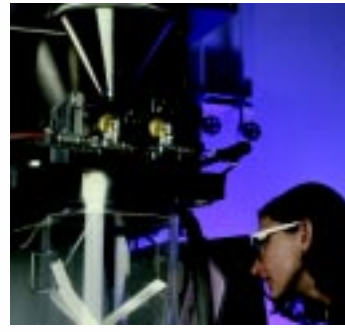
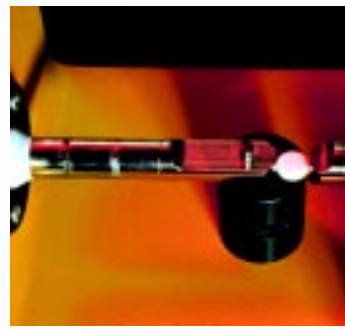
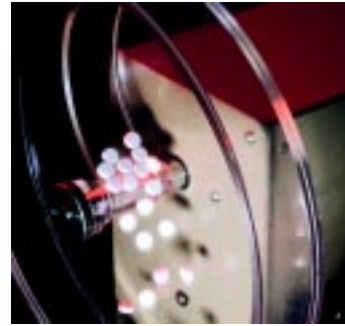
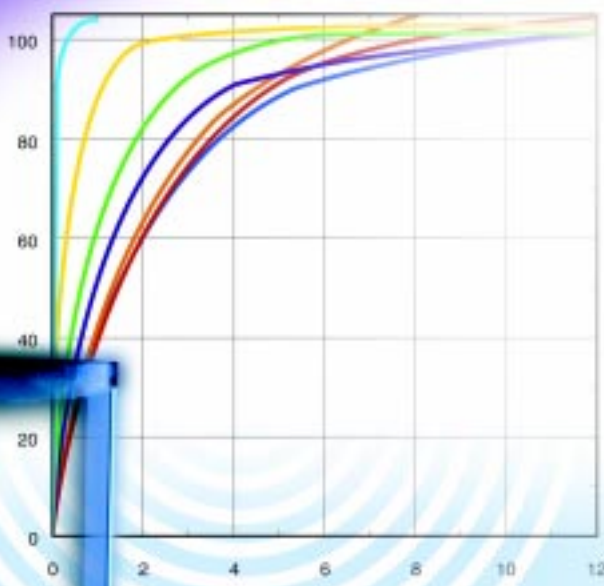
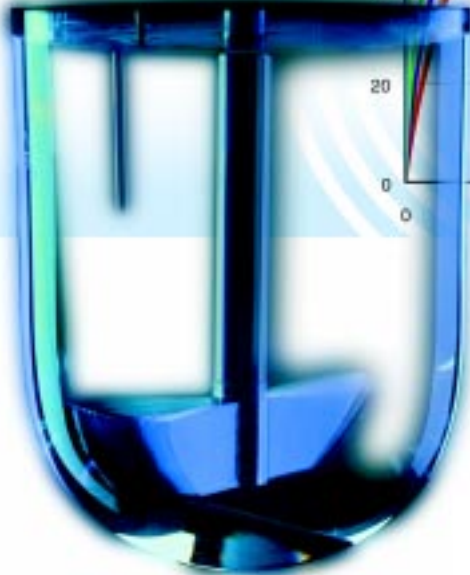
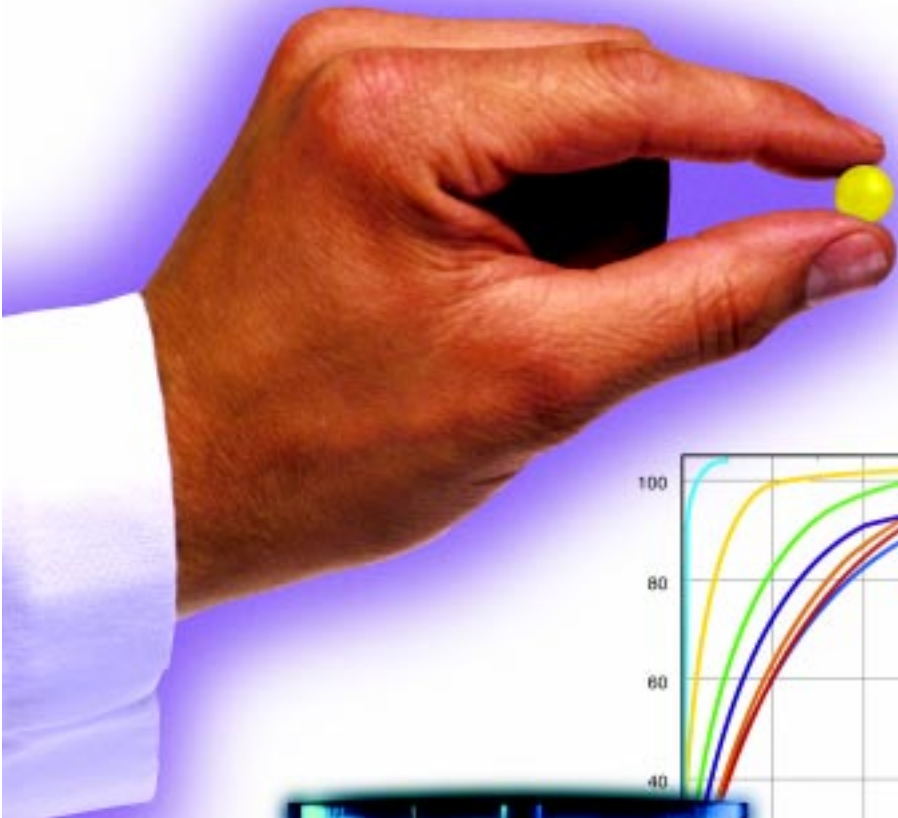




**Using METHOCEL Cellulose Ethers
for Controlled Release of Drugs
in Hydrophilic Matrix Systems**





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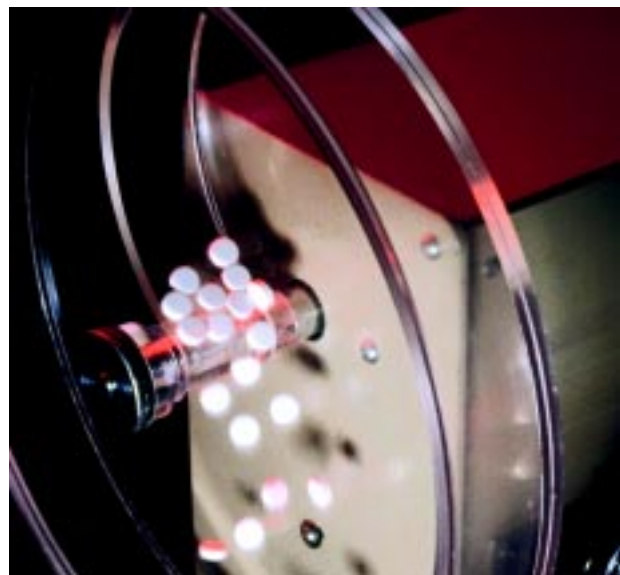
Introduction

METHOCEL* cellulose ethers are water-soluble polymers derived from cellulose, the most abundant polymer in nature. These products have been used as key ingredients in pharmaceutical and other applications for over 50 years.

This handbook describes how to select and use METHOCEL products for controlled release of drugs in hydrophilic matrix systems. Of all drug forms, solid oral dosage is overwhelmingly preferred by patients, and hydrophilic matrix systems are among the most widely used means of providing controlled release in solid oral dosage forms.

METHOCEL hydroxypropyl methylcellulose as the controlled-release agent in hydrophilic matrix systems offers a wide range of properties, consistently high quality, and broad regulatory approval. In addition, METHOCEL products are supported by Dow's extensive experience in pharmaceutical applications and a broad body of technical knowledge.

