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

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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

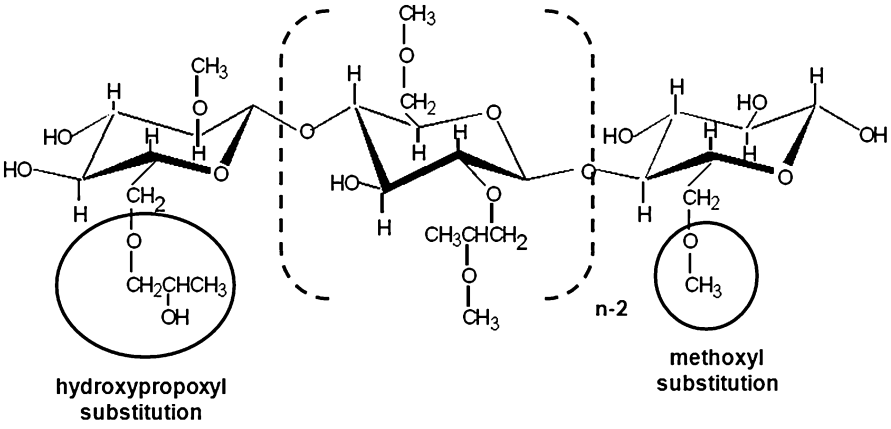

Fig. 2.1 The chemical structure of HPMC (hypromellose). This is an illustrative diagram. The degree of substitution and position of the methoxyl and hydroxypropoxyl groups are not the same on each anhydroglucose unit. (Reproduced with permission of Colorcon Inc.)

(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].

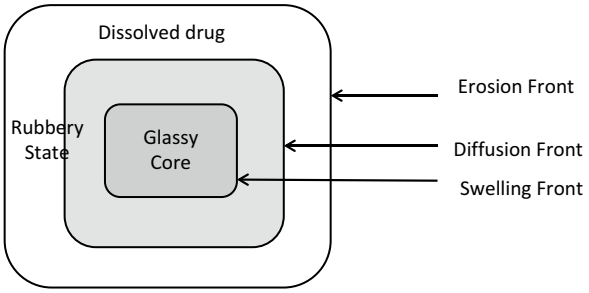

Fig. 2.2 Schematic cross section through an HPMC matrix following exposure to an aqueous fluid and partial release of drug. The three moving fronts are clearly delineated. The rubbery state will contain both dissolved drug and undissolved drug particles

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

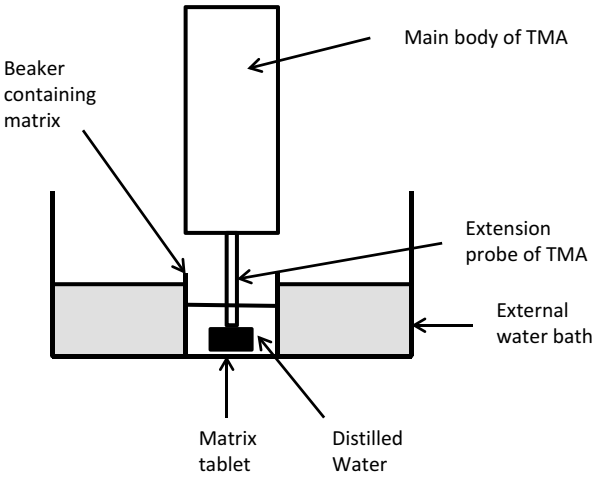

Fig. 2.3 The thermal mechanical analyser geometry used to measure the rate and extent of swelling in cellulose ether matrix tablets. (Reproduced from [59].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/ textbook via Copyright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

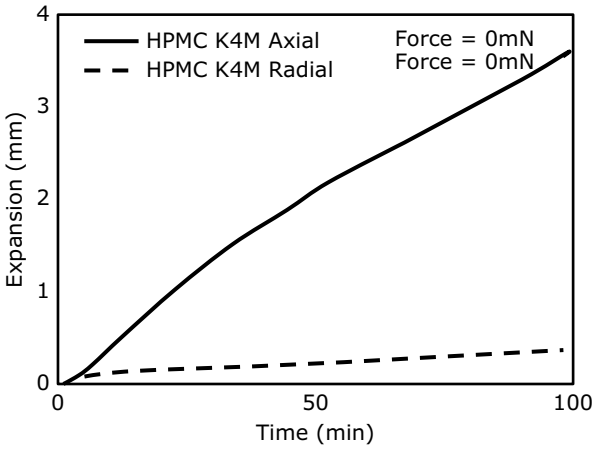

Fig. 2.4 Axial and radial expansion of a compact containing HPMC 2209 (Methocel K4M) at 37 °C measured by thermal mechanical analysis. (Reproduced from [59].) International journal of pharmaceutics by Elseviers BV. Reproduced with permission of Elsevier BV in the format reuse in a book/ textbook via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

