose, the release profile showing no inflection associated with change of release rate when the release test medium was switched from pH 3.0 hydrochloric acid to pH 7.4 phosphate buffer. This study utilised a range of basic drugs including the antifilarial drug centperazine and several beta blocker drugs [55–58]. The faster erosion of the hydrated tablet matrix in the higher pH medium was associated with the presence of the ionic polymer, and this was suggested as responsible for the mitigation of the effect of changing medium pH on drug release rate. It was proposed that slower erosion of pure HPMC matrices, resulting in increasing diffusional path length with time, was the reason for decreased drug release rate from such formulations in higher pH media [55–57]. Texture analyser investigations further supported the changing erodibility of these mixed polymer matrices as a result of changing medium pH [58]. The effect of the ionisable polymer on microenvironmental pH was not considered to contribute to the modulation of drug release rate in the test media studied.

In the case of hydrophilic matrix tablets containing mixtures of sodium alginate and HPMC, it is again the increased erosion of the matrix resulting from the increased solubility of the anionic polymer at pH 7.4, relative to pH 1.2, which has been proposed as the mechanism by which drug release rate is increased in higher pH media. This is in comparison with the rates observed in hydroxypropyl methylcellulose matrices, and the mixture leads to an essentially pH-independent in vitro release profile (Fig. 11.5) [59–61]. Additionally, it was suggested that the formation of the poorly soluble alginic acid in these hydrated matrices at low pH provided for a more robust gel layer, resistant to erosion, and the matrix was found to exist as a resilient, pasty mass, wet through to the core. It showed limited erosion after 6 h of drug release, whereas the same formulation studied at the same time point in pH 7.4

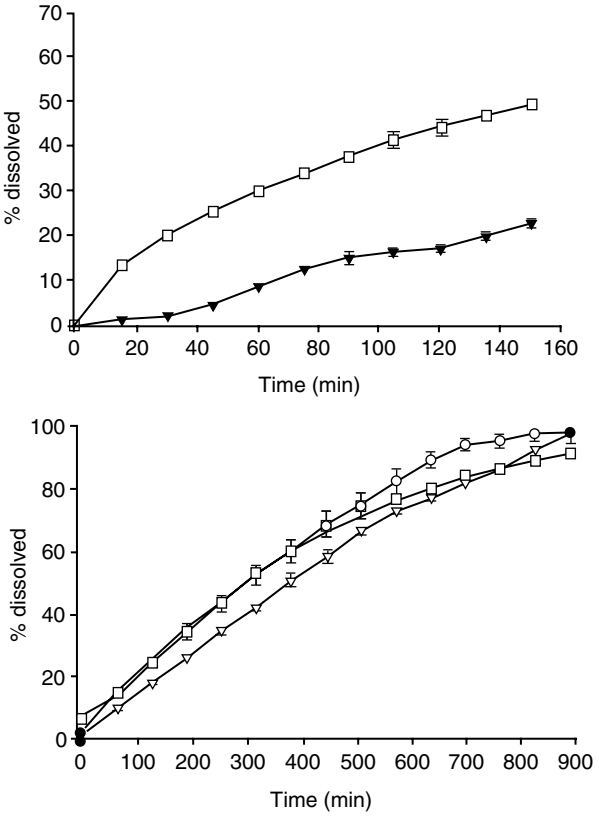

Fig. 11.5 Use of mixed non-ionic and anionic polymers to achieve pH-independent release of a basic drug. *Upper plot* shows in vitro release of verapamil hydrochloride from HPMC matrix at *open circle* pH 1.2, *open inverted triangle* pH 7.5; *lower plot* shows in vitro release of verapamil hydrochloride from mixed HPMC/sodium alginate matrix at *open circle* pH 1.2, *open square* pH 4.5, *open inverted triangle* pH 7.5 (Reproduced from [59] by permission of the copyright owner)

medium, with the same extent of drug released, showed a fragile gelled mass which had undergone significant erosion [59].

Using cryo-SEM to study the effect of dissolution medium pH on sodium alginate matrices, it was observed that these systems formed a particulate porous matrix when exposed to an acidic environment. This included regions where the polymer had gone into solution and held particles of poorly hydrated insoluble alginic acid together in a coherent barrier layer around the hydrated tablet. A highly hydrated, readily erodible continuous gel layer was observed to result when the same formulation was exposed to pH 7.5 buffered test medium [62].

Cationic drugs formulated with anionic polymers have shown different release properties, compared with anionic drugs, and effect which has been attributed to ionic interactions [63]. It has been demonstrated spectroscopically, by dialysis and by monitoring counterion release, that a drug/anionic polymer interaction can be formed in dosage which affects the drug release in media of varying pH [64–68]. Additionally polymer/polymer interactions, which affect drug release, have been observed in mixed non-ionic and ionic polymer formulations [68]. This proposed concept of drug/polymer interaction, as an approach to developing pH-independent drug release, was first developed by making the complex first and then including it

in a hydrophilic matrix system. For example, diltiazem, a basic drug normally used as a hydrochloride salt and exhibiting very high aqueous solubility, was reacted with the naturally occurring sulphated polysaccharide lambda carrageenan to yield a solid complex with low aqueous solubility of diltiazem. Incorporating this complex into an HPMC matrix tablets provided near pH-independent diltiazem release [69]. The dependency of drug release rate on tablet surface area-to-volume ratio, and using the power law equation to fit the drug release data, it would appear that the mechanism of pH independence was related to poor drug solubility across the pH range and a high dependency of drug release on matrix erosion. The use of mixtures of carrageenan and HPMC to form a tablet matrix which exhibited pH-independent release of basic drugs has also been described [70].

Incorporating the non-swelling anionic methacrylic acid polymer Eudragit L100-55 into HPMC matrix tablets improved pH dependency of the release of trimethoprim but did not ameliorate the effect of pH on release rate completely [14]. It was observed that the reduction in drug release rate at low pH was the primary mechanism by which pH dependency was reduced, rather than an increase in the rate at higher pH which might be anticipated from the reduction in microenvironmental pH. Having the acidic polymer present in the HPMC matrix reduced the microenvironmental pH under pH 6.8 phosphate buffer challenge from pH 6.8 to pH 4.5 for placebo matrices. However, when the basic drug was added, the microenvironmental pH was reduced to only pH 6.6 as the acidic polymer was competing with two buffering agents: the pH 6.8 buffer and the free base drug (pH of saturated solution 8.5) [14]. Interestingly, papaverine hydrochloride release from hydroxypropyl methylcellulose matrices at pH 6.8 has been enhanced by the incorporation of Eudragit L100-55 or carbomer (Carbopol 71G, an acrylic acid polymer), with drug release rate increasing as the content of ionic polymer is increased. This enhancement was related to the reduction of microenvironmental pH by the added acidic polymers, improving the solubility of the drug in the hydrated matrix [71]. Similarly, the acrylic acid polymer increased the release of verapamil hydrochloride from the HPMC matrices, but methacrylic acid polymer (Eudragit L100-55) resulted in retardation of release. This was due to formation of a poorly soluble interaction product between verapamil and methacrylic acid. The degree of ionisation at pH 6.8 was proposed as the reason for the effect of the formation of the interaction product between verapamil and the acid polymer, but not with another basic drug, papaverine [71].

Some authors have attributed the enhancement of release by enteric coating polymers such as Eudragit L100-55 to their increased solubility at the high pH, resulting in the creation of pores in the matrix thus facilitating drug release [43]. The acidic nature of the enteric polymers has also been implicated as the mechanism for their release rate enhancement. It has been indicated that microenvironmental pH lowering may be the more predominant mechanism and not the pore forming ability. The replacement of the enteric polymer by a water-soluble excipient failed to enhance the release rate. While the water-soluble excipients were also capable of creating pores in the matrix, they lacked the pH-modifying effect and hence did not enhance drug release [71]. Similar to organic acids, the acidic

polymers lowered the microenvironmental pH of the matrix and increased the drug solubility within the matrix. Compared to organic acids, enteric polymers have the added advantage of slower release from the matrix themselves, due to their lower solubility and higher molecular weight.

Another anionic polymer, hydroxypropyl methylcellulose acetate succinate (HPMCAS), added to EC-based matrix tablet of verapamil hydrochloride, also showed reduced drug release rates. In this case, it was likely that an interaction complex formed between the cationic drug and the anionic enteric polymer. However, its inclusion in hydrophilic matrix tablets based on HPMC did not result in release rate modulation and to pH-independent drug release. Failure was attributed to the inability of the macromolecular HPMCAS to dissolve in the phosphate buffer drug release test medium within the swollen HPMC network and for that network to accommodate the diffusing HPMCAS, so impairing the ability of the polymer to modulate microenvironmental pH [43].

An aminoalkyl methacrylate copolymer (Eudragit E100) has been successfully employed to raise microenvironmental pH in an HPMC matrix tablet delivering divalproex sodium in a pH 1.2 dissolution medium. Adding this polymer reduced the exponent n in the power law equation from 0.99, implying a predominantly erosion-driven drug release mechanism, to 0.76, suggesting a greater role for diffusional drug release [54]. This suggests that presence of the polymer increased drug dissolution in the hydrated matrix relative to the formulation without the aminoalkyl polymer was providing a greater driving force for drug release.

Chitosan is a polysaccharide derived from chitin (from crustaceans) by partial deacetylation, yielding a linear polymer of random β-(1,4) glucosamine/*N-acetylglucosamine* (deacetylation liberating primary amino groups). Owing to its low cost and high availability, low toxicity and biocompatibility, it is finding increasing pharmaceutical and medical uses. It has been used in combination with carbomer to produce an interpolymer complex employed in extended-release matrix tablets. Theophylline release from matrix tablets based on this complex has been compared with matrix tablets containing pure chitosan, pure carbomer and HPMC [72]. When the rate control polymer was chitosan alone, the rate of theophylline release was faster at pH 6.8 than in at pH 1.2 medium. The matrix exhibited good gel formation at low pH but poor gel formation or disintegration at neutral pH. With carbomer alone as the rate control polymer, there was poor gel formation at low pH, but good formation of a viscous gel layer at pH 6.8, resulting in slower drug release in neutral than in acidic conditions. The chitosan–carbomer complex tablet showed slower drug release in pH 6.8 buffer compared with tablets made with chitosan or carbomer alone. In this medium, the HPMC tablets showed similar drug release rates. At pH 1.2, the drug release rate for the chitosan–carbomer complex tablets was similar to that at pH 6.8 and to HPMC tablets. Swelling and erosion studies suggested that the chitosan–carbomer complex tablet swelled more and had a more pronounced rate of erosion at pH 6.8 compared to tablet performance in pH 1.2 media. This observation may offer a mechanistic insight to the interplay of processes governing drug release from this system [72]. The effect of pure anionic polymer behaviour in a hydrophilic matrix tablet has been demonstrated using

either carbomer or xanthan gum with oxybutynin hydrochloride as a model drug. The pH-dependent gelling behaviour of the polymers, with poor gel formation at the lower pH, and the pH-dependent solubility of the drug resulted in faster release at pH 1.2 relative to that at pH 6.8 [52].

Generally, there is a need to include additional polymer to achieve adequate gel formation also at the lower pH, as has been demonstrated in a number of other studies [59–68, 73–77]. For example, in the case of HPMC and sodium alginate [74], it was shown that the effect of combination of HPMC and sodium alginate was the most influence factor on the drug release from extended-release matrix tablets. The mechanism of drug release from extended-release matrix tablets was dependent on the added amount of alginate. The release kinetics of nicardipine hydrochloride from HPMC matrix tablets with alginate followed a zero-order release pattern.

In developing mixed polymer systems, there may be significant experimentation required to select the grades and amounts of each component required to achieve the required release rate, if this is undertaken by a trial and error approach. A relatively recent study has applied a method utilising an artificial neural network (ANN) to optimise the pH-independent release of weakly basic drug (carvedilol) from an HPMC-based matrix formulation. Owing to the weakly basic nature of carvedilol, the drug showed pH-dependent solubility, and an enteric polymer Eudragit L100 was added to formulations to overcome the pH-dependent solubility of the drug. The effects of the quantity of HPMC K4M and Eudragit L100 content on drug release were investigated. For this purpose, 13 different formulations were prepared at three different levels of each variable. Two formulation parameters, the amounts of HPMC K4M and Eudragit L100 at three levels (−1, 0, 1), were selected as independent variables. In vitro dissolution sampling times at twelve different time points were selected as dependent variables. By using dissolution results and amount of HPMC K4M and Eudragit L100, percentage of dissolved carvedilol was predicted by ANN. The similarity factor (f_2) between the predicted and experimentally observed profile was calculated, and the f_2 value showed no difference between predicted and experimentally observed drug release profiles. As a result, it was concluded that ANNs can be successfully used to optimise the formulation composition of these controlled release drug delivery systems. Other workers have employed simplex optimisation [59, 61] and response surface methodology [74, 78] statistical optimisation to quickly arrive at the formulation with the desired performance characteristics. These approaches offer a rigorous experimental approach minimising the number of iterations needed to quickly identify the polymer ratios required to achieve pH-independent release.