We invite you to use this handbook while you develop new hydrophilic matrix drug formulations or when improvements in existing formulations are necessary. See why METHOCEL is the brand of choice for controlled release.



*Trademark of The Dow Chemical Company



Why Hydrophilic Matrix Systems Based on HPMC Are The Logical Choice For Controlled Drug Release

Hydrophilic Matrix Systems Are Familiar, Proven, and Easy to Produce

Patients overwhelmingly prefer solid oral dosage over other drug forms. And hydrophilic matrix systems are among the most widely used means for controlled drug delivery in solid oral dosage.

Hydrophilic matrix systems have been proven for over four decades. Matrix controlled-release tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods, and end-use conditions than coated controlled-release tablets and other systems. This results in more uniform release profiles with a high resistance to drug dumping.

Matrix systems are relatively easy to formulate. The performance of many products is already well documented, providing a body of data to refer to and rely upon. This helps speed development work and can shorten approval times as well.

Matrix systems are easy to produce. Tablets are manufactured with existing, conventional equipment and processing methods. This is true for almost any size tablet, whether it involves direct compression, dry granulation, or wet granulation.

Matrix systems are economical. Beyond the possibility of lower development costs and the use of conventional production methods, the ingredients normally used are cost-effective.

HPMC Has Familiar, Well-Understood Properties

Of the available range of cellulosic controlled-release agents, hydroxypropyl methylcellulose (HPMC) is the most widely used. HPMC is a well-known excipient with an excellent safety record. All needed data are readily available. This can further speed developmental work. HPMC has broad FDA clearance as a direct food additive. This can contribute to shorter approval times. And because HPMC is so widely used, techniques and equipment for formulation development and drug production are readily available and understood.

HPMC is Nonionic, Tolerant of Most Formulation Variables

HPMC polymers are very versatile release agents. They are nonionic, so they minimize interaction problems when used in acidic, basic, or other electrolytic systems. HPMC polymers work well with soluble and insoluble drugs and at high and low dosage levels. And they are tolerant of many variables in other ingredients and production methods.

HPMC Delivers Consistent, Reproducible Performance

HPMC polymers are produced under very controlled conditions that yield consistent properties and reproducible performance, lot to lot. They're not subject to the range of variability sometimes encountered with polymers like guar, shellac, and other botanical extracts.

And HPMC products typically provide outstanding controlled-release performance by themselves, eliminating the potential performance variations that may arise in multi-polymer systems.

Strong, Viscous Gels Control Diffusion of Water and Drug Release

To achieve controlled release through the use of a water-soluble polymer such as HPMC, the polymer must quickly hydrate on the outer tablet skin to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core.

Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion.

Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role. Evidence suggests that the chemistry of HPMC encourages a strong, tight gel formation compared to other cellulose derivatives. As a result, drug-release rates have been sustained longer with HPMC than with equivalent levels of methylcellulose (MC), hydroxyethylcellulose (HEC), or carboxymethylcellulose (CMC). For these reasons, HPMC is very often the polymer of choice over other cellulose derivatives.

Why METHOCEL Premium Products Are Often The Brand Of Choice

A Wide Range of Polymer Choices

METHOCEL Premium cellulose ethers, specifically the K and E series of products, have been the preferred brand of HPMC in matrix systems for many years.

The family of METHOCEL Premium products is the broadest in the industry. This means unmatched flexibility for fine-tuning matrix release profiles and optimizing ingredient costs, tablet size, and production methods.

Highest Quality and Purity for Consistent, Reproducible Performance

METHOCEL Premium products are produced under very tight Statistical Quality Controls to the exacting standards of Good Manufacturing Practices (GMPs). You can rely on their excellent consistency and high quality for repeatable performance.

The manufacturing facilities where these products are made are registered and periodically inspected by the FDA. METHOCEL Premium products are produced from dedicated processes and equipment to further ensure their consistency and purity.

METHOCEL Premium products are available which meet and exceed the requirements of U.S., Japanese, and European Pharmacopeias, the requirements of Food Chemicals Codex, and the International Codex Alimentarius. Plus, we offer a certificate of analysis with every shipment so you have documentation of product quality and the consistency of that quality from shipment to shipment.

Dow's Expertise Can Speed Development and Approvals

METHOCEL Premium products are supported by Dow's extensive experience in pharmaceutical applications and the broad body of knowledge that has been developed regarding the behavior of METHOCEL Premium products in matrix systems. The major system variables and their interactions have been identified, isolated, and studied extensively. That's an additional advantage that can quickly pay off in reduced development and approval times.

No Special Licensing Required

Unlike many "branded" delivery systems, choosing a METHOCEL polymer for controlled release doesn't require licensing agreements. That means lower costs and less paperwork over the commercial life of your product.

In short, there are many good reasons to select HPMC as the release agent for your controlled-release formulations and METHOCEL Premium as the HPMC brand of choice. The objective of this handbook is to provide the information that you need to select the appropriate METHOCEL product for your formulation and use it effectively.





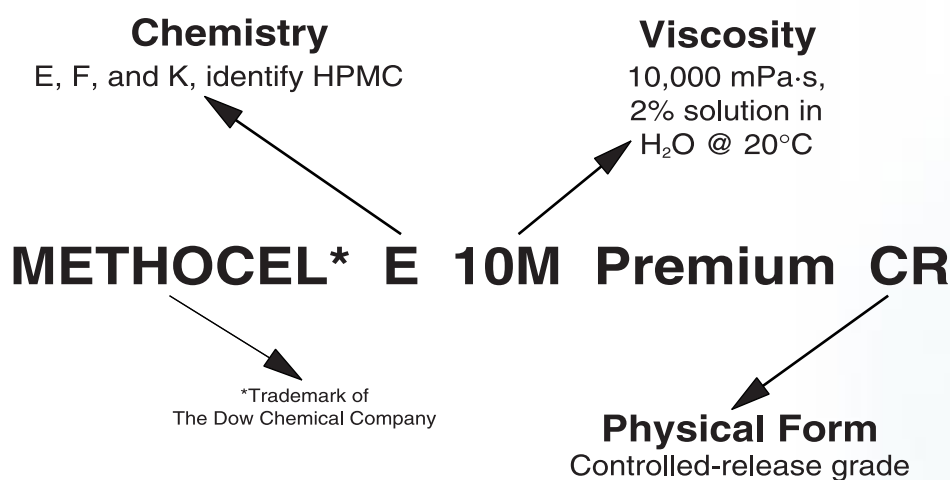
Nomenclature

METHOCEL is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identifies the type of cellulose ether, its “chemistry.” “A” identifies methylcellulose (MC) products. “E,” “F,” and “K” identify different hydroxypropyl methylcellulose (HPMC) products (Figure 1). METHOCEL E and METHOCEL K are the most widely used for controlled-release drug formulations.

The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C.[†] In designating viscosity, the letter “C” is frequently used to represent a multiplier of 100, and the letter “M” is used to represent a multiplier of 1000.

Several different suffixes are also used to identify special products. “P” is sometimes used to identify METHOCEL Premium products, “LV” refers to special low-viscosity products, “CR” denotes a controlled-release grade, and “LH” refers to a product with low hydroxypropyl content. “EP” denotes a product that meets European Pharmacopeia requirements; “JP” grade products meet Japanese Pharmacopeia requirements.

Figure 1: Example of nomenclature for a METHOCEL E cellulose ether



[†]Note: mPa·s (millipascal-seconds) is equivalent to centipoise.

Regulatory and Compendial Information

All METHOCEL Premium products are produced under current Good Manufacturing Practices for Finished Pharmaceuticals specified by the U.S. Food and Drug Administration within Code of Federal Regulations, Title 21, Part 211. Additionally, the facilities that produce METHOCEL products have received ISO 9001 Certification.