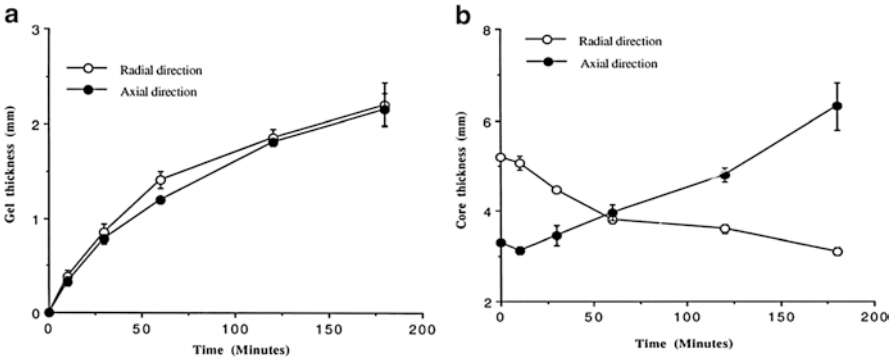

Fig. 2.5 Gel layer growth (**a**) and dimensional changes in the dry core (**b**) in HPMC2208 (Methocel K4M) matrix tablets during hydration, measured from MRI images. (Reproduced from [62].) Journal of controlled release: official journal of the Controlled Release Society by controlled release society. 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

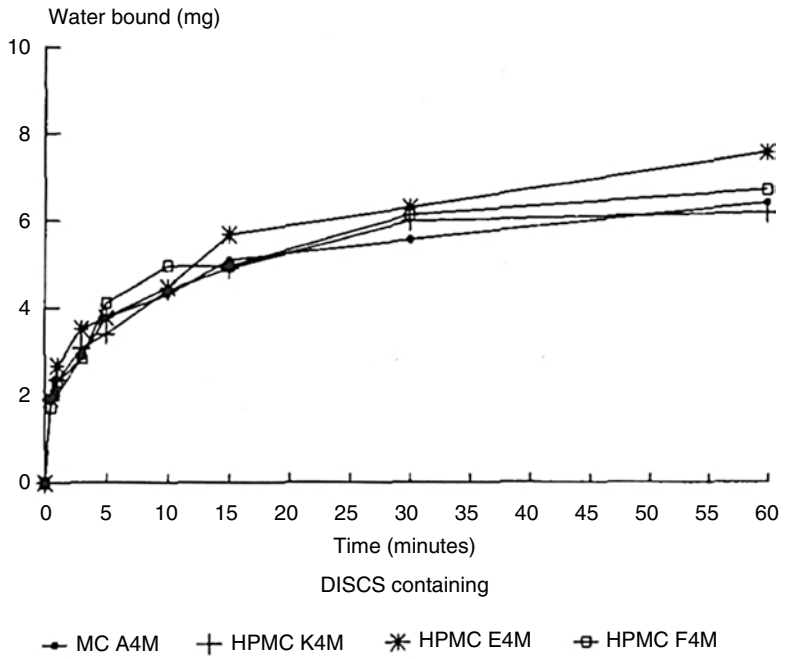

Fig. 2.6 The water bound by discs of different HPMC types over a period of 60 min hydration. (Reproduced from [59].) International journal of pharmaceutics by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance Center

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].