Bringing the concepts presented in the preceding sections together and combining the use of non-ionic and anionic polymers along with organic acid pH modifiers in a matrix formulation has found utility in achieving sustained release dosage forms with minimised pH dependency of drug release. They offer an acidic microenvironment and also pH-dependent polymer erosion to further enhance drug release in neutral pH environments where a weakly basic drug and their salts would be expected to release slowly due to their solubility characteristics in such media [79].

11.5 Conclusions

The level and extent of hydrogen ion activity in the hydrated microenvironment can have significant impact on the performance of hydrophilic matrix tablets. Modulation of this microenvironmental pH provides an effective means for optimising dissolution profiles of certain solid systems. However, despite research efforts in this area, there is still need to better define the concept of solid microenvironmental pH and continue to establish methodologies which provide more reliable tools for its measurement in situ. The limitations of the current methods and the inherent difficulties associated with the heterogeneity of solid systems make modulation of the microenvironmental pH an empirical endeavour. At the present time, there are few rules available to precisely predict a priori how a pH modifier would modulate the microenvironmental pH and subsequently the performance of a formulation.

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Chapter 12
Evolving Biopharmaceutics Perspectives for Hydrophilic Matrix Tablets: Dosage Form–Food Interactions and Dosage Form Gastrointestinal Tract Interactions

Fiona MacDougall, Lee Ann Hodges, and Howard N.E. Stevens

12.1 Introduction

Hydrophilic matrix tablets remain the central approach used by pharmaceutical researchers to achieve sustained drug release via the oral route. There have been significant improvements in our understanding of the behaviour of this type of formulation; however the extensive literature still being published around both in vitro and in vivo research in this area indicates that there remains much to learn. In particular, it has become increasingly recognised that in some cases, despite extensive in vitro evaluation, a very different outcome to that expected is observed when the formulation is administered to man.

Designing robustness into the formulation is key to achieving reproducible behaviour in vivo. To do that, it is essential to understand the complexities of the local environment of the gastrointestinal tract and its influence on formulation performance. This chapter will first consider the issues and challenges in the interactions between oral dosage forms and gastrointestinal (GI) physiology. Following a summary of the risks, challenges and issues unique to the individual GI segments, this chapter will present a series of case studies to illustrate these scenarios.

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12.1.1 Physiological and Local Factors in the GI Tract Affecting Dosage Form Performance

There are a plethora of physiological and local environmental factors in the human gut which have the potential to interact with and affect the performance of an oral tablet dosage form, and it is crucial that those which are pertinent to the desired target behaviour of the formulation are considered. For example when formulating a tablet which is designed to target drug release in the colon, it may be tempting to only consider testing in media which simulates the colonic environment; however that tablet will first be subjected to the local conditions in the oesophagus, stomach and small intestine prior to reaching its target.

12.1.2 Transit Through the Oesophagus

Many may not give much consideration to the oesophagus, due to the apparent transient nature of the tablet's residence in this area. The anticipated rapid transit can be identified using scintigraphic images similar to Fig. 12.1. However, the phenomenon of oesophageal adhesion of oral formulations of different compositions, sizes and shapes is well documented in the literature [1–3].

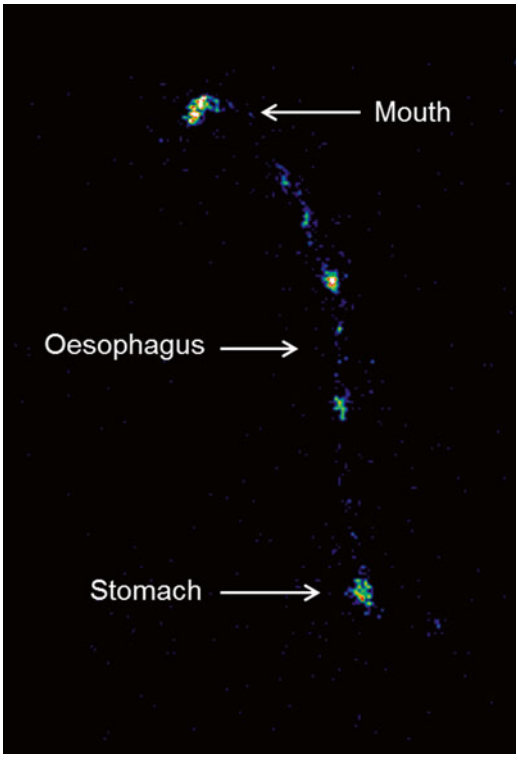

Fig. 12.1 Gamma scintigraphic image showing rapid oesophageal transit of a radiolabelled film coated tablet, from the mouth, through the oesophagus, to the stomach

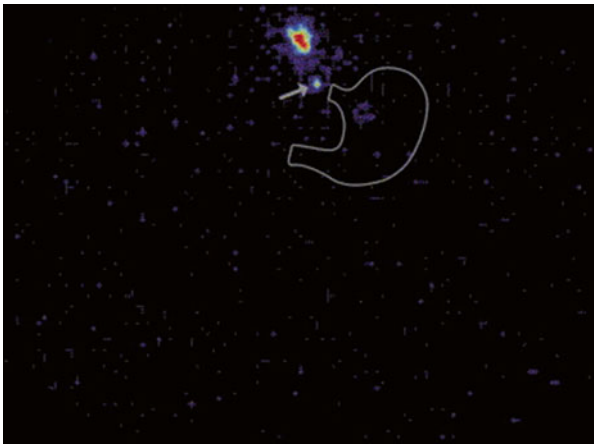

Fig. 12.2 Gamma image of a chitosan granule containing capsule 5 min after capsule administration, showing the capsule still located in the oesophagus. The *arrow* indicates a positional ^{57}Co marker at the tip of the sternum. Reprinted from Säkkinen et al. [5] with permission from Elsevier

The moisture content of the oesophagus is relatively low, and due to the propensity of the surface of hydrophilic dosage forms to hydrate rapidly on contact with water, a tacky gel surface can be quickly formed [4]. A study using gamma scintigraphy to monitor the oesophageal transit of granules of the hydrophilic matrix forming polymer chitosan contained within gelatin capsules suggested that following disintegration of the adhered capsule shell, the chitosan contained within also began to adhere to the oesophagus, demonstrating that it is not only the surface or outer coating of the formulation that must be considered [5]. The adhesion of the radiolabelled capsule to the oesophagus could clearly be observed in the scintigraphic images obtained 5 min after administration, as shown in Fig. 12.2. If the patient has swallowing difficulties such as the dysphagia often reported in older patients [6, 7], or has perhaps simply swallowed the tablet with a minimal volume of or no water, then the tablet may adhere to the epithelial surface of the oesophagus for some time, with only one-third of the volunteers in a study on barium tablets being aware of this occurrence [8].

The recognition of the damage that this can cause (in addition to the effect of food and drinks on bioavailability [9]) led to the strict dosage instructions for Fosamax, an immediate release formulation, which include swallowing the tablet with a full glass of water (not less than 200 ml), and remaining upright for 30 min after taking the tablet [10–14]. Setting aside the potential for damage to the oesophageal epithelia as a result of raised local concentrations of the API [15], hydrophilic matrix formulations present a risk of swelling in response to ingested water. It has been demonstrated that a paracetamol immediate release tablet which became adhered to the oesophagus of a volunteer in a study produced a pharmacokinetic profile that was greatly altered from the expected target [16]. Extrapolating this to the performance of hydrophilic matrix formulations in this minimal moisture, low hydrodynamic environment, the formulation will clearly be unlikely to achieve the desired release profile. Using an appropriate coating can help to ameliorate this problem [17, 18], and it would be prudent to consider these issues in formulation development.

12.1.3 The Stomach

12.1.3.1 The Fasted Stomach

From a biopharmaceutics perspective, the stomach represents an environment which presents the potential for multiple physiological interactions with the dosage form, in conjunction with the effects of any food which is consumed by the patient. In this respect, the fasted state represents a somewhat more simplistic challenge for an oral formulation, and the length of its exposure to this environment will be relatively short in comparison to other sections of the gut. In the fasted state, the stomach cycles through varying degrees of motility, in a largely quiescent cycle which lasts approximately 2 h, called the migrating myoelectric complex, or migratory motor complex (MMC).

A non-disintegrating monolithic formulation will remain in the fasted stomach until the onset of phase III of the MMC, powerful sweeping contractions which are designed to empty any larger undigested particles from the stomach, often referred to as the 'housekeeper wave'. Thus the residence time in the fasted stomach will vary between individuals, depending on the time of administration in relation to the MMC phase they are in. During this time, the pH of the fasted stomach should remain relatively low at around 1.5–2.7, although it should be remembered that the pH is not 'homogeneous' throughout the stomach, but that somewhat different values can be detected in the body and antrum [19].

12.1.3.2 The Fed Stomach

When food is consumed, the stomach converts from the MMC to a 'fed state', focused on processing and grinding down the meal to begin digestion. The local pH is transiently buffered by the presence of food, before secretion of HCl gradually returns it to a more acidic level, and the extent of this can be dependent on the type and quantity of food consumed. The body of the stomach acts simply as a reservoir for the food, while the antrum engages in the process of physically milling the food before it is passed into the duodenum. Antral milling is achieved by way of peristaltic contractions, and any non-disintegrating monolithic dosage form present in the fed stomach will at some point be subject to these high forces.

The volume and nutritional content of the meal can have a significant influence on the duration of the fed state, with fat in particular being a major determinant in the time taken to return to the fasting stage of the MMC [20]. Given that it is quite possible that a patient may consume another meal before the fasting MMC has even returned, the potential for an oral matrix tablet to reside in the stomach and be subject to antral forces for extended periods of time must be considered. In vivo measurement of the forces in the stomach has variously reported values of 1.50 N in the fasted stomach and 1.89 N in the fed stomach using tablets of different crushing strengths [21], and between 0.53 and 0.78 N using agar beads [22], and a matrix formulation which is to retain its extended release profile must be sufficiently robust to withstand this.

12.1.3.3 Dose Dumping in the Stomach

The combined effects of physical abrasion from food, antral grinding and high osmotic pressure, could have a significantly detrimental effect on a less robust hydrophilic matrix, and this can lead to the phenomena of dose dumping, where the formulation fails to control drug release at the desired rate, and instead releases a significant amount of API over a shorter period of time. Dose dumping has been defined by the European Medicines Agency (EMA) as "Unintended, rapid drug release of the entire amount or a significant fraction of the active substance contained in a modified release dosage form" [23], while the Food and Drug Administration (FDA) describe a situation "in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects" [24].

Theories of the mechanism of 'dose dumping' centre around a lack of robustness of the matrix, due to inadequate formation of a coherent gel structure, rendering the formulation susceptible to the physical pressures exerted in the gut [25]. This may be a result of an inhibition of the hydration of the polymer, hampering complete interaction and gel formation, or an insufficient quantity of polymer in the formulation to form a network. The physical abrasion of the presence of food and pressures exerted by the physiological action of the gut then enable shearing of segments of the tablet away from the core, rather than the slow erosion of the matrix which was originally designed [26, 27]. The use of imaging studies can help to evaluate the robustness of this erosion process in vivo, as shown in Fig. 12.3.

There are obvious clinical implications for the patient of more rapid and extensive exposure to drug than expected, in terms of both therapeutic efficacy and the potential for serious side effects or even overdose. Examples of dose dumping in the presence of food have been cited in the literature [28–30], and it is known that alcohol may also have an impact on dosage form failure [31, 33, 34, 124], as highlighted by the FDA alert on an alcohol interaction with the Palladone (hydromorphone) extended release formulation [35].

12.1.3.4 The Effect of Food

On the other hand, rather than dose dumping occurrences, there are examples in the literature where food induced a delay in the onset of absorption of compounds [36, 37]. A general example of this effect was reported for immediate release hydroxypropylmethyl cellulose (HPMC) film coated fosamprenavir tablets in a clinical study, where it was concluded that pH-dependent in vitro dissolution profiles could not entirely explain the in vivo profiles shown in Fig. 12.4, which show a delay in onset of local fosmaprenavir dissolution in the stomach in the presence of food. Subsequent in vitro assessment using TIM-1 (see Sect. 12.1.6) and magnetic resonance imaging (MRI) demonstrated that in the presence of a nutritional shake, water ingress into the formulation was impaired, with the authors also suggesting that a food precipitation layer may also have formed on the surface of the HPMC coated tablet, further impeding drug release [37].