Harmonization

The Japanese Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for HPMC and MC. A draft monograph for each of the products was published in the Japanese Pharmacopeial Forum, Vol. 5, No. 4 (1996). An official inquiry state of the drafts was reproduced in the Pharmacopeial Forum, Vol. 24, No. 5 (September-October 1998). The proposals have not been finalized, but the process is well underway with the three major pharmacopeias.

United States

Premium USP grades of METHOCEL products meet the specifications of the United States Pharmacopeia (24 or current edition). Drug Master Files for METHOCEL A (methylcellulose) and METHOCEL E, F, and K (hydroxypropyl methylcellulose) are on file at the U.S. FDA to support new drug applications.

Europe

Premium EP grades of METHOCEL products meet the specifications of the European Pharmacopeia (EP III or current edition) and the United States Pharmacopeia. In Europe, the EP monograph name “hypromellose” is used. The information required to gain Certificates of Suitability for METHOCEL products has been filed.

Legislation in the 15 member states of the EU gives legal status to the monographs of the European Pharmacopeia. However, the European Pharmacopeia has the “force of law” for all 28 members of the European Pharmacopeia Convention, including countries that are not members of the EU. Sixteen observers to the convention exchange information and may use some standards as national legislation. In addition, METHOCEL Premium EP products meet the specifications of pharmacopeias of specific countries, e.g., British Pharmacopeia and French Pharmacopeia.

Japan

Premium JP products meet the specifications of the Japanese Pharmacopeia and the United States Pharmacopeia.

Global Regulations

In the U.S., methylcellulose is approved as a multiple-purpose GRAS food substance according to 21CFR 182.1480. Hydroxypropyl methylcellulose is approved for direct food use by the FDA under 21CFR 172.874. In the European Union, METHOCEL Premium products are approved for use by European Directive 95/2/EC. Hydroxypropyl methylcellulose and methylcellulose are included in Annex 1 of this Directive.

Polymer Properties

Only METHOCEL Premium products can be used in controlled-release formulations (Table 1). Typical products used in controlled release include METHOCEL K100 Premium LV, K4M Premium, K15M Premium, K100M Premium, E4M Premium, and E10M Premium CR. All of these products are available in controlled-release (CR) grades, which are specially produced, ultra-fine particle size materials. Table 2 lists the properties of METHOCEL Premium products generally used for controlled release.

Table 1. Product description of METHOCEL Premium products

Physical form:	off-white powder
Particle size	
Premium grades:	99% < 40 mesh screen
CR grades:	E series, min. 95% < 100 mesh screen K series, min. 90% < 100 mesh screen
Packaging:	50-lb, multiwall paper bags 25-kg and 50-kg fiber drums
Shelf life:	bags: 3 years drums: 5 years

Table 2. Properties[†] of selected METHOCEL products for use in pharmaceuticals

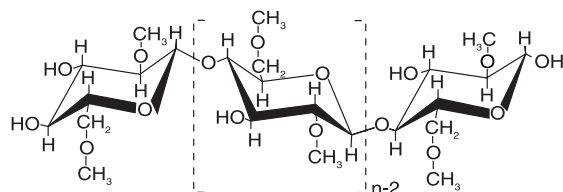
METHOCEL Premium product grade	—	K100 Premium LV	K4M Premium	K15M Premium	K100M Premium	E4M Premium	E10M Premium CR
Methoxyl, %	USP	19–24	19–24	19–24	19–24	28–30	28–30
Hydroxypropoxyl,%	USP	7–12	7–12	7–12	7–12	7–12	7–12
USP substitution type	USP/EP	2208	2208	2208	2208	2910	2910
Chlorides, max., %	EP	0.5	0.5	0.5	0.5	0.5	0.5
Apparent viscosity, 2% in water at 20°C, cP	USP	80–120	3000–5600	11250–21000	80000–120000	3000–5600	7500–14000
Apparent viscosity, 2% in water at 20°C, mPa·s	EP	78–117 [98 Nom]	2308–3755 [2903 Nom]	6138–9030 [7382 Nom]	16922–19267 [18243 Nom]	2308–3755 [2903 Nom]	4646–7070 [5673 Nom]
ID Test A, B, C	USP	Pass	Pass	Pass	Pass	Pass	Pass
ID Test A, B, C, D, E, F	EP	Pass	Pass	Pass	Pass	Pass	Pass
Opalescence of solution	EP	Pass	Pass	Pass	Pass	Pass	Pass
Solution color, yellowness, 1% in water	EP	Pass	Pass	Pass	Pass	Pass	Pass
pH, 1% in water	EP	5.5–8.0	5.5–8.0	5.5–8.0	5.5–8.0	5.5–8.0	5.5–8.0
Loss on drying, max., %	USP/EP	5.0	5.0	5.0	5.0	5.0	5.0
Organic impurities, volatile	USP	Pass	Pass	Pass	Pass	Pass	Pass
Residue in ignition, max., %	USP	1.5	1.5	1.5	1.5	1.5	1.5
Ash, sulfated, max., %	EP	1.0	1.0	1.0	1.0	1.0	1.0
Heavy metals, as Pb, max., ppm	USP/EP	10	10	10	10	10	10

[†]The data provided are typical values, intended only as guides, and should not be construed as sales specifications.

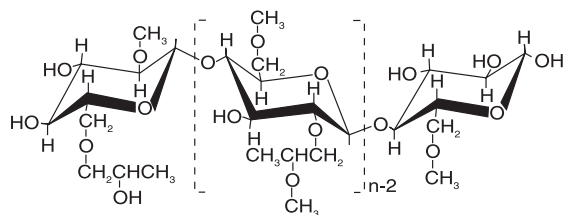
Polymer Structure

METHOCEL products are available in two basic types: methylcellulose and hydroxypropyl methylcellulose. Both types of METHOCEL have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units (Figure 2). During the manufacture of cellulose ethers, cellulose fibers are treated with caustic solution, which in turn is treated with methyl chloride and/or propylene oxide. The fibrous reaction product is purified and ground to a fine powder.

Figure 2: Typical chemical structures of METHOCEL products

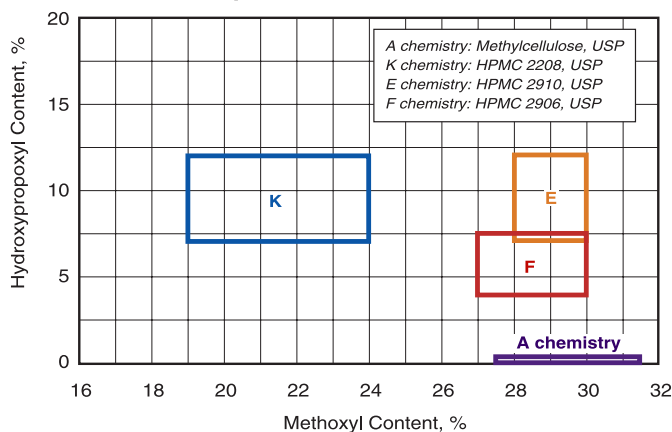


Methylcellulose
METHOCEL A brand products



Hydroxypropyl Methylcellulose
METHOCEL E, METHOCEL F, and METHOCEL K brand products

Figure 3: Substitution levels in METHOCEL products



Substitution

The family of METHOCEL products consists of products that vary chemically and physically according to the desired properties. The major chemical differences are in degree of methoxyl substitution (DS), moles of hydroxypropoxyl substitution (MS), and degree of polymerization (measured as 2% solution viscosity). There are four established product “chemistries” or substitution types for METHOCEL products, defined according to the combination of their percent methoxyl/DS and percent hydroxypropoxyl/MS.