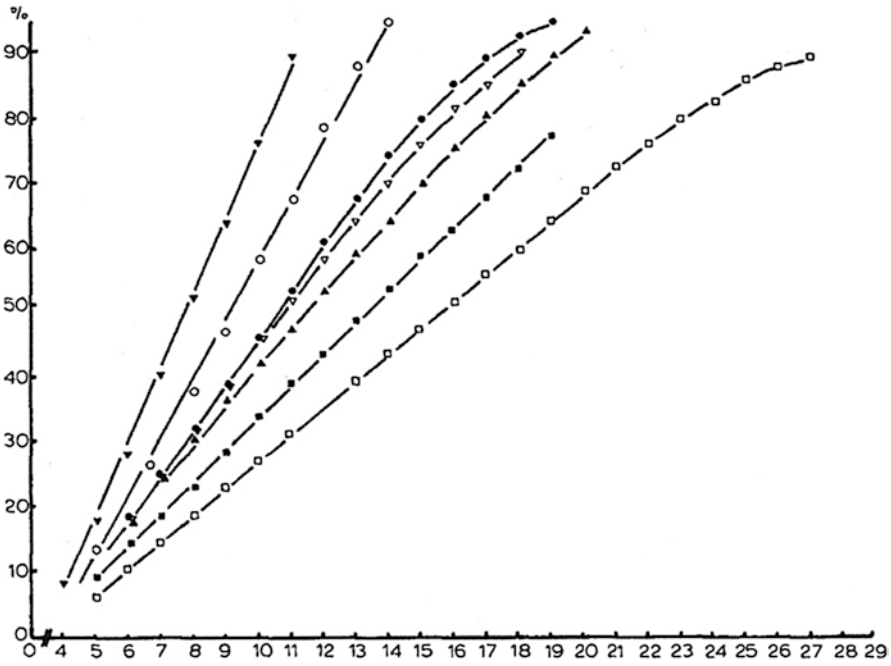

Fig. 2.7 The effect of promethazine hydrochloride: HPMC 2208 (Methocel K15M) variation on the promethazine release of 25 mg promethazine into water at 37 °C from tablets containing (mg of HPMC) *filled inverted triangle*, 20; *open circle* 25; *filled circle*, 40; *open triangle*, 50; *filled triangle*, 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

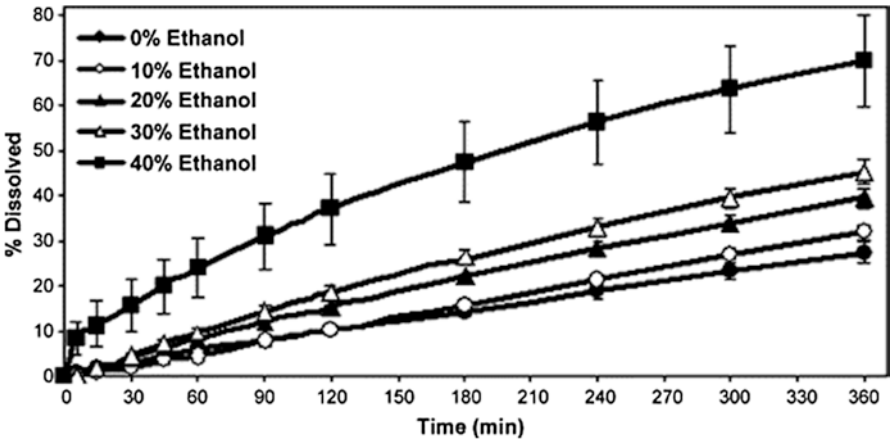

Fig. 2.8 The effect of ethanol concentration on the release of aspirin from HPMC matrices in hydro-alcoholic media. (Reproduced from [91].) International journal of pharmaceutics. Online by Elsevier BV. Reproduced with permission of Elsevier BV in the format reuse in a book/textbook via Copyright Clearance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

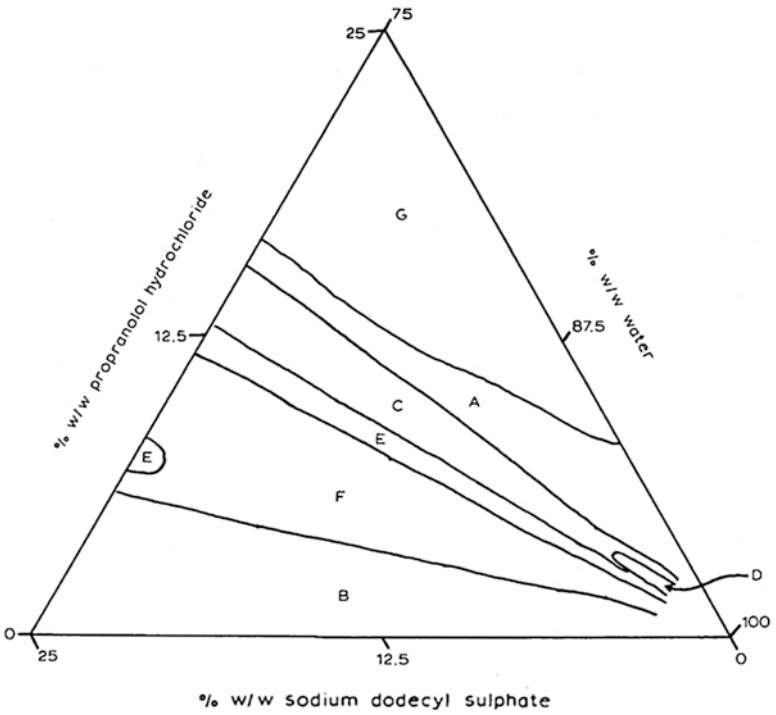

Fig. 2.9 Ternary phase diagram of the propranolol hydrochloride—sodium dodecyl sulphate—water system containing >75 % water. Key (A) isotropic liquid, (B) isotropic liquid, (C) two immiscible liquid phases, (D) anisotropic liquid (liquid crystal), (E) liquid + propranolol dodecyl sulphate (precipitate), (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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