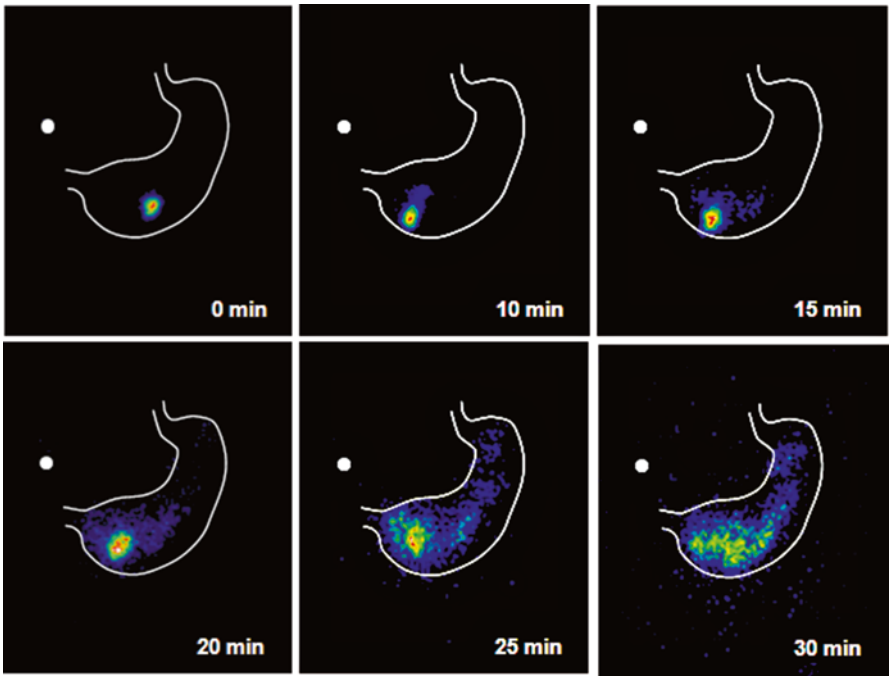

Fig. 12.3 Gamma scintigraphic images showing erosion and spread of a radiolabelled matrix tablet in the stomach with time

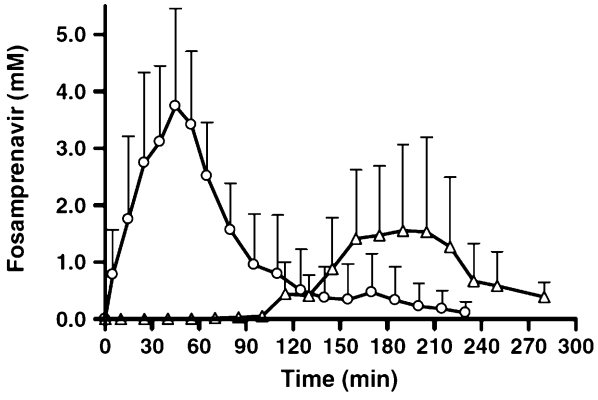

Fig. 12.4 Gastric concentration–time profiles of an immediate release formulation of fosamprenavir in vivo showing an example of delayed dissolution in the fed state (*open triangle*) when compared with the fasted state (*open circle*) (Brouwers et al. [36]). With kind permission from Springer Science and Business Media

In animal studies, one group of researchers demonstrated that a delay in disintegration in vivo was due to precipitation of a protein film on the surface of the tablet, and suggested that some relatively simple in vitro tests using nutritional drinks could be used to monitor this effect [38]. These examples for immediate release formulations have obvious implications for hydrophilic matrix formulations, and many cases of food altering the pharmacokinetics in such dosage forms have been reported [26, 39–42].

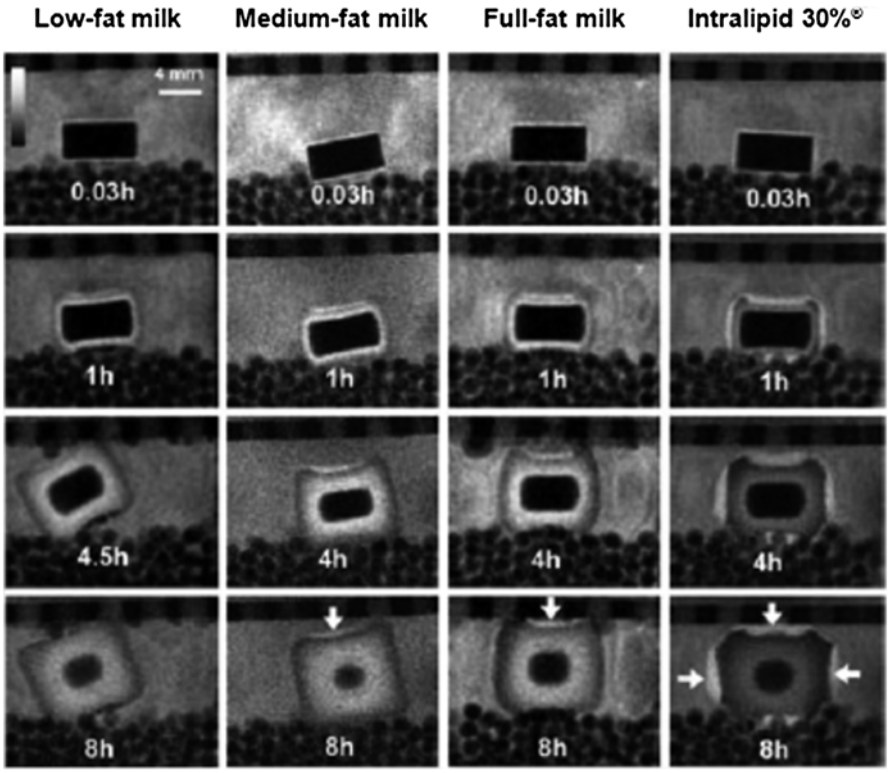

Fig. 12.5 MRI images of an HPMC matrix hydrating in different fat emulsions in vitro, with *arrows* highlighting solid deposits on the surface of the matrix gel layer. Reprinted from Williams et al. [43] with permission from Springer Science and Business Media

A detailed in vitro investigation of hydrophilic matrix HPMC tablets using techniques, such as confocal microscopy for early gel layer formation and MRI, demonstrated that fat deposits on the surface of the tablet retarded drug release [43]. A series of images obtained illustrated the effect of different types of lipid emulsions on the extent of hydration of the matrix with time, along with evidence of solid deposits on the surface of the gel matrix layer increasing in response to fat concentration (Fig. 12.5). It was suggested that this effect appeared to be due to the polymer imbibing the aqueous component of the emulsion in preference to the fat component which then accumulates on the surface. The authors recognised that the situation may be slightly more complex in vivo, where shearing forces in the stomach may counteract the accumulation of a fatty layer deposition.

As a result of the significant impact that food can have on formulation performance, regulatory bodies commonly specify that modified release products must be tested in the fed state to ensure robustness [23, 24]. This is also a specific requirement of bioequivalence studies of modified release formulations [23, 24], particularly as it has often been reported that products which were designed to be

interchangeable produced significantly different pharmacokinetic profiles when administered in the fed state. Test meals are recommended to be composed of 800–1,000 cal, of which 50 % should be derived from fat, in order to test food effects to the extreme [23, 24].

12.1.4 The Environment of the Small and Large Intestine

Beyond the stomach, generally speaking the local pH gradually increases as the dosage form progresses along the small and large intestines [44, 45], and the availability of free water decreases [46], which will impact on polymer hydration and thus robust matrix formation, with a concomitant effect on dosage form disintegration and dissolution of the active pharmaceutical ingredient (API). In the small intestine, there exist localised mixing contractions, as well as peristaltic propulsive contractions, and these may still have the potential to influence erosion. Digestive enzymes and bile salts are secreted, and as a result of the gradual absorption of nutrients and water, changes in the osmotic strength of the environment will occur [47].

It has been observed that dosage forms can experience a period of stagnation at the ileocaecal junction (ICJ) [48, 49]. The ICJ represents another area of the gut where a high pressure zone has been identified [50], and there have been reports in the literature of formulations which break down on transit from the ileum to the ascending colon, sometimes by design [51]. In the colon, there is also a huge increase in bacterial activity, which has the potential to further affect formulation behaviour [52].

12.1.5 Circadian Effects and Other Considerations

There are other factors which may also be considered relevant to some types of formulation. It has for example also been identified that some processes of the gut vary depending on the time of day, displaying a circadian rhythm in their function. Gastric emptying of food is faster in the morning than in the evening [53], basal stomach pH is raised in the evening [54], and overall GI transit is slower overnight than in the daytime [55].

There are many excellent, more extensive and detailed reviews of the nature of the local environment of the gastrointestinal tract, and it is highly recommended that any researcher embarking in a career in oral formulation development, hydrophilic matrix related or otherwise, consult these and similar documents to inform their Quality by Design development strategies [56–62]. However, the main in vivo factors which can affect oral dosage performance can be summarised as in Table 12.1.

Table 12.1 Physiological factors and their potential effects on dosage form performance

Physiological factor	Parameter affected
Changing pH	Dissolution rate of API Performance of pH dependant coatings
Gradual reduction in water availability, and increase in viscosity of luminal contents	Hydration rate of polymer Formation of robust gel matrix Dissolution of API Diffusion of API
Mixing and propulsive movements	Mechanical breakdown/erosion of matrix Dose dumping
Presence of food	Hydration rate of polymer Formation of robust gel matrix Physical abrasion of gel matrix Dose dumping Deposits on surface slowing release Delay in onset of plasma levels
Excretions, e.g. bile salts	Dissolution rate of API
Changes in ionic strength	Hydration rate of polymer Formation of robust gel matrix Dissolution of API Diffusion of API
Circadian fluctuations	Changes in transit rate Changes in acid secretion
Microflora	Degradation of API/excipients

12.1.6 In Vitro Testing of Hydrophilic Matrix Formulations

While this chapter focuses on in vivo case studies, it is useful to briefly mention some of the various in vitro methods that have been used in attempts to simulate the interactions that may occur between hydrophilic matrix dosage forms and the GI environment in vivo, as these methods will often have been used to evaluate such dosage forms prior to clinical study. More in-depth reviews of in vitro testing methods can be found in the literature [63–65].

By far the most commonly reported method of assessing in vitro release rates reported in the literature for evaluation of hydrophilic matrix dosage forms is the United States Pharmacopoeia (USP) II dissolution apparatus. The USP II dissolution apparatus is designed as a simple standardised test to characterise release from dosage forms under sink conditions [66, 67], and is often used as a Quality Control (QC) tool. It is widely acknowledged, however, that while it is a useful investigative tool for evaluation of formulation performance, the hydrodynamic forces and conditions created in the dissolution vessels are not representative of those exerted in vivo.

As a result of this, there are a range of methods reported by researchers in attempts to develop in vitro tests which are more predictive of in vivo behaviour in the GI tract. These range from relatively simple methods such as the rotating beaker method [25], or the dissolution stress test device which attempts to simulate the pressures

and forces in the GI tract by incorporating a flexible balloon within a chamber in which a test tablet is contained [68, 69] to the TIM-1, a complex multi-compartmental computer controlled system which attempts to simulate the local environment, hydrodynamic forces and peristaltic activity of different stages of the GI tract from stomach to ileum, using data derived from fed and fasted in vivo studies [37, 70]. A fed stomach model has been reported using an adaptation of the USP II paddle apparatus, with small glass beads which are moved by blades to create movement of the dosage form. This apparatus was used to study the behaviour of a diclofenac bilayer hydrophilic matrix tablet using different test scenarios based on in vivo literature data, and showed promising results as a biorelevant in vitro test [71].

The use of biphasic dissolution media in the USP II dissolution apparatus, composed of an aqueous and an organic layer, has been proposed as means of maintaining sink conditions for evaluating formulations containing compounds with low solubility [72–75] including pH-dependent poorly soluble compounds [76]. This was considered to be a preferable alternative to the addition of surfactants to the media which may interact with cellulose ethers, and it was demonstrated that this approach could be used to discriminate between the performance of nifedipine containing hydrophilic matrix tablets composed of different HPMC concentrations, using a water/octanol system [75].

The USP apparatus III (Reciprocating Cylinder), also referred to as Bio-dis, represents a compendial attempt to better simulate the conditions in the GI tract for biorelevant testing. It consists of a series of smaller vessels in which the media representing different stages of the GI tract can be placed, and a reciprocating cylinder which is dipped into the dissolution medium to create agitation. The Bio-dis was shown to provide a good in vitro in vivo correlation (IVIVC) for drug release for a pH- and time-dependent multiparticulate dosage form. A pH gradient method used in the in vitro apparatus to simulate residence time and local conditions in the GI tract was able to predict the outcome of an in vivo study of the formulation [77].

The Dynamic Gastric Model (DGM) is composed of three main sections (Fig. 12.6): the main body, antrum and valve assembly, which are capable of accommodating up to 800 ml, equivalent to a large meal such as the FDA high fat test meal described in Sect. 12.1.3.4. The main body simulates the lack of mixing in the body of the stomach after a meal, while the in vivo milling action of the antrum is simulated by a piston which slides through a barrel, forcing the media through an elastic annulus which sieves the material [78].