Methylcellulose is made using only methyl chloride. These are METHOCEL A cellulose ethers (methylcellulose, USP). For hydroxypropyl methylcellulose products, propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units (Figure 3). Hydroxypropyl methylcellulose products include METHOCEL E (HPMC 2910, USP), METHOCEL F (HPMC 2906, USP), and METHOCEL K (HPMC 2208, USP) cellulose ethers.

The hydroxypropyl substituent group, $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$, contains a secondary hydroxyl on the number two carbon and may also be considered to form a propylene glycol ether of cellulose. These products possess varying ratios of hydroxypropyl and methyl substitution, a factor which influences properties such as organic solubility and the thermal gelation temperature of aqueous solutions.



Thermal Gelation

Substitution has a very significant impact on the performance of methylcellulose and hydroxypropyl methylcellulose in hydrophilic matrix systems. A useful way to examine how substitution affects polymer properties is the phenomenon of thermal gelation.

When aqueous solutions of METHOCEL products are heated, they gel at temperatures that are specific for each product type. These gels are completely reversible in that they are formed upon heating yet will liquefy upon cooling. This unique bulk thermal gelation of an aqueous solution of METHOCEL cellulose ether is a valuable property for many end uses. The bulk gelation phenomenon of an aqueous solution of METHOCEL cellulose ether has been postulated to be primarily caused by the hydrophobic interaction between molecules.¹

In a solution state at lower temperatures, molecules are hydrated, and there is little polymer-polymer interaction other than simple entanglement. As the temperature increases, the molecules gradually lose their water of hydration as reflected by a decrease in viscosity. Eventually, when a sufficient (but not complete) dehydration of the polymer occurs, a polymer-polymer association takes place, and the system approaches an infinite network structure as reflected by a sharp rise in viscosity.

Table 3. Approximate gel points of METHOCEL products (2% aqueous solution)

Brand	Gelation Temperature °C
A	48
F	54
E	56
K	70

The specific bulk thermal gelation temperature is governed by the nature and quantity of the substituent groups attached to the anhydroglucose ring and thus will vary with each type of cellulose ether. Increasing the concentration will decrease the thermal gelation temperature. Table 3 shows the approximate gelation temperature for a 2% aqueous solution of each brand of METHOCEL cellulose ether.

The temperature at which bulk gelation occurs in solutions containing METHOCEL products plus drugs or other excipients may be quite different from the characteristic value for the specific HPMC substitution type. Some excipients (e.g. spray-dried lactose) and drugs (e.g. theophylline) have virtually no effect on gelation when present at low concentrations. Some drugs dramatically raise the gelation temperature while others dramatically lower the gelation temperature.

The texture and the strength of gel produced by METHOCEL products varies with the type, viscosity grade, and concentration of METHOCEL used. In general, the strength of the gel increases with increasing molecular weight. However, gel strength may level off at molecular weights greater than approximately 150,000 (approx. 100 mPa·s for a 2% aqueous solution). Additives will also affect the gel strength of METHOCEL products.

Molecular Weight and Viscosity

Hydroxypropyl methylcellulose, being a semi-synthetic material derived from cellulose, is a linear polymer comprised of etherified anhydroglucose rings. The degree of polymerization (DP) is varied in production to give a polymer with the desired properties. For products typically used in controlled release applications, DP is adjusted to a range between 100 and 1500. Like all polymers, HPMC macromolecules exist as a distribution and may be characterized by parameters such as the number average molecular weight (\bar{M}_n), the weight average molecular weight (\bar{M}_w), and the polydispersity (\bar{M}_w/\bar{M}_n).

These molecular weight moments may be determined by a number of techniques, such as osmometry, light scattering, or size exclusion chromatography. In addition, molecular weight information can be obtained from intrinsic viscosity data with the application of the Mark-Houwink-Sakurada equation and appropriate constants. All of these techniques present experimental difficulties and must be applied with caution. Previous work based primarily on size exclusion chromatography with polysaccharide standards has tended to show that high molecular weight HPMC is highly polydisperse. However, more recent studies indicate that HPMC may not be as polydisperse as previously believed.

The difference in molecular weight of various METHOCEL products is reflected in the viscosity of an aqueous solution of a standard concentration. Viscosity of polymer solutions is the result of hydration of polymer chains, primarily through H-bonding of the oxygen atoms in the numerous ether linkages, causing them to extend and form relatively open random coils. A given hydrated random coil is further H-bonded to additional water molecules, entrapping water molecules within, and may be entangled with other random coils. All of these factors contribute to larger effective size and increased frictional resistance to flow. In discussions on controlled release, the term “viscosity” or “viscosity grade” and the associated value for the 2% w/w aqueous solution is frequently used as a way to refer to the molecular weight of the polymer.

Particle Size Distribution and Flow Properties

The particle size distribution may be characterized in a number of ways. Most common are analytical sieving (use of an air-jet sieve is highly recommended) and laser light-scattering techniques. Particles are predominantly irregularly shaped granules, with relatively few large particles. Methylcellulose

(METHOCEL A) and HPMC substitution type 2208 (METHOCEL K) contain a greater number of long, fibrous particles relative to HPMC substitution type 2910 (METHOCEL E).

Within the general scheme for categorizing powders, METHOCEL Premium products would be classed as “very fine.” It is essential that the powder be quite fine for it to function as a rate-controlling polymer. METHOCEL cellulose ethers, like many other very fine powders, flow satisfactorily but should not be considered free flowing. For those products most commonly used in controlled release, METHOCEL E cellulose ethers have somewhat better flow properties than METHOCEL K cellulose ethers. Depending on the particular components of a formulation, it may be necessary to improve the overall flow properties through the use of an appropriate granulation process.

Rheological Behavior

Within a functioning hydrophilic matrix tablet, HPMC exists in a number of states, from the dry state in the core, through a sequence of partially hydrated states, to the completely hydrated state at the outer surface. An understanding of the properties of aqueous solutions of HPMC is an important starting point for the formulator.

Rheology of an aqueous solution of METHOCEL is affected by its molecular weight, concentration, temperature, and by the presence of other solutes. In general, at temperatures below the incipient gelation temperature, aqueous solutions of METHOCEL exhibit pseudoplastic flow. Pseudoplasticity increases with increasing molecular weight or concentration. However, at very low shear rates, all solutions of METHOCEL cellulose ether appear to be Newtonian, and the shear rate below which the solution becomes Newtonian increases with decreasing molecular weight or concentration. Below the gelation temperature, the rheology of solutions of METHOCEL in water is not affected by the type or degree of substitution.

Effect of Concentration on Viscosity

The equation that expresses the approximate relationship between solution viscosity and polymer concentration is $\eta = (1+KC)^8$, where η is the solution viscosity in mPa·s, C is the polymer concentration in solution (expressed in percent), and K is a constant specific to the molecular weight and the manufacturing lot. The value of K may be calculated by substitution and may then be used to calculate the approximate viscosity at the desired concentration.

Blending for Intermediate Viscosity

METHOCEL products of the same substitution type but different viscosity grades can be blended to obtain an intermediate viscosity grade. This relationship may be expressed mathematically as: $\eta_B^{1/8} = F_1\eta_1^{1/8} + F_2\eta_2^{1/8}$, where F_1 and F_2 are the weight fractions of components 1 and 2, respectively.

Effect of pH on Viscosity

Because METHOCEL products are nonionic, the viscosity of their solutions is generally stable over a wider pH range than are the viscosities of polymers that are ionic in nature.

Effect of Additives on Viscosity

Occasionally, viscosity may be considerably higher than expected. This phenomenon can be caused by the interaction of METHOCEL with one or more of the formula ingredients.

Hydration and Erosion Rates

Polymer hydration, gel formation, and polymer erosion have been active areas of research. Evidence is building that suggests that the kinetics of initial hydration of cellulose ethers is quite fast and relatively independent of substitution. According to work from Melia's group at the University of Nottingham, the kinetics of gel growth is also very similar for all substitution types of HPMC; the observed apparent differences in swelling behavior are attributed to differential expansion of the glassy core.²

The amount of water bound to HPMC is related to both the substitution and the polymer molecular weight. Within the gel layer, there obviously exists a moisture gradient from the outside surface in contact with liquid to the inner dry core. Water appears to exist in at least three distinct states within a hydrated gel of pure polymer; the addition of drugs and presumably other excipients to the polymer matrix alters the relative amounts of water in each of the states.³ Upon complete polymer hydration at the outer surface, chain disentanglement begins to occur, i.e., erosion of the matrix.

The rate of erosion is related to molecular weight over a wide range by an inverse power law. In addition, erosion rate is affected by the composition and ionic strength of electrolytes in the liquid medium and by the composition and level of drugs and other additives within the matrix.

One possible explanation for differences in performance of the various HPMC substitution types may be found in the measurement of the self-diffusion coefficient (SDC) of water in pure gels of the polymers.⁴ The SDC as a function of position within the gel is virtually identical for METHOCEL E4M Premium and METHOCEL F4M Premium. However, the SDC at a given position within a gel of METHOCEL K4M Premium is significantly and consistently lower. This implies that the mobility of water within the gel layer is lower within a matrix containing METHOCEL K4M Premium, leading to greater diffusional resistance to water. This directly reduces the diffusion of drug out of the matrix and indirectly affects the state of hydration within the gel, thus affecting that component of drug release due to erosion of the dosage form.



Formulation Factors

Hydrophilic Matrix Systems

A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer (Figure 4). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion.

The sections of the handbook that immediately follow discuss the selection of METHOCEL and the effects of specific parameters on formulation and tablet properties.

Selection of METHOCEL Polymers Type

The flexibility in using METHOCEL products in controlled-release matrix tablets stems from the different types of polymer grades. The two polymer grades of METHOCEL most commonly used in controlled-release applications are K (HPMC 2208, USP) and E (HPMC 2910, USP). F-chemistry products (HPMC 2906, USP) are used less commonly. Methylcellulose (A-chemistry) has been found in very few cases to perform as a rate-controlling polymer.

A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediately disintegrating, resulting in premature drug release. Fast polymer hydration and gel layer formation are particularly critical when formulating with water-soluble drugs and water-soluble excipients.

The hydration rates of the various grades of METHOCEL products differ because of varying proportions of the two chemical substituents, hydroxypropoxyl and methoxyl substitution, attached to the cellulose backbone of HPMC. The hydroxypropoxyl substitution is relatively hydrophilic in nature and greatly contributes to the rate of hydration of METHOCEL. The methoxyl substitution is relatively hydrophobic in nature and does not contribute significantly to the rate of hydration of METHOCEL. K-chemistry METHOCEL products usually establish the gel barrier the quickest among the product grades because K-chemistry has the highest ratio of hydroxypropoxyl to methoxyl substitution. F-chemistry METHOCEL products have the slowest rate of hydration.

Based on studies examining the effect of substitution on release rate from hydrophilic matrix tablets, K-chemistry results in the slowest release compared to other polymers of similar molecular weight.^{5,6}

In another example, the effect of different cellulose ether derivatives on the controlled release of drugs was examined for formulations containing theophylline, polymer, and spray-dried lactose. The dosage form contained the various cellulose ether polymers at a 25% level, and the majority of the bulk was spray-dried lactose, a water-soluble filler. The formulations were dry-blended, and the tablets were manufactured by direct compression. The compression forces were adjusted for the different formulations to obtain similar tablet hardness. Figure 5 depicts the drug-release profiles for this series of polymers.

Figure 4: Drug release from a matrix tablet.

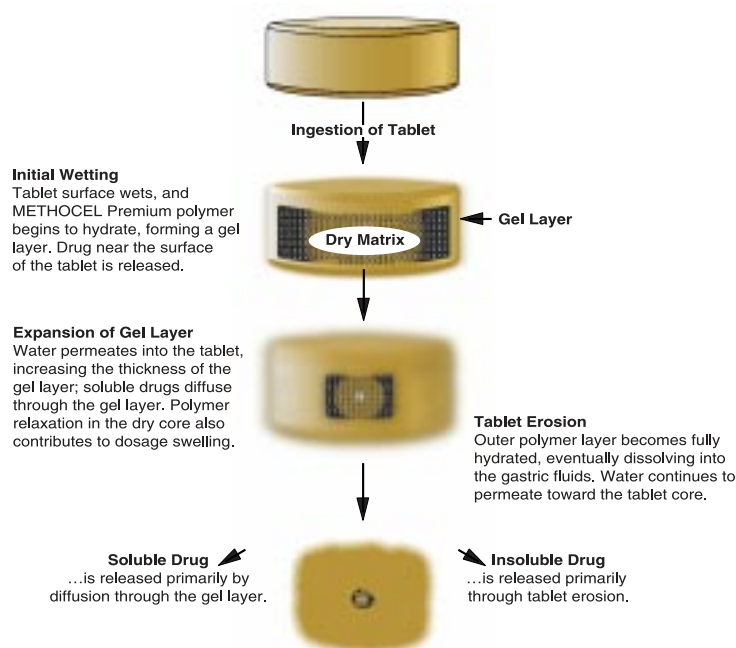
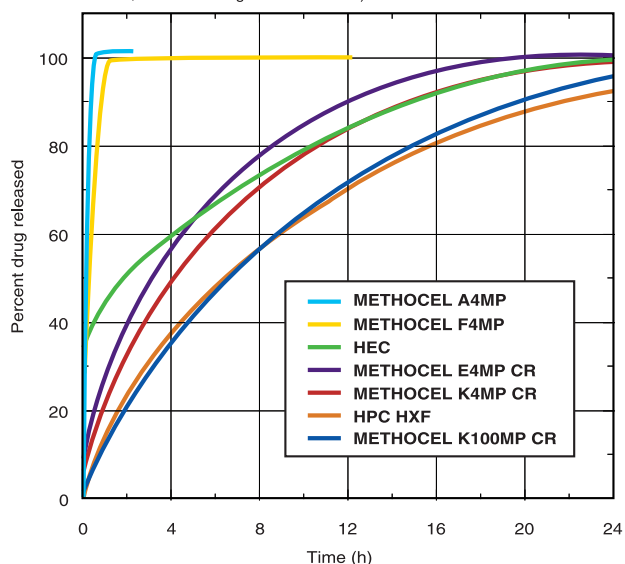


Figure 5: Effect of cellulose ether selection on release of theophylline

(25% rate-controlling polymer, 26.7% theophylline, 47.8% spray-dried lactose, and 0.5% magnesium stearate)



The results indicate that of the polymers of similar molecular weight, METHOCEL K4M Premium CR produced the slowest release relative to METHOCEL E4M Premium CR and METHOCEL A4M Premium. METHOCEL A4M Premium apparently did not form a gel fast enough to provide any controlled release of theophylline. In comparison, the release profile for HEC indicates this polymer may be slower in hydrating or producing an effective gel structure than the comparable HPMC products.

The higher molecular weight polymers METHOCEL K100M Premium CR and hydroxypropylcellulose (HPC) HXF showed similar release profiles. This suggests that these two polymers have similar rates of hydration and possibly similar rates of erosion. These polymers produce a slower release rate relative to the lower molecular weight polymers.

Polymer Level

There must be sufficient polymer content in a matrix system to form a uniform barrier. This barrier protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form.⁷ In most studies, increased polymer level in the formulation results in decreased drug-release rates.