The DGM was used to examine the behaviour of the agar beads which had previously been used to determine gastric forces in vivo as described in Sect. 12.1.3.2. The robustness of the beads to conditions in the DGM and USP II paddle dissolution apparatus was compared in locust bean gum preparations designed to simulate high and low viscosity test meals [78]. At the end of the test, none of the beads had broken in the USP II dissolution apparatus, whereas breakage in the DGM model correlated well with the previously reported in vivo data. The authors discussed the hydrodynamic flow and forces in the two apparatus as a means of explaining the findings, suggesting that the high hydrodynamic flow rates and low shear forces which maximise the rate of dissolution or disintegration are the opposite of the low shear rates and high forces experienced in vivo. The DGM was also capable of

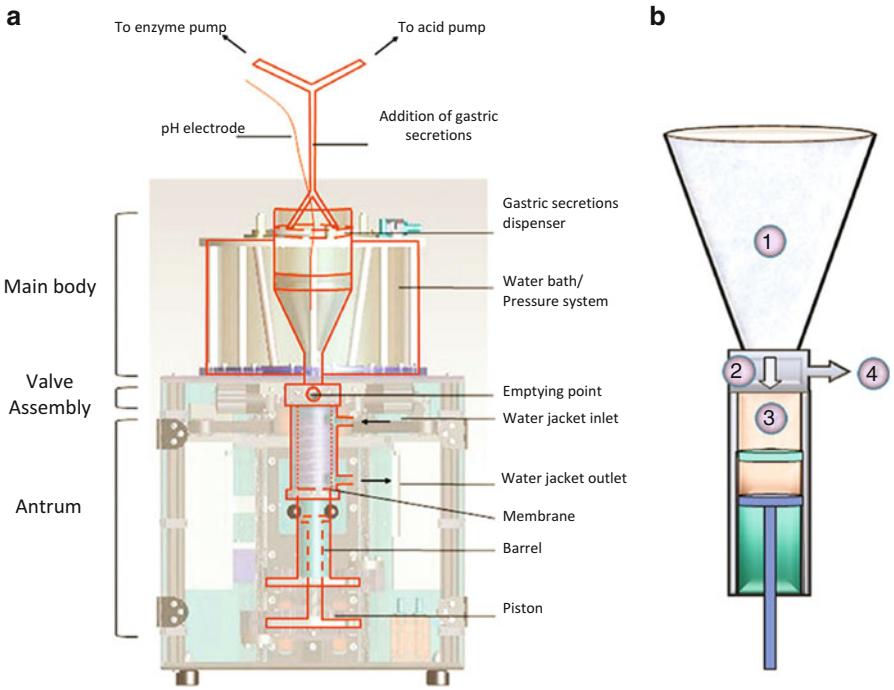

Fig. 12.6 Schematic representations of the Dynamic Gastric Model. (**a**) Depicts the main components of the DGM, while (**b**) illustrates the mechanism of the mechanical digestion: (1) The meal/gastric content in the main body is inhomogeneously mixed with the gastric secretions through application of pulsatile contractions. (2) The content is allowed to go into the antrum through the valve assembly. The inlet valve is open during the process allowing reflux and mixing between the main body and the antrum. (3) The chyme is processed mechanically by the movement of the piston and barrel, and it is forced through an annular membrane. (4) The chyme is emptied from the antrum and collected for analysis (Vardakou et al. [78]). With kind permission from Springer Science and Business Media

discriminating between two different meal substitutes, which may help differentiate between the behaviour and mixing of a dosage form in liquid gastric contents, versus the high shear forces generated by more viscous gastric bolus content which may cause some formulations to fail.

Concurrently with the design of apparatus to simulate the mechanical forces exerted by the gut, there have also been extensive attempts to compose in vitro media in which to carry out the tests. These range from simple media such as milk and ethanol, through physiologically relevant hydrogen carbonate buffers and ionic strengths, to complex media simulating different stages in the GI tract [79–87].

As a result of these investigations, highly relevant information relating to hydrophilic matrix performance has been disseminated, such as the effect of agitation, hydrodynamic, physical stress, ionic strength, the presence of salts and sugars, the presence of alcohol, erosion rate, gel strength, matrix hydration rate, pH effects and viscosity [64]. However, despite the significant advances in in vitro testing systems

that have been achieved in recent years, it is very difficult to design an apparatus which simultaneously represents the all aspects of the complexities of the gut, and as of yet there is no definitive and practical test which can ensure prediction of in vivo performance. The ongoing European ORBITO (Oral Biopharmaceutical Tools) initiative seeks to improve this situation through integration of different arms of research, with the aim of speeding up the formulation development process, and in the longer term perhaps reducing the need for animal and clinical studies [64, 88]. Ultimately, development of hydrophilic matrix formulations requires confirmation of robust clinical performance, and at present the best and definitive test for this is to investigate and understand its behaviour in man.

12.1.7 In Vivo Imaging for Evaluation of Oral Hydrophilic Matrix Performance

It is clear from the non-exhaustive list of influencing factors involved that the potential for interactions between dosage forms and food and dosage forms and the GI tract are numerous, and it is not the intention of this chapter to attempt to cover all possibilities. Rather, some case studies are presented to demonstrate instances where product performance has clearly been influenced by the presence of food or by GI transit parameters.

One of the key tools used in the literature and the case studies presented is gamma scintigraphy, where a component of the formulation being studied is radiolabelled with a gamma emitting radioisotope. This is then administered to the volunteer, who stands in front of a detector as shown in Fig. 12.7. The detector contains a lead collimator to screen out any radiation not travelling directly towards the detector, a sodium iodide crystal and an array of photomultiplier tubes which allow conversion

Fig. 12.7 A volunteer in front of the detector of a gamma camera. Image courtesy of Siemens

of the incoming gamma radiation into an onscreen image. This enables monitoring of the location of the tablet in the GI tract at any given time, along with quantitative data on the amount of radiolabel in a particular area, allowing processes such as erosion of a tablet to be determined. Figure 12.8 shows an example series of images

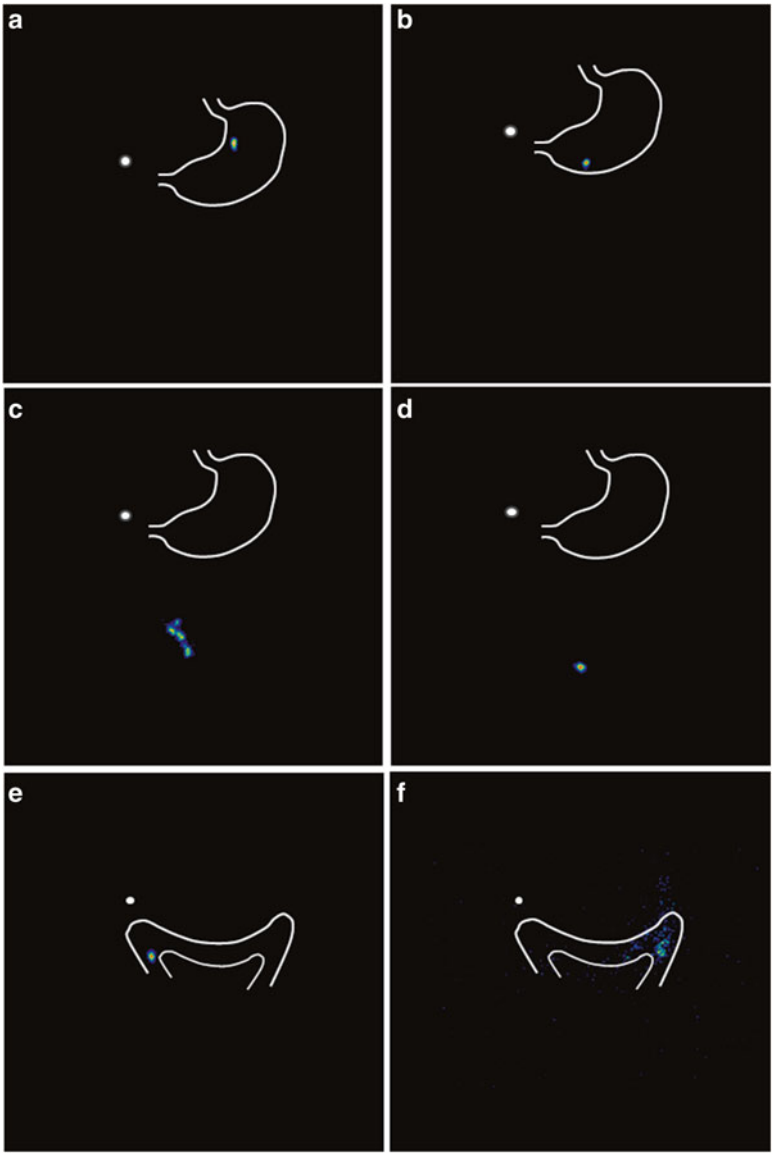

Fig. 12.8 Example images of a radiolabelled hydrophilic matrix obtained using gamma scintigraphy, showing (**a**) a tablet just after ingestion in the fed stomach, (**b**) the tablet remaining in the stomach a few hours after ingestion, (**c**) movement of the tablet in the small intestine just after gastric emptying, (**d**) intact tablet in the small intestine, (**e**) intact tablet entering the ascending colon and (**f**) erosion of the tablet in the distal colon

obtained following the transit of a hydrophilic matrix tablet through the GI tract. When pharmacokinetic blood sampling is carried out simultaneously, the technique is known as pharmacoscintigraphy, which provides a useful means of interpreting unexpected pharmacokinetic (PK) data.

As the following case studies demonstrate, imaging studies can provide crucial insight into the in vivo performance of hydrophilic matrix tablet formulations, interactions between the dosage form, food and the GI tract. The lessons learned from such studies should be used to feedback into development programmes with the aim of producing sustained release products that are robust enough to perform as independently as possible of local conditions.

12.2 Case Study 1: Dose Dumping from an HPMC Matrix Tablet Caused by the Presence of Food in the Stomach

As outlined in the introduction, in order to ensure that a controlled release matrix formulation performs safely in a clinical setting, it is imperative to ensure a robust matrix is formed in vivo in order to avoid the risk of dose dumping. As discussed, it is known that the presence of food in the stomach may increase the propensity of a formulation to display this behaviour, and examples of this phenomenon have been reported in the literature [32, 89–91].

12.2.1 Background

UK 294,315 is an α-1 antgonist developed at Pfizer as a treatment for prostatic hyperplasia, and pharmacokinetic studies showed extensive absorption via the oral route in humans, with only 14 % of the administered dose excreted unchanged in the faeces [92]. It was subsequently formulated into the hydrophilic matrix modified release (MR) dosage forms described in Table 12.2, with in vitro release of 20 mg over a 6 h period, and 100 mg over an 18 h period as shown in Fig. 12.9 [40]. The 100 mg matrix formulation was progressed into clinical studies; however upon analysis of the pharmacokinetic data it became apparent that while the formulation performed robustly as designed in fasted volunteers, when it was administered with a

Table 12.2 The composition of UK 294,315 hydrophilic modified release tablets used to achieve in vitro dissolution of 6 and 18 h duration, summarised from McInnes et al. [40]

20 mg MR	6 h in vitro	100 mg MR	18 h in vitro
HPMC	Dry blend	HPMC	Wet granulation
Lactose		Lactose	
Aerosil		Povidone	
Magnesium stearate		Magnesium stearate	

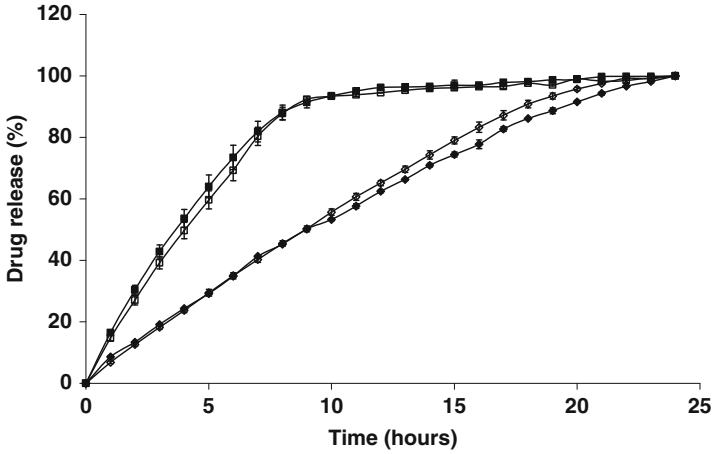

Fig. 12.9 In vitro dissolution profiles from HPMC matrix formulations of UK 294,315 designed to achieve 6 h (*squares*) and 18 h (*diamonds*) controlled release (McInnes et al. [40]). With kind permission from Springer Science and Business Media

high fat meal PK profiles were suggestive of dose dumping, manifesting itself in the plasma data as an increase in both the maximum plasma concentration (C_{max}) and area under the curve (AUC) [39].