Because hydrophilic matrix tablets containing HPMC absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration of macromolecular disentanglement^{8,9,10} or surface erosion¹¹. The polymer concentration at the matrix surface is defined as the polymer disentanglement concentration.

It is important to note that polymer level in a formulation may not always affect drug release in the same way because of potential drug/excipient/polymer interactions, but most studies indicate that higher polymer levels result in slower release rates.

In the case of the model drug propranolol HCl, Figure 6 shows the effect of increasing level of METHOCEL K4M Premium hydroxypropyl methylcellulose on drug release. For this model system, a level of polymer less than 20 to 30% is insufficient to produce adequate controlled release of propranolol HCl.

This effect of slower release for higher polymer levels is due to the longer period of time required to reach the disentanglement concentration at the tablet surface, which in turn equates to greater resistance to surface erosion. There is a threshold level of retardation of drug-release rate that is achievable where a further increase in polymer loading does not result in further decrease in drug-release rate. This is because drug release does not result solely from polymer erosion, but also from drug diffusion through the hydrated polymer layers.

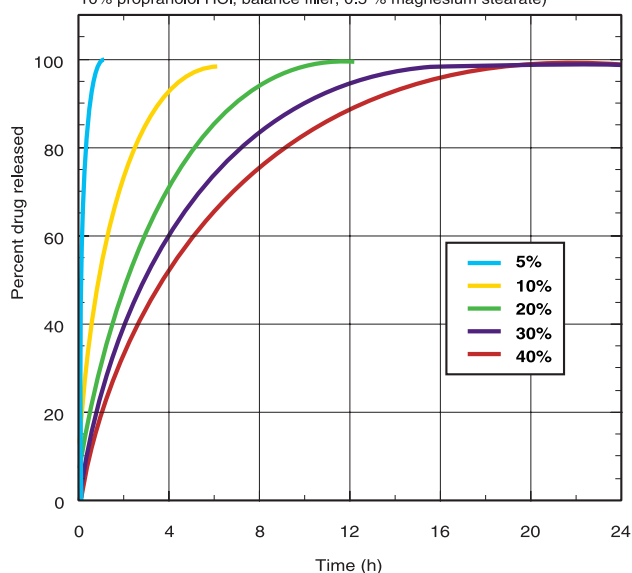




An increase in polymer level also tends to decrease the sensitivity of the formulation to minor variations in the raw materials or the manufacturing process. More polymer in the matrix also means more polymer on the tablet surface. Wetting is more readily achievable, so gel formation is accelerated. As a result, a polymer grade that does not sufficiently retard drug release at a lower level may provide sufficient controlled release at a higher level.

Figure 6: Effect of level of METHOCEL K4M Premium on release of propranolol HCl

(varying levels of METHOCEL K4MP hydroxypropyl methylcellulose, 10% propranolol HCl, balance filler, 0.5 % magnesium stearate)



Molecular Weight and Viscosity

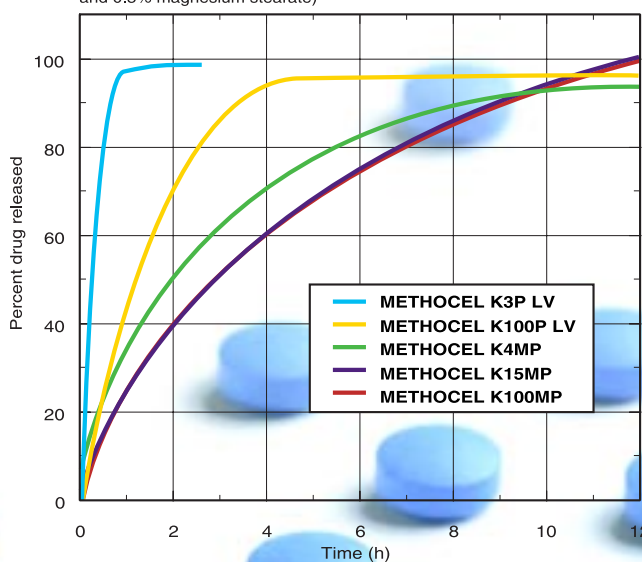
The molecular weight of the HPMC polymer in a matrix tablet, and therefore the apparent viscosity of the hydrated polymer, is important in determining the drug-release properties. It is generally accepted that drug dissolution from tablets is slower for higher molecular weight HPMC polymers. However, there have been several instances in the literature that report no difference in release for different molecular weights. Salomen et al. reported that the release rate of KCl from matrix tablets containing METHOCEL K100 Premium LV was not different than the release rate from matrix tablets containing K15M Premium, but the higher molecular weight polymer did increase the lag time before establishment of quasi-steady state.¹²

In another study, drug-release rates of promethazine hydrochloride from METHOCEL K4M Premium, K15M Premium, and K100M Premium were similar despite differences in polymer molecular weight.¹³ However, drug release from matrix tablets with METHOCEL K100 Premium LV gave the highest release, and this is believed to be due to a greater degree of polymer erosion.

These results suggest that polymer erosion for different viscosity grades of METHOCEL and the effect of erosion on drug release may have a transitional region in the lower molecular weight range, specifically between METHOCEL K100 Premium LV and K4M Premium. In like manner, the overall release profiles for salbutamol sulfate from matrix tablets containing METHOCEL K4M Premium, K15M Premium, and K100M Premium were not significantly different.¹⁰ Similar conclusions were reached by Franz et al., who found that as HPMC molecular weight increased, a lower limiting value of the release rate was reached.¹⁴ Therefore, the variations in drug release between the higher viscosity grades of METHOCEL K4M Premium, K15M Premium, and K100M Premium may not significantly differ. In the model system of theophylline with several different viscosity grades of K-chemistry METHOCEL products, shown in Figure 7, the release rates decrease with increasing polymer molecular weight. Similar to the reports in the literature, the release rates for matrices containing K15M and K100M are similar for this formulation.

Figure 7: Effect of viscosity of K-chemistry METHOCEL products on release of theophylline

(20% rate-controlling polymer, 5% theophylline, 74.5% lactose, and 0.5% magnesium stearate)



Viscosity/Concentration Relationships and Blending

The effects of polymer concentration and viscosity (i.e., molecular weight) on drug-release rates are interrelated and can be predicted using the Phillipof equation:

$$\eta = (1+KC)^8 \quad \text{eq. 1}$$

Strictly speaking, this equation relates concentration to solution viscosity (η = viscosity in mPa-s), K = constant for each individual polymer batch, and C = concentration expressed as a percentage. However, it can be useful in modifying formulations containing HPMC to achieve composition goals while maintaining similar release characteristics.

For example, suppose a formulation had been developed using 25% METHOCEL K4M Premium HPMC, which gave a desired release profile. A similar release profile can be achieved in one of two ways.

First, METHOCEL K4M could be replaced with a lower viscosity polymer, for example, METHOCEL K100 Premium LV, used at some higher concentration. The level of METHOCEL K100 Premium LV required can be simply calculated by the following concentration equation:

$$C_{K100 \text{ Premium LV}} = \frac{K_{K4M \text{ Premium}} (0.25)}{K_{K100 \text{ Premium LV}}} \quad \text{eq. 2}$$

Alternatively, if it is desirable to use a specific higher level of polymer, such as 35%, a blend of METHOCEL K100 Premium LV and K4M Premium could be prepared to produce the same drug-release rate as the system with 25% METHOCEL K4M Premium. For example, assume that the METHOCEL K4M Premium to be used in the new formulation has a 2% viscosity of 4100 mPa-s, and the METHOCEL K100 Premium LV has a 2% viscosity of 110 mPa-s. An equation derived from the Phillipof equation can be used to predict the proper ratio.