In order to gain a more useful insight into the lack of in vitro/in vivo correlation (IVIVC) and an increased understanding of the PK data obtained, a clinical pharmacoscintigraphic study of this formulation was carried out by Davis et al. in healthy male volunteers to elucidate the mechanism of the apparent dose dumping effect [39]. An immediate release tablet was compared to the modified release tablet with 18 h in vitro profile, and both formulations were labelled with the gamma emitting isotope samarium-153 (^{153}Sm) to allow visualisation of location in the gastrointestinal tract along with quantification of the rate of erosion.

12.2.2 Practical Considerations for In Vivo Gamma Scintigraphic Studies

In order to accurately quantify the erosion of a formulation in vivo, it is essential that the isotope that is used as a radiolabel is distributed homogeneously throughout the matrix. It is also essential that the radiolabel is present in an insoluble form, as on hydration of the matrix a soluble isotope would have the ability to diffuse out from the formulation, giving a false impression of the rate of erosion. Samarium-152 (^{152}Sm) oxide is insoluble, and inclusion of a very small amount in the formulation is sufficient to enable quantitative analysis of the scintigraphic images. ^{152}Sm itself is not radioactive, and so after incorporation into the formulation it is exposed to a neutron flux, resulting in the formation of the gamma emitting isotope ^{153}Sm.

Following incorporation of a radiolabel into a formulation, it is always crucial to validate in vitro that the incorporation of the radiolabel has not altered the behaviour of the formulation, and this can be even more important when ^{153}Sm is used as a radiolabel in hydrophilic matrix formulations, as the neutron bombardment process has been reported to have detrimental effects on some polymers. This is thought to be the impact of the heat that is generated during this process on the polymer, subsequently affecting its ability to control release of drug in the desired manner [93].

12.2.3 In Vivo Pharmacoscintigraphy in the Fed and Fasted State

The modified release matrix formulation was administered in both the fed (FDA high fat meal [24]) and fasted states, and by using the radioactivity emitted from the tablets to quantify matrix erosion over time in individual subjects, it was clearly observed that in the fed state the MR tablets eroded significantly faster than in the fasted state, as shown in Fig. 12.10. Pharmacokinetic blood sampling was carried out simultaneously with the scintigraphic imaging regimen, and the general observation of an increased erosion rate in the fed state was confirmed by the clear increase in C_{max} when compared to the PK profiles of those obtained in the fasted state.

A key finding of this particular case study demonstrated the significant influence that the presence of food in the gut can have on the performance of hydrophilic matrix systems, and provided crucial evidence on the mechanism of the apparent dose dumping effect. This arose from the ability to correlate the scintigraphic analysis of erosion with the location of the tablets in the GI tract. By doing this, the authors established that while in the fasted state the tablets emptied from the stomach and exhibited complete disintegration in the colon, in the fed state the majority of tablets remained in the stomach at the time of complete erosion (Table 12.3).

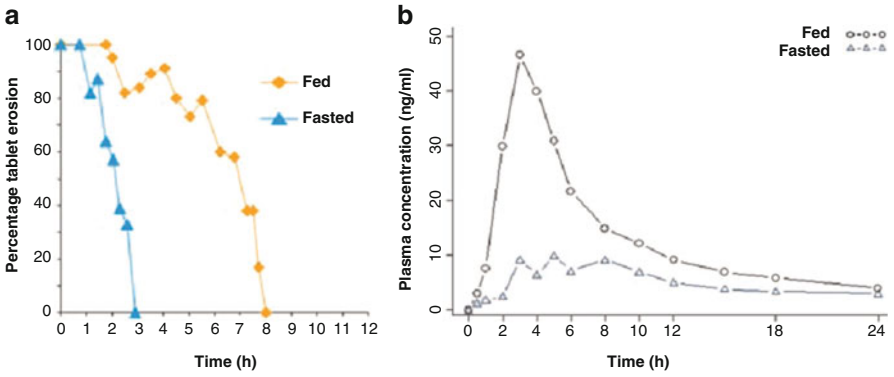

Fig. 12.10 Effect of food on UK 294,315 hydrophilic matrix tablet erosion in one subject (**a**), and simultaneous pharmacokinetic profiles from the same subject (**b**) (Davis et al. [39])

Table 12.3 Time and location of complete in vivo disintegration of a modified release HPMC matrix tablet formulation in the fed and fasted states, evaluated using gamma scintigraphy. Redrawn from Davis et al. [39]

	Fasted		Fed	
Subject number	Time	Anatomical site	Time	Anatomical site
1	9.64	Colon	6.98	Small intestine
2	7.88	Colon	2.73	Stomach
3	12.67	Colon	6.70	Stomach
4	6.48	Colon	4.04	Stomach
5	9.13	Colon	4.88	Stomach
6	8.78	Colon	6.21	Stomach
7	10.11	Colon	5.68	Stomach
8	11.79	Colon	5.36	Small intestine
9	7.98	Colon	10.49	Stomach
Mean	9.38		5.90	
SD	1.95		2.18	
Median	9.13		5.68	

The retention of the tablets in the stomach and exposure to the grinding and milling forces that are exerted in the presence of food were concluded to have been the likely cause of the accelerated physical erosion and matrix breakdown observed, which subsequently translated into a faster rate of absorption observed in the pharmacokinetic data. The food effect was considered to be a local mechanical effect rather than a pharmacokinetic effect per se, as the AUC_{inf} was comparable between the fed and fasted arms of the study, despite the greater C_{max} observed in the fed arm of the study.

12.2.4 Effect of Tablet Location in the Gut on Drug Absorption

Further demonstrating the usefulness of the combined pharmacoscintigraphic approach for providing key insight into formulation behaviour in vivo, the authors suggested that the higher C_{max} observed was also a function of the relative absorptivity of the epithelial location of the tablet at the time of complete disintegration [39]. In this case the location of the formulation in fed volunteers was demonstrated to be the stomach as a result of the gastrointestinal motility patterns induced by the presence of food, while in the fasted state scintigraphic imaging demonstrated that most of the drug release is likely to have occurred in the colon, where absorption of the compound in question is relatively low, indicating a dual effect of food and GI interactions with this particular hydrophilic matrix dosage form.

12.2.5 Preclinical In Vivo Models

To mitigate the risk of undertaking clinical studies on a formulation that could ultimately show some unpredicted interactions with food or the GI tract, it may be tempting from a formulation development point of view to carry out preclinical PK studies as a means of assessing the robustness of a novel matrix formulation. Using preclinical models may present a cost-effective option for early formulation assessment and screening; however there are several considerations which must be taken into account.

In the first instance, for orally administered doses the animal must be large enough to administer the full-sized human formulation in order to rule out any scaling effects. Once the animal model is selected, it is essential to bear in mind the differences between the particular species and man. For example, while the MMC of the dog is of a similar periodicity to man [45], other differences between the GI tracts of the dog and man have been well documented. These include raised stomach pH, increased antral grinding forces, slightly higher intestinal pH, shorter GI tract and a more permeable epithelium [45, 94–99].

There have been some reports of attempts to mitigate the differences in gastric pH [99]; however one study in particular warned that care should be taken when extrapolating data obtained in the dog to man, due to extended gastric emptying times observed for a controlled release hydrophilic matrix tablet [123]. It should be noted that in these studies the animals were fed a small meal, while the volunteers were not, and this may have influenced the outcomes. Another study demonstrated that while the absorption of 64 orally administered compounds in the rat/mouse correlated well with man, there was poor correlation in the absorption of 43 compounds administered to the dog when compared with man [97], showing the danger of unquestioningly extrapolating the intricacies of PK data.

The pig has been suggested as an alternative to the dog as the small intestinal transit times reported are much closer to that of man [100], although while scintigraphic studies have demonstrated its usefulness, the gastric emptying of formulations may be significantly slower than in man [100, 101], and there may also be differences in intestinal pH [102].

12.2.6 Over-prediction of HPMC Matrix Breakdown in the Dog

As a useful extension to the UK 294,315 dose dumping case study, this MR formulation was subsequently studied in the dog model using pharmacoscintigraphy [40], allowing a direct comparison between the effects of food and GI location on the formulation in a commonly used animal model with those obtained in man. As mentioned, many of the physiological differences between animal models and man, and in particular the dog, are well documented in the literature, and as such it was

considered useful to investigate whether such a preclinical model would have predicted the lack of formulation robustness. In this case the 'dose dumping' formulation was compared with an MR hydrophilic matrix designed to release the drug over 6 h as a control (composition described in Table 12.2).

It was found that the 18 h MR hydrophilic matrix formulation dose dumped in both the fed and fasted states in the dog model, an occurrence which can be linked to the reportedly higher forces exerted by the dog stomach in the fasting state in comparison to the human stomach [90]. This over-prediction of the propensity of the matrix to break down in vivo therefore suggests that caution should therefore be exercised when using preclinical models as a means of testing for food or gut interactions with a matrix dosage form, although in this case it could be concluded that the model represented the ultimate challenge, and that a dosage form which demonstrated robustness in this animal would be more likely to perform well clinically.

These studies clearly demonstrated the differences in hydrodynamic effects on a matrix formulation between the dissolution apparatus and in vivo, and the requirement to ensure the robustness of the hydrophilic matrix in order to achieve the desired profile in vivo.

12.2.7 Key Findings from Case Study 1

- The physical presence of food in the stomach can have a significant influence on the in vivo performance of hydrophilic matrix formulations.
- Extended residence in the fed stomach prolongs exposure to antral forces, which can cause accelerated erosion and breakdown of the matrix.
- Dose dumping can lead to a rate of drug absorption that is higher than anticipated or desired, an effect which can be exacerbated where permeability of the API is greater in the upper small intestine.
- Preclinical models can be useful for early formulation assessment, but results should be interpreted with caution and not necessarily considered predictive.

12.3 Case Study 2: Susceptibility to Food Effects—Comparison of Nifedipine Hydrophilic Matrix and Osmotic Pump Formulations

12.3.1 Background

The concept of the propensity for erosive hydrophilic matrix formulations to exhibit some degree of dose dumping in the presence of food has been explored in other extended release formulations. Of particular interest are a series of studies where a comparison of the robustness of hydrophilic matrix formulations in the presence of

food has been compared to oral dosage forms with a different mechanism of drug release, osmotic pumps. Nifedipine is a calcium channel blocker, which is used clinically for the treatment of angina and hypertension. As a result of its very short plasma half-life [103] it is an ideal candidate for administration using extended release formulations to maintain constant plasma levels, reduce side effects and improve convenience for the patient [104].

12.3.2 The Effect of Food on Nifedipine Matrix and Osmotic Pumps

A study by Abrahamsson et al. [26] compared the in vivo behaviour of an osmotic pump formulation of nifedipine, Procardia XL®, with a nifedipine containing hydrophilic matrix tablet developed in-house using HPMC as the gel forming agent. Pharmacokinetic studies on the two formulations in healthy volunteers showed that when administered in the fasted state, the absorption profiles for the two formulations were very similar, with consistent input observed over a 24 h period. However, when the doses were administered following a high fat, high protein breakfast, the hydrophilic matrix formulation demonstrated a substantial increase in the rate of absorption when compared to the fasted state, and also when compared to the osmotic pump formulation in fed subjects.

While the increase in AUC of the matrix formulation compared to the osmotic pump was not deemed to statistically significant, closer observation of the plasma profiles for the matrix tablet in the fed state revealed that there was an initial slow phase of absorption lasting around 1 h, followed by a rapid absorptive phase lasting approximately 3–4 h. This resulted in a significant increase in the time to C_{max} (T_{max}) of the matrix formulation under fed conditions when compared to both the same formulation in the fasted state and the osmotic pump in the fed state, as shown by the PK parameters described in Table 12.4.

Table 12.4 Comparison of pharmacokinetic parameters of an osmotic pump (XL) and hydrophilic matrix (ER) formulation of nifedipine, showing a significant increase in the T_{max} for the ER hydrophilic matrix formulation in fed conditions

	Mean (SD)			*p*-Value		90 % CI	
	ER food	ER fast	XL food	ER food vs. ER fast	ER food vs. XL food	ER food vs. ER fast	ER fed vs. XL food
AUC (ng h/ml)	1,277 (549)	725 (378)	1,168 (556)	<0.001	0.11	1.61–1.91	1.00–1.19
C_{max} (ng/ml)	137 (52)	34 (23)	71 (29)	<0.001	<0.001	3.53–4.45	1.71–2.16
t_{max} (h)	5.9 (3.0)	13.4 (9.3)	8.4 (3.3)	<0.001	0.17	–	–

Reprinted from Abrahamsson et al. [26] with permission from Elsevier

12.3.3 In Vivo Erosion of the Felodipine HPMC Matrix

In order to elucidate the physical mechanism of the effect on PK profiles in response to food, the researchers then studied the in vivo erosion of the matrix formulation using pharmacoscintigraphy [26]. They found that individual erosion profiles correlated well with the PK data for fed subjects, with a lag time of around 1 h before the onset of erosion, followed by a rapid phase of erosion between 1 and 4 h. This rapid phase of erosion was observed to occur while the tablets were in the upper GI tract. Two subjects were administered the radiolabelled matrix formulation in the fasted state, and the consistent slow absorption of nifedipine observed was mirrored by a gradual erosion of the tablet.