This equation is derived assuming that the constant K for a blend of products is equal to the proportional contribution from each of the components:

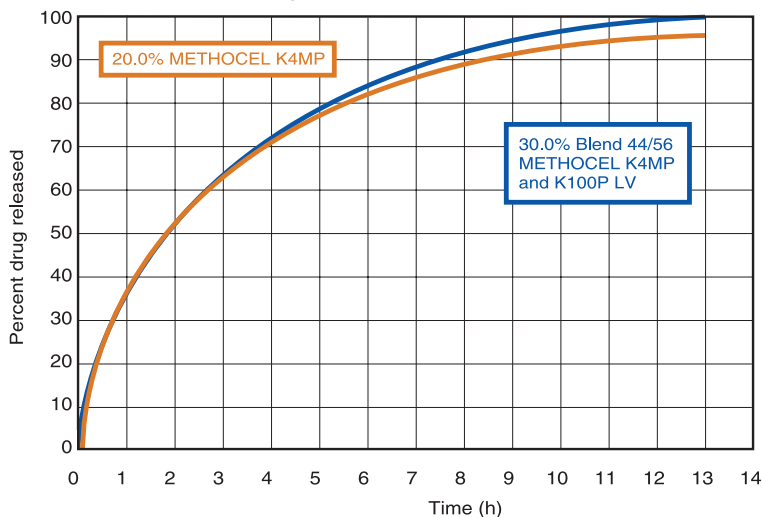
$$F_1 = \frac{\left(\frac{K_1 C_{\text{orig}}}{C_{\text{blend}}} - K_1 \right)}{(K_1 - K_2)} \quad \text{eq. 3}$$

- K_1 = Constant for polymer with higher molecular weight (solved with Phillipof equation, solution viscosity from the Certificate of Analysis, and concentration = 2.00%)
- K_2 = Constant for polymer with lower molecular weight (solved with Phillipof equation, solution viscosity from the Certificate of Analysis, and concentration = 2.00%)
- C_{orig} = Original polymer level in tablet
- C_{blend} = Desired polymer level in reformulated tablet
- F_1 = Wt. fraction (in the blend) of polymer with higher molecular weight

Solving eq. 1 for the METHOCEL K4M Premium and K100 Premium LV to be used in the blend gives $K_1 = 91.4$ and $K_2 = 40.0$. In this example, $C_{\text{orig}} = 0.25$ and $C_{\text{blend}} = 0.35$. Substituting these values into eq. 3 and solving gives $F_1 = 0.48$. A mixture of 48% w/w METHOCEL K4M Premium and 52% METHOCEL K100 Premium LV, used at a 35% level, should give approximately the same release profile as the initial formulation. Differences may arise due to changes in the amount of other, noncellulosic excipients. Laboratory experiments confirm the utility of these equations, as shown in Figure 8.

Figure 8: Effect of changing polymer concentrations for equivalent release rates on release of pseudoephedrine HCl.

(varying levels of rate-controlling polymer, 16% pseudoephedrine HCl, balance lactose, 0.7% magnesium stearate)





Effect of Particle Size

The particle size of HPMC polymer can greatly influence polymer performance in the hydrophilic matrix. Fractions of HPMC polymers with smaller particle size have more surface area relative to equivalent weights of fractions with larger particle size. The greater surface area provides for better polymer-water contact, thus increasing the overall rate at which complete polymer hydration and gelation occurs. This leads to the more effective formation of the protective gel barrier so critical to the performance of hydrophilic matrix tablets.

Alderman found that matrices containing coarse particles (200 to 300 μm) of K-chemistry METHOCEL products did not form a sufficient gel barrier to prevent the premature release of riboflavin.¹⁵ In general, matrices containing larger particle sizes (greater than 200 μm) disintegrated before a protective layer was formed, while matrices made of smaller-size fractions (less than 150 μm) formed an exterior gel layer that protected the matrix and effectively retarded release.

A study by Mitchell et al. showed that the release rate of propranolol HCl from matrices containing METHOCEL K15M Premium generally decreased as the polymer particle size decreased.¹⁶ They also observed that as the level of HPMC increased in the formulation, the dependency of drug release on particle size decreased.

To demonstrate the effect of particle size of HPMC on the rate of drug release, various sieve cuts were used in a model controlled-release formulation containing 20% METHOCEL K4M Premium and sufficient quantity of spray-dried lactose to make up the remainder of the formulation. The model actives were theophylline (Figure 9) as the slightly soluble drug, at a level of 5% in the formulation; promethazine HCl (Figure 10) as the soluble drug, at a level of 2% in the formulation; and metoprolol tartrate (Figure 11) as the very soluble drug at a level of 5% in the formulation.

In all cases, tablets made with very coarse polymer particles (>177 μm) disintegrated and resulted in immediate drug release. A sufficient amount of polymer surface area was not exposed to the infusing medium to allow for a protective gel layer to form. However, in all cases, matrices containing smaller polymer particles, and therefore having a greater total surface area, did hydrate fast enough and form a protective gel that slowed both water penetration into the tablet and drug release out of the matrix.

Finally, it appears that the more soluble the drug, the more susceptible the formulation is to polymer particle size. As seen in Figure 11, there is more spread between the release profiles for the different sieve cuts for release of metoprolol tartrate. This suggests that more soluble drugs require a faster rate of gel formation to sufficiently control drug release.

Figure 9: Effect of particle size of METHOCEL K4M Premium on release of theophylline

(20% METHOCEL K4MP, 5% theophylline, 74.5% lactose, and 0.5% magnesium stearate)

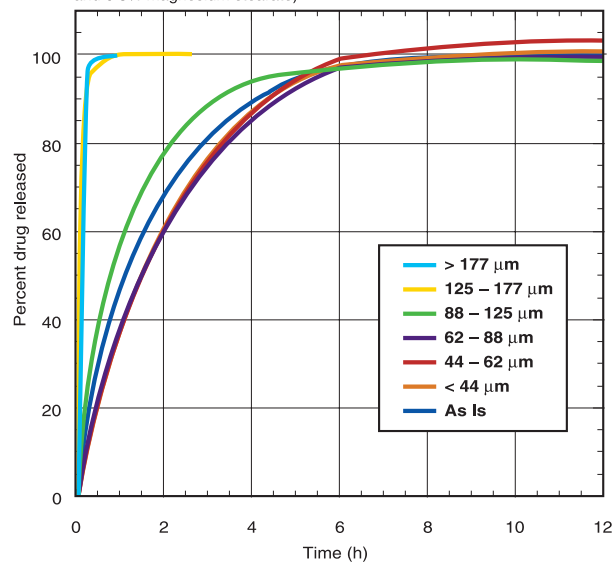
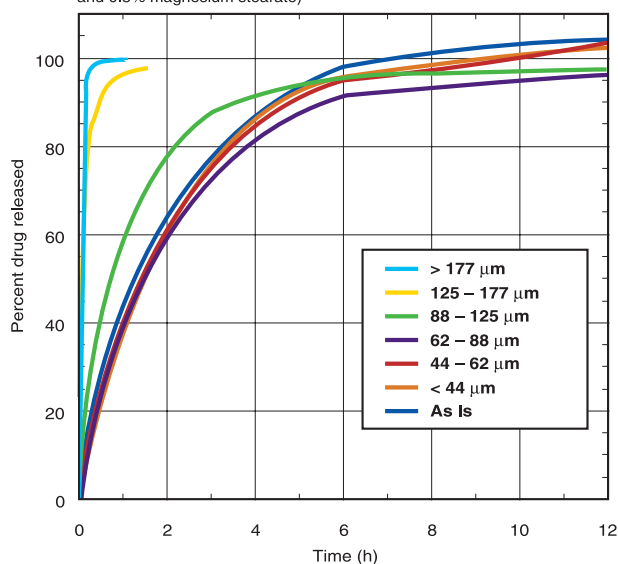
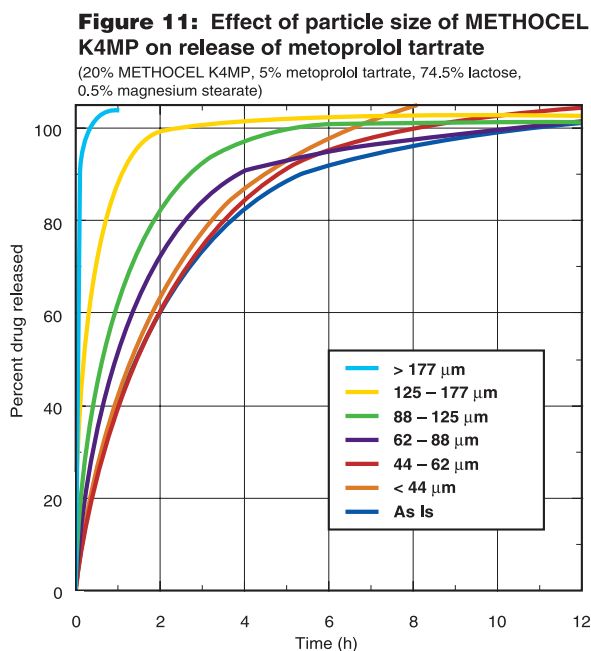