The authors discussed the variability of this problem between different matrix formulations, citing examples where similar formulations did not exhibit this dose dumping effect [105]. It was concluded that as the formulations were located in the upper GI tract at the time of the rapid phase of erosion, a combination of physicomechanical and physico-chemical food effects influenced the outcome.

12.3.4 Correlation of In Vitro Data with In Vivo Findings

In a subsequent study, the authors went on to attempt to define in vitro conditions which might simulate the outcomes of this study by using the USP dissolution apparatus [27]. They compared the nifedipine hydrophilic matrix formulation which was observed to dose dump in the fed state [26], with a similar felodipine hydrophilic matrix formulation whose erosion rate was not affected by the presence of food in vivo [105]. While the best correlation was observed using the USP II basket method, the results from experimentation with different apparatus, settings and media type illustrate the difficulty of using the USP dissolution apparatus to predict food effects and performance in vivo.

12.3.5 Combined Effect of Food on Erosion and Local pH

Another pharmacokinetic study of nifedipine extended release formulations reported very similar outcomes to those detailed in the previous example [41]. The eroding hydrophilic matrix formulation CORAL® was compared with the osmotic pump formulation Adalat® OROS. The results clearly demonstrated that in the fed state the CORAL® formulation failed to control the release of nifedipine in the same manner as in the fasted state, while the Adalat® OROS formulation was unaffected by food (Fig. 12.11). This dose dumping resulted in plasma concentrations in half of the volunteers that were three- to fourfold higher than for the osmotic pump formulation, and it was noted that there was a corresponding increase in the number of subjects who reported headache as an adverse event during the study.

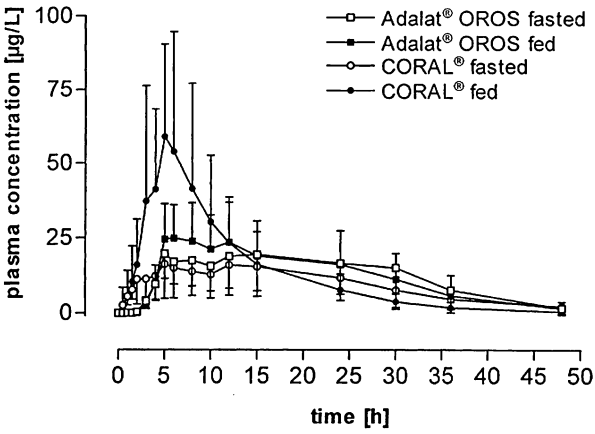

Fig. 12.11 Mean plasma concentration vs. time curves of nifedipine determined in healthy volunteers after oral administration of an osmotic pump formulation (Adalat® OROS) and an eroding hydrophilic matrix extended release formulation (CORAL®), showing dose dumping in the fed state for the hydrophilic matrix formulation. Reprinted from Schug et al. [41] with permission from Elsevier

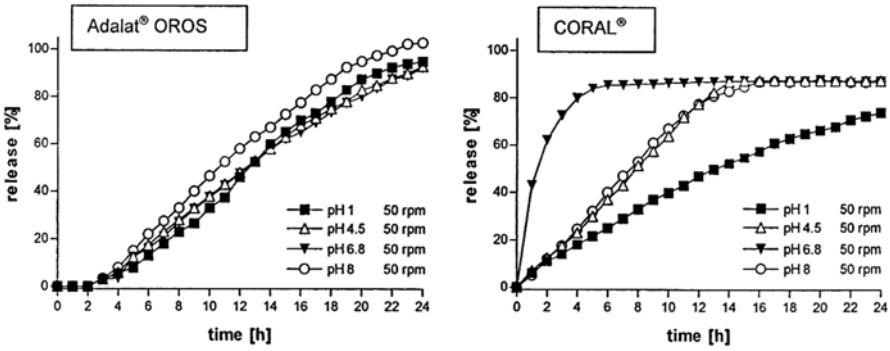

Fig. 12.12 Mean in vitro dissolution profiles of a nifedipine osmotic pump formulation Adalat® OROS and an eroding hydrophilic matrix extended release formulation CORAL®, showing the pH dependency of the CORAL formulation, and no effect of pH on release from the Adalat® OROS formulation. Reprinted from Schug et al. [41] with permission from Elsevier

Studies had shown that while in vitro release profiles for the CORAL® formulation were not influenced by variables such as agitation and osmotic pressure, release was influenced by the pH of the media, with faster release as the pH was increased (Fig. 12.12). The authors suggested that this lack of robustness to local pH conditions may have partly explained the difference in in vivo behaviour, as in the fed stomach the local pH would be expected to increase to values of around 4–6 for some time. Subsequent studies of other nifedipine matrix formulations have all identified the effect of food in vivo when compared to the osmotic system, ranging from a delay in onset of absorption [41] to dose dumping [41, 106], and identified other instances of pH-dependent release profiles in vitro [106].

12.3.6 Biorelevant In Vitro Testing

In the continued attempts to develop biorelevant in vitro test systems, Garbacz et al. studied three of the nifedipine controlled release systems in different types of in vitro apparatus, namely USP II, USP III, rotating beaker and the stress test apparatus [107]. In the tests which introduced a degree of mechanical stress a lack of robustness was identified for the erosive hydrophilic matrix formulations, reflecting the outcomes observed in the various clinical studies. No such effect was observed for the OROS formulations which had performed consistently in all of the in vivo studies.

Some of these in vitro results were further supported by data from the Dynamic Gastric Model, where the lack of lag time and increased rate of release for the CORAL® formulation when compared to the osmotic pump system was confirmed [108]. While these results gave a clear indication of the tendency of the matrix formulation to be susceptible to in vivo conditions, and in particular the presence of food, the authors cautioned that further work is still required to adequately simulate the postprandial environment of the stomach [107].

For the examples discussed in this case study, authors of the in vivo studies concluded that the various eroding hydrophilic matrix formulations could not be considered bioequivalent, and therefore were not interchangeable from a therapeutic perspective. Significant alteration of in vivo drug release may have significant clinical implications for patients.

The cumulative findings in this case study highlight the importance of testing hydrophilic matrix formulations in a range of conditions, particularly those that will stress the formulation, to establish robustness of performance. While biorelevant in vitro testing may instil a degree of confidence in the product, ultimately in vivo testing currently represents the only method to absolutely establish bioequivalence of a product.

12.3.7 Key Findings from Case Study 2

- In the fasted state, nifedipine hydrophilic matrix and osmotic pump formulations showed bioequivalence.
- The rate of absorption substantially increased for the hydrophilic matrix formulation when administered in the fed state.
- Performance of the osmotic pump formulation was not affected by food.
- Gamma scintigraphy was used to correlate the in vivo erosion rate of the matrix tablet with absorption profiles, demonstrating the increased erosion rate in the presence of food.
- The effect of food on local pH in the stomach can further affect behaviour.

12.4 Case Study 3: Robustness of an HPMC Matrix Tablet in the Context of Percolation Theory

12.4.1 Background

The previous case studies describe formulations where a weakness in the integrity of the matrix was identified in the fed state despite suitable performance in fasted volunteers, suggesting a lack of robustness in performance. The literature extensively describes the mechanism of gel formation in HPMC matrices, progression of the gel front and the complexity of erosion and diffusion as mechanisms of drug release. It is clear however that the gel matrix formed should be robust to the in vivo environment, in order to ensure the release rate of the API in vivo is equivalent to that designed in vitro to produce the desired pharmacological effect. Sections of the literature on hydrophilic matrix formulation suggest that 'percolation theory' provides an explanation of the level of matrix forming polymer that is required to produce robust performance [109–111].

12.4.2 Percolation Threshold

The percolation threshold is described as the level below which the matrix forming polymer exists as independent clusters of material existing alongside the other components of the formulation, and above which the polymer is present in sufficient quantity to provide a continuous interconnecting matrix structure, or 'infinite cluster' [112]. The percolation threshold for matrix forming tablets comprising HPMC as the rate controlling polymer has been reported to be in the region of 30 %; however the majority of these studies were performed in vitro, and the difficulties of extrapolating in vitro results to in vivo outcomes have already been discussed.

A scintigraphic erosion study was therefore undertaken using two tablets with HPMC above (40 %) and below (20 %) the percolation threshold to attempt to examine in more detail how this factor mechanistically influences performance in vivo [113].

12.4.3 In Vitro Validation of Radiolabelling for Quantification of Erosion

The full details of the formulations are listed in Table 12.5, and in this case the non-soluble radiolabel was incorporated in the form of ^{99m}Tc radiolabelled activated charcoal in the dry blend, which would enable gradual release of the radiolabel as erosion of the tablet proceeded. Prior studies had demonstrated that following adsorption of ^{99m}Tc-DTPA onto activated charcoal there was no leaching of the

Table 12.5 Composition of two hydrophilic matrix tablet formulations used in in vitro validation and gamma scintigraphic studies to examine the effect of polymer concentration on erosion behaviour in vivo

Tablet code	HPMC % (w/w)	Lactose % (w/w)	DCP % (w/w)	Magnesium stearate % (w/w)
Tablet A	20	69	10	1
Tablet B	40	49	10	1

HPMC grade used = 100 cP. Reprinted from Ghimire et al. [113] with permission from Elsevier
DCP dicalcium phosphate anhydrous

radiolabel [114], and in vitro validation prior to commencement of this clinical study confirmed that the incorporation of the radiolabel did not affect the erosion rate of the formulations when assessed gravimetrically [113]. In vitro erosion profiles were also generated from radiolabelled tablets using the gamma camera, establishing a correlation between the gravimetric and scintigraphic techniques in assessing this property.

12.4.4 In Vivo Scintigraphic Evaluation of Formulations Above and Below HPMC Percolation Threshold

Subjects were dosed with a tablet following a light snack, and the scintigraphic data obtained an erosion profile for both formulations in each of the volunteers. In both instances, it was identified that there was a delay of around 20 min before the onset of erosion in vivo, despite the observation that the erosion process began in under 30 s in vitro. The authors suggested that this may have been attributable to the higher viscosity of the fluid in the stomach when compared to the in vitro dissolution media, slowing down hydration and perhaps presenting a viscous barrier to the erosion process [115]. This finding once again emphasises the caution required when extrapolating in vitro data to in vivo, and the conundrum of balancing the need for simple and relatively rapid formulation assessment tools against the complexities and expense of more 'biorelevant' media and mechanical stresses.

On analysis of the scintigraphic images in individual volunteers, as expected, a clear difference in the rate of erosion between the two tablets was observed, with the 40 % HPMC tablet eroding more slowly. Figures 12.13 and 12.14 show representative images from an individual subject for both formulations, with clear differences in the erosion behaviour. The formulation which contained a higher level of HPMC performed robustly in vivo, with the scintigraphic erosion profiles produced showing low inter-subject variability, and excellent overall correlation with the gravimetrically determined in vitro erosion rates (Fig. 12.15).