Figure 10: Effect of particle size of METHOCEL K4MP on release of promethazine HCl

(20% METHOCEL K4MP, 5% promethazine HCl, 74.5% lactose, and 0.5% magnesium stearate)





Effects of Drug Properties

Level and Particle Size

In most studies, increased drug concentration leads to increased drug-release rates. In a few cases, increased drug concentration leads to decreased drug-release rates. One possible explanation for the latter behavior is the effect of drug-HPMC interactions. Ford examined how variations in drug particle size can alter drug release.^{13,17} In general there was little effect of drug particle size on drug release. Only in the extreme case of very large drug particles in formulations containing relatively small amounts of HPMC was there a significant change in the drug-release rate.



Solubility

Higher solubility of the drug generally leads to faster release. To make exact comparisons, very detailed data are needed regarding dissolution rates, drug solubility, diffusion coefficients, pH dependence of solubility, and drug-polymer interactions. Higher solubility drugs release at faster rates in most examples because their diffusional driving force would be highest. Drug dose is also an important issue, in that a high solubility drug at a dose higher than its solubility in the matrix can have an increased erosional release component because of a dissolution limitation. Other exceptions can also occur; for example, the drug can “salt out” or “salt in” the polymer.

Tahara et al. investigated the effect of drug solubility on release using seven different drugs of widely varying solubility.¹⁸ Tablets were prepared by wet granulation to minimize the influence of drug particle size on the observed release profiles. Soluble drugs had mean dissolution rates close to the mean water infiltration rates. As drug solubility declined, there was an increased contribution from erosion to drug release.

Tahara’s work shows a wide variation in release rates, with one experimental drug dissolving more slowly than the erosion rate from a placebo control. Measured release rates (assuming a square root of time dependence) were plotted against drug solubility. Above a solubility of 1.2 mg/mL, there was a plateau in the dependence of drug release vs. solubility, but there was also a statistically significant variation in drug release that did not correlate to solubility. This second-order effect could be the result of variations in diffusivity of these molecules owing to different molecular sizes or differing interactions with the polymer.

Tahara did not measure the erosion and water uptake for tablets containing each drug, so the impact of the individual drugs on polymer erosion and matrix hydration is not known. The authors suggest that the behavior of hydrophilic matrices falls into three regimes determined by the solubility of the drug, the amount of drug present in the tablet, and the resulting porosity (interspace volume) of the matrix. In the case of drugs with low solubility, controlling erosion is most effective; for drugs with moderate or high solubility, the most effective approach to control drug dissolution is to control infiltration of the medium.



In work done in Geneva, a large number of drugs with widely varying solubilities were examined.¹⁹ Among the 23 drugs examined by Ranga Rao et al., however, there were a number of anomalies. In this paper the authors suggest that in addition to solubility and molecular weight and size, there are other factors governing the release of drugs from cellulose ether matrices: interactions, solvent penetration, erosion, influence of drug on erosion, and solubilization of the drug by the polymer.

In another study, Ranga Rao et al. looked at six drugs of 1/0.9 to 1/10,000 solubility.²⁰ From a matrix containing METHOCEL K4M Premium, there was very little difference in the release of pindolol (1/10,000), allopurinol (1/2000), and salicylic acid (1/460), while Na salicylate (1/0.9) was much different. However, when the polymer erosion was measured for drug-polymer compacts and for HPMC itself, all drugs in the study caused an equivalent increase in the extent of erosion.

Baveja et al. compared three beta blockers: alprenolol HCl, metoprolol tartrate, and propranolol HCl.²¹ These drugs all have similar molecular weights, structures, and solubilities. Data comparing drug: HPMC compacts at a variety of ratios for these three drugs are given. At a 1:3 ratio, the time for 50% drug release was about 2 h 20 min for alprenolol HCl, 3 hr 30 min for metoprolol tartrate, and 4 hr 5 min for propranolol HCl. This implies that drug release can be affected by small differences in structure within a family of compounds.

In another study, Baveja et al. examined seven bronchodilators having approximately the same solubility properties and structures.²² The authors attempt to correlate drug release from 1:1 compacts of the drugs with METHOCEL K4M Premium, K15M Premium, and K100M Premium with structural features of the drug molecules. Reasonable agreement was found between the experimentally determined rates of drug release and calculations of the “accessible surface area” (in nm²) of the drug, and a regression was both predictive and internally consistent. Release rates (from Higuchi $t^{1/2}$ plots) decreased as the accessible surface area increased.

Hydrophilic matrices have been proven useful in the formulation of drugs with a wide range of aqueous solubilities. Formulations of very highly soluble drugs at very high dosage levels are the most difficult because of the extreme demands on polymer hydration and gelation.

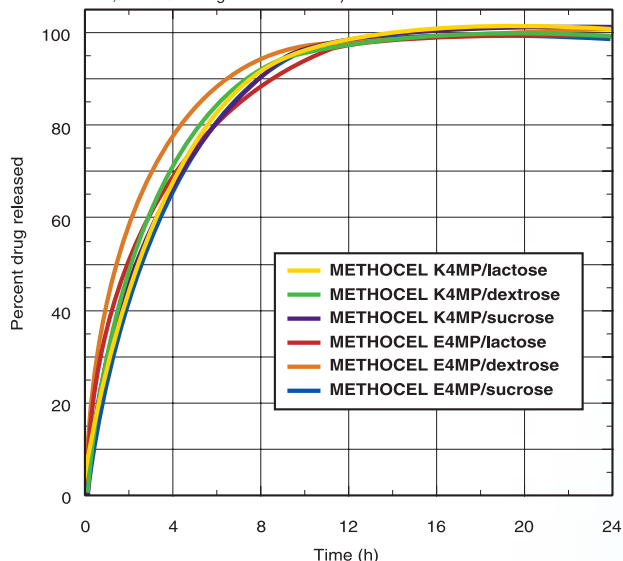
Effects of Fillers

The effect of fillers on drug release is dependent on the drug substance, the polymer level, and the level of the filler itself in the hydrophilic matrix tablet. Figure 12 and Figure 13 show the drug-release profiles obtained when three soluble fillers—lactose, sucrose, and dextrose—are incorporated into controlled-release formulations.

Figure 12 shows essentially no difference in the release of slightly soluble theophylline when these fillers are used in conjunction with either METHOCEL K4M Premium or E4M Premium.

Figure 12: Effect of various soluble fillers on release of theophylline