The formulation with less HPMC, however, did not perform robustly in vivo. There was a significant degree of inter-subject variability, and poor correlation with in vitro erosion data. An observation of note for the low-level HPMC tablets was the

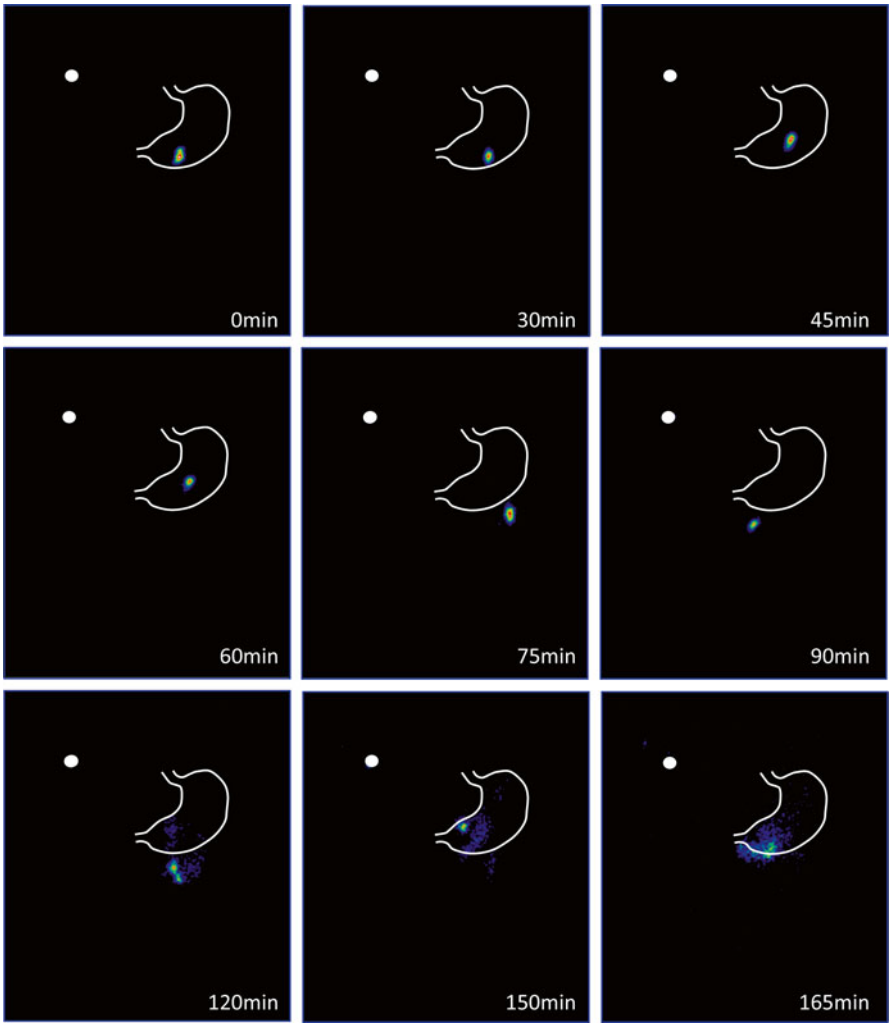

Fig. 12.13 Individual scintigraphic images from one subject showing the in vivo erosion of a 20 % HPMC hydrophilic matrix formulation at different times and locations in the GI tract

finding that in all but one of the subjects studied, a 'rapid phase' of erosion was observed, where at least 34 % of the radioactivity was released in a 15 min period. While it might have been expected that this was due to the higher forces exerted in the antrum of the stomach, the authors could find no correlation between the location of the tablet and the onset of the rapid erosion phase.

This important observation identifies a crucial moment where a massive failure of a hydrophilic matrix occurred, which would most likely lead to dose dumping in API containing formulations. It also reaffirms the requirement for the design of the matrix to take into account the physical challenges of the GI tract in order to achieve robust performance in vivo.

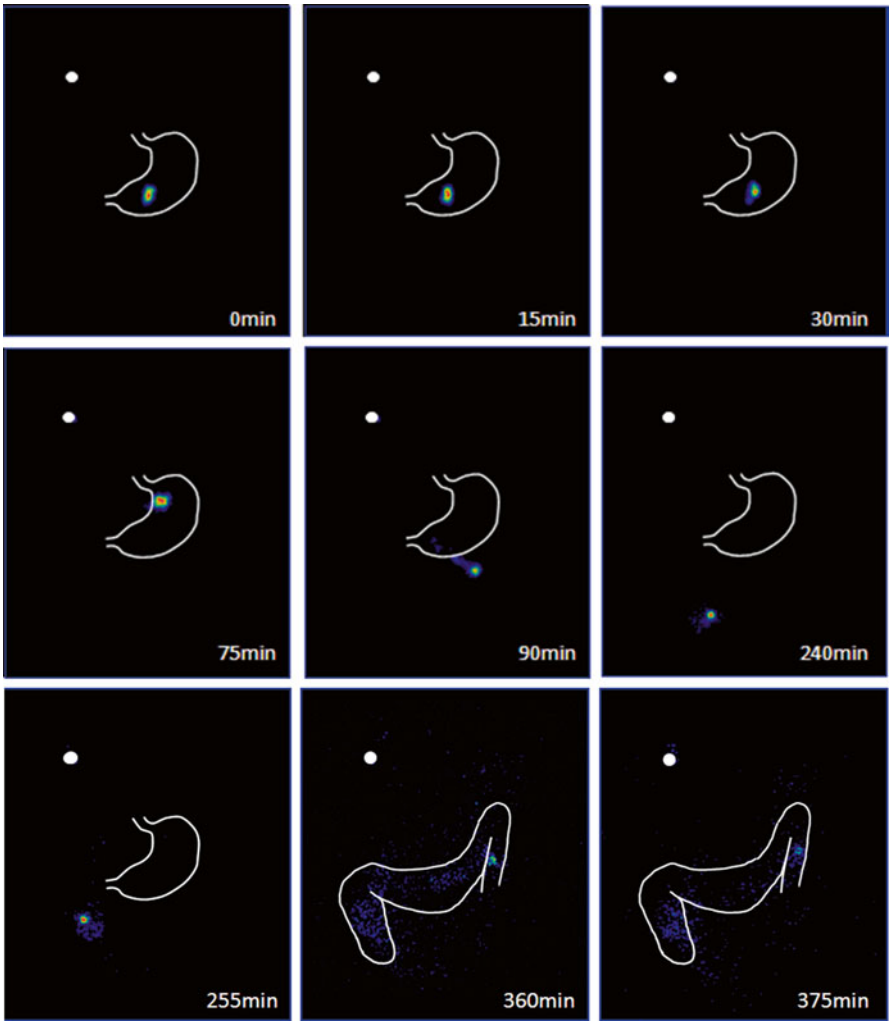

Fig. 12.14 Individual scintigraphic images from one subject showing the in vivo erosion of a 40 % HPMC hydrophilic matrix formulation at different times and locations in the GI tract

12.4.5 Key Findings from Case Study 3

- Percolation theory describes a critical threshold for the polymer concentration in hydrophilic matrix formulations, above which a continuous robust matrix is formed.
- The observed delay in onset of erosion in vivo when compared to in vitro using gamma scintigraphy illustrates the difficulty in simulating the complex environment of the gut in vitro, and the caution required in extrapolating results to in vivo.

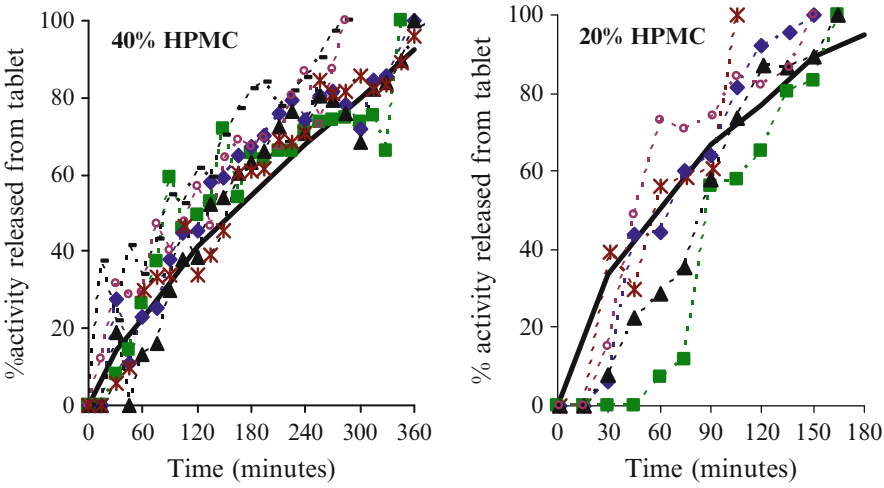

Fig. 12.15 Individual in vivo erosion profiles of two different HPMC matrix tablets quantified using gamma scintigraphy in six subjects (S1:*filled square*; S3:*filled diamond*; S4:*filled triangle*; S5:*open square* and S6:*asterisk*), and comparison to mean in vitro gravimetric erosion profile (*solid line*). Reprinted from Ghimire et al. [113] with permission from Elsevier

- The formulation composed of 40 % HPMC performed robustly in vivo, with low inter-subject variability in erosion rate.
- Reduction of the HPMC content to 20 % resulted in significant variability of erosion rates between subjects, and the observation of a crucial moment of massive failure of the matrix in all but one subject.
- Matrix failure of the 20 % HPMC formulation was independent of location in the GI tract.

12.5 Case Study 4: The Effect of Specific Location within the Stomach on Dose Dumping from an HPMC Matrix Tablet

12.5.1 Background

In the previous case studies we have seen examples of how co-administration of food resulted in dose dumping of a matrix formulation, and also an example of a formulation which was designed to provide constant release irrespective of the fed or fasted conditions. For a hydrophilic matrix formulation, in most cases it is assumed that an increased C_{max} observed in the fed state is a result of the increased physical stress that the matrix is placed under in the fed state, by both physical abrasion from solid food and viscous materials and the increased forces generated in the antrum. The combination of these effects is proposed to increase the rate of erosion of less robust matrices.

12.5.2 *In Vivo Magnetic Marker Monitoring of Hydrophilic Matrix Performance*

Weitschies et al. decided to probe further the mechanism of an apparent dose dumping effect in felodipine ER tablets, which incorporated HPMC as the main hydrophilic matrix forming component to control drug release [116]. To do this, they used the technique of Magnetic Marker Monitoring (MMM), which required the inclusion of 5 mg of ferromagnetic black iron oxide in each tablet. In MMM studies, prior to administration to the volunteer, the tablet is placed in a magnetic field, aligning the magnetic moments of the iron oxide particles in the tablet, allowing the tablet to be detected as a 'magnet'. To eliminate external electromagnetic interference, subjects are required to sit in a magnetically shielded room, allowing the biomagnetic measurement device to distinguish the tablet from other magnetic sources.

The measurement device contains superconducting interference devices (SQUIDs), and can translate the data obtained into a three-dimensional representation of the movement of the tablet over time [117]. As the tablet swells and erodes, the previously aligned magnetic moments become misaligned, resulting in a gradual loss in the magnetic moment which can be detected. In this case, a correlation could be determined between the in vitro release of felodipine and the in vitro decrease in the magnetic signal (Fig. 12.16), allowing estimation of in vivo drug release.

In a two-way crossover study, volunteers were administered the hydrophilic matrix tablet following an overnight fast or after a standardised breakfast, with a standard lunch consumed 4–5 h later. While the T_{max} determined for the two treatments was comparable, the median C_{max} was over 1.7 times greater in the fed state than in the fasted state (Table 12.6). There was also a significant increase in the T_{lag}, from 19 min in the fasted state to 77 min in the fed state.

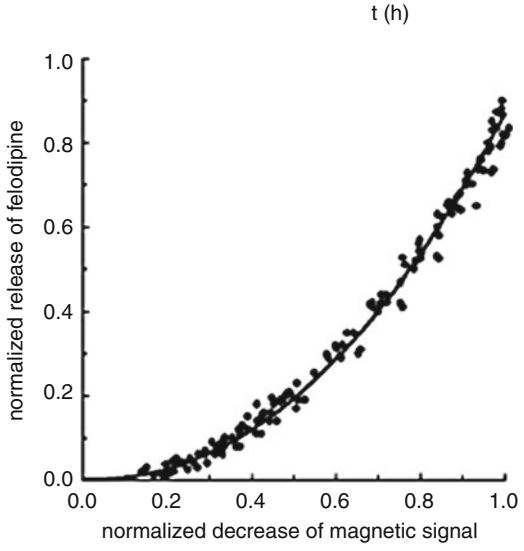

Fig. 12.16 Correlation between the normalised release of felodipine and the normalised decrease of magnetic signal in vitro determined using MMI. Reprinted from Weitschies et al. [116] with permission from Elsevier

Table 12.6 Pharmacokinetic parameters of a felodipine ER hydrophilic matrix tablet in the fed and fasted states, showing significant increase in T_{lag} and C_{max} in response to the fed condition

Pharmacokinetic parameters			
Subject	T_{lag} (min)	T_{max} (min)	C_{max} (nmol/l)
Fasting			
1	18	318	4.1
2	20	170	8.8
3	0	266	8.5
4	80	230	61.1
5	18	228	11.8
6	19	259	6.1
Median	*19*	*245*	*8.7*
Mean (SD)	*26 (28)*	*245 (49)*	*16.7 (21.9)*
Breakfast			
1	134	374	9.6
2	16	194	14.9
3	75	286	12.8
4	224[a]	288	86.5
5	49	259	23.5
6	79	229	16.3
Median	*77*	*273*	*15.6*
Mean (SD)	*96 (73)*	*272 (62)*	*27.3 (29.4)*

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[a]Very low plasma felodipine concentrations were observed in plasma before 224 min

Using the images obtained (Fig. 12.17), the gastrointestinal transit parameters for each tablet in the individual subjects were analysed, and correlated with the calculated in vivo release. It was shown that in the fasted state, the absorption profiles correlated closely with tablet erosion. In the fed state, where increases in C_{max} had been observed, a more detailed analysis of the data was able to determine that the resultant PK data was directly influenced by the location of the tablet in the fed stomach, rather than the fed state per se.

12.5.3 Effect of Specific Location in the Stomach

When the tablet was located in the distal stomach, there was a clear correlation between the release profile and the observed effect on plasma felodipine concentration [116]. However, when the tablet was located in the proximal stomach for a significant period of time, it was observed that there was a low rate of drug release as a consequence of the limited mixing and movement of the stomach in this region. This resulted in an extended lag phase before appearance of drug in the

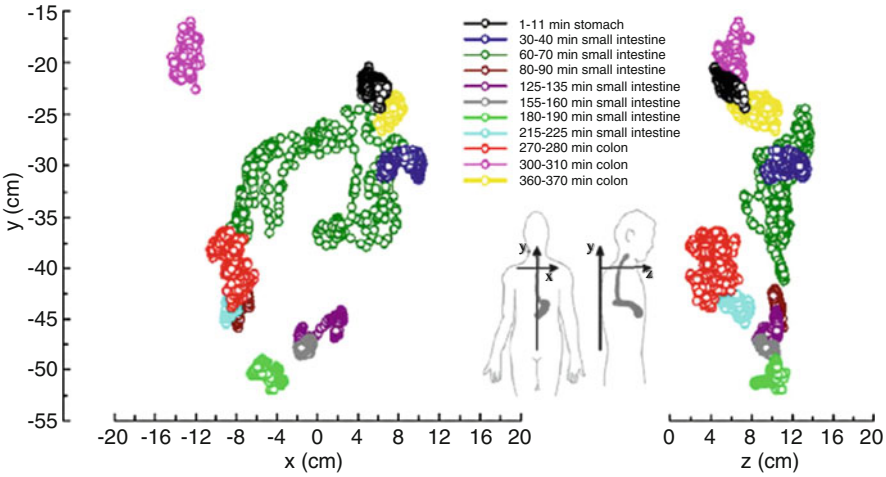

Fig. 12.17 Typical images obtained using Magnetic Marker monitoring, showing the gastrointestinal transit of an ER hydrophilic matrix tablet following administration to a fasting subject. Reprinted from Weitschies et al. [116] with permission from Elsevier

plasma, and on movement to the distal stomach resulted in a much more rapid phase of absorption.

The authors concluded that in many cases this could have been interpreted as a dose dumping formulation effect, when in fact it was simply the influence of the intragastric location of the tablet. This study provides an interesting additional piece of the jigsaw puzzle in the effects of food on the administration of hydrophilic matrix tablet formulations, and indicates that there is much which still remains to be adequately understood. In any case, there was still a clear effect of the consumption of food, and more evidence that this should be carefully considered in the design of a formulation and its subsequent clinical dosing guidelines.

12.5.4 Key Findings from Case Study 4

- The in vivo imaging technique Magnetic Marker Monitoring was used to demonstrate that in vivo absorption profiles from an HPMC matrix formulation correlated closely with tablet erosion in the fasted state.
- When the tablet was in the distal fed stomach, the correlation between erosion and absorption was also clear.
- When the tablet was in the proximal fed stomach, however, limited mixing resulted in a lag phase before appearance of drug in the plasma, prior to rapid absorption as the formulation progressed to the distal stomach.

12.6 Case Study 5: In Vivo Validation of Hydrophilic Gel Matrix Performance and Independence from Food Effects

12.6.1 Background

As outlined in the introduction, one of the factors confounding reliable performance of oral hydrophilic matrix formulations is the gradual reduction in the volume of water available for polymer hydration and drug dissolution as it travels down the gut. This problem is particularly pertinent when considering formulations which are designed primarily for targeting drug release in the colon.

Using MRI, it has been established that the volume of free water available in the colon is only 13 mL [46], and it must be remembered that in this unstirred semi-solid environment this is likely to be present as localised pockets of water, rather than a homogenous distribution. This can present a significant challenge to achieving adequate hydration for the matrix to control drug release at the appropriate rate, provide a barrier to drug dissolution, and may result in significantly different performance to that observed in vitro.

12.6.2 The Oral Controlled Absorption System

Researchers from Astellas Pharma (Europe) presented a formulation designed to overcome such issues and achieve constant release of tamsulosin throughout the entire GI tract, by using a combination of gel forming and gel enhancing components to produce a hydrophilic matrix tablet [118]. The formulation is designed to achieve rapid and substantial hydration as it travels through the stomach and small intestine, with complete hydration prior to arrival at the colon, as depicted in Fig. 12.18. The strong gel matrix is expected to behave independently of food intake, unlike the MR pellet containing capsule formulation, which is recommended to be taken after a meal to avoid adverse events caused by an increase in the C_{max} when administered in the fasted state [121]. This technology is named the Oral Controlled Absorption System (OCAS), which has been used in the commercially available product Flomatra® XL [122].

12.6.3 Gamma Scintigraphic Validation of Performance in Fed and Fasted States

The concept of attaining consistent plasma profiles and an improved cardiovascular safety profile, irrespective of fed or fasted status, was proven in clinical studies in healthy volunteers [119, 120]; however it was suggested that drug release from the conventional capsule was impeded in the colon [118], and as such questions on

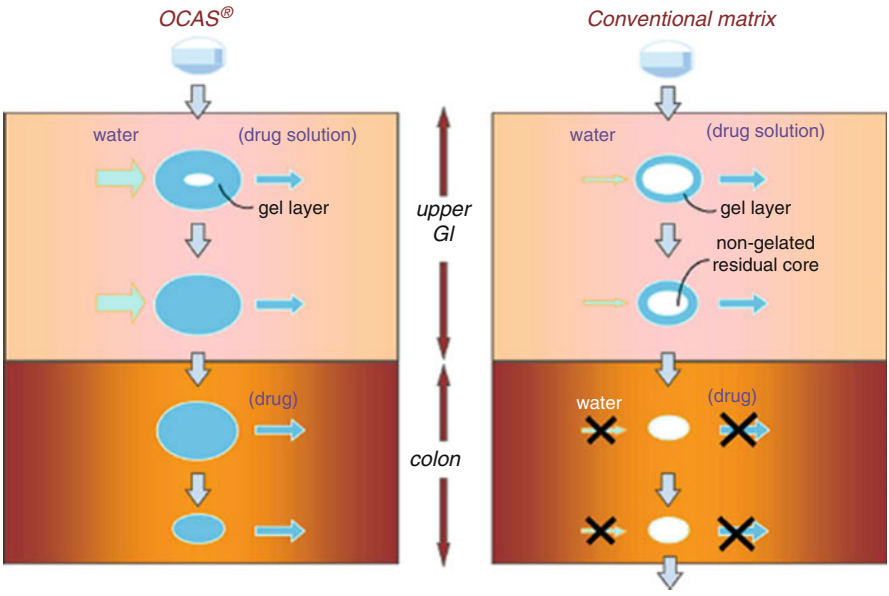

Fig. 12.18 Schematic representation of OCAS hydration and drug release in small intestine and colon compared with conventional matrix hydration. Reprinted from Michel et al. [120] with permission from Elsevier

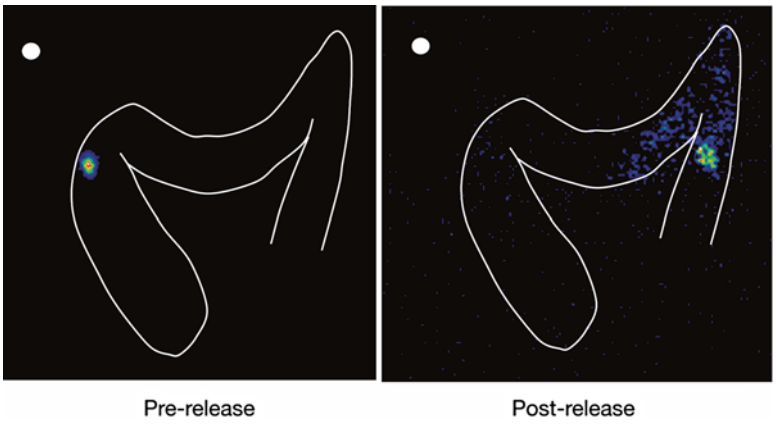

Fig. 12.19 Scintigraphic images from subject 7 before and after release of radiolabel in the colon from a single tamsulosin OCAS tablet 0.4 mg labelled with ^{99m}Tc (Stevens and Speakman [118]). Reproduced with permission of Informa Healthcare

the relationship between particular pharmacokinetic events and location of the formulation in the GI tract on this remained unanswered. For this reason a gamma pharmacoscintigraphic study was carried out in healthy volunteers, where a ^{99m}Tc radiolabel was incorporated into the tablet to visualise its location (Fig. 12.19) and monitor the GI transit parameters such as gastric emptying time and small

Table 12.7 GI transit parameters for the tamsulosin OCAS formulation determined using gamma scintigraphy (Stevens and Speakman [118])

Subject	Gastric emptying (h post-dose)	Small intestine transit time (h)	Colonic arrival (h post-dose)	Time of release (h post-dose)
1	3.9	2.2	6.1	9.1
2	2.4	10.0	12.4	13.1
3	10.1	1.4	11.5	13.9
4	3.4	5.7	9.1	13.1
5	2.8	2.8	5.6	11.9
6	3.4	2.5	5.9	NR
7	3.9	1.2	5.1	12.4
8	2.9	3.2	6.1	NR
Mean	4.1	3.6	7.7	12.3
SD	2.5	2.9	2.9	1.7

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intestinal transit time, along with location of the formulations at the time of release of radiolabel from the core (Table 12.7).

Overall, the results confirmed the continuous release of drug throughout the GI tract; however the use of an imaging technique also aided in identifying instances where unusual GI transit behaviour resulted in a noticeable effect on the PK profile in that individual. While the mean gastric emptying time of the tablet, administered following a light breakfast, for the 8 volunteers was 4.1 h, in one subject it was 10.1 h. In this subject the overall absorption of tamsulosin was somewhat higher than for the mean population (Subject 3, Fig. 12.20), which reflected the extended stay in the stomach allowing prolonged opportunity for released drug to be absorbed from the more permeable region of the upper small intestine. In one other instance, the PK absorption profile appears low compared to the mean population, and in this individual this was explained by secretion of the intact tablet, with no release of radiolabel observed from the core.

It was clear, however, irrespective of the location in the GI tract, in particular the instance of extended residence in the high mechanical forces of the stomach, that the integrity of the matrix structure of the formulation was robust, with no instances of unexpectedly early release of radiolabel from the core.

12.6.4 Key Findings from Case Study 5

- The hydrophilic matrix OCAS formulation achieved continuous release of tamsulosin throughout the GI tract, independent of fed and fasted states.
- Gamma scintigraphy was used to demonstrate the effect of unusual GI transit behaviour on PK profiles.

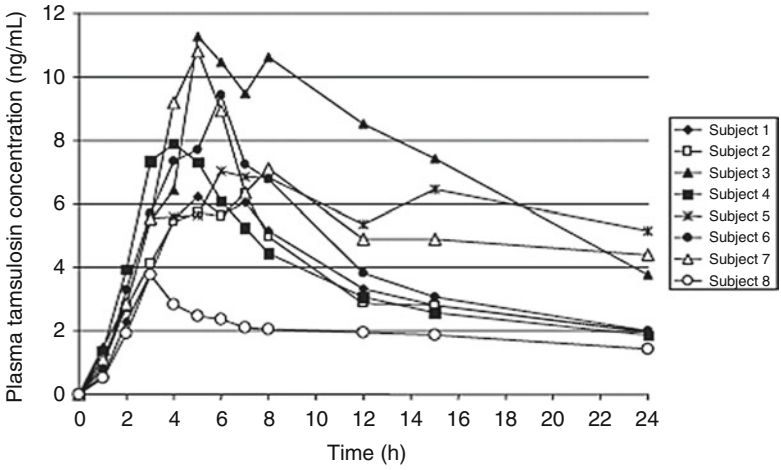

Fig. 12.20 Individual plasma concentration–time curves of single doses of tamsulosin OCAS 0.4 mg under fed conditions (Stevens and Speakman [118]). Reproduced with permission of Informa Healthcare

12.7 Conclusion

The information presented in this chapter gives some indication of the complexity of the human gastrointestinal tract, and the influence these variables can have on dosage form performance. While there has been significant progress in the design of in vitro tests and equipment used in attempts to simulate in vivo conditions and predict product performance, there are still many instances reported where the physiology of the GI tract produced unexpected behaviour. The case studies presented here demonstrate different mechanisms through which hydrophilic matrix tablets can interact with the GI tract and the food contained within it, and serve as reminder to those developing such formulations of the potential issues they must bear in mind. In many cases, it has been the use of in vivo imaging techniques which has provided key insight into the mechanism of the formulation behaviour and resultant pharmacokinetics.

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Index

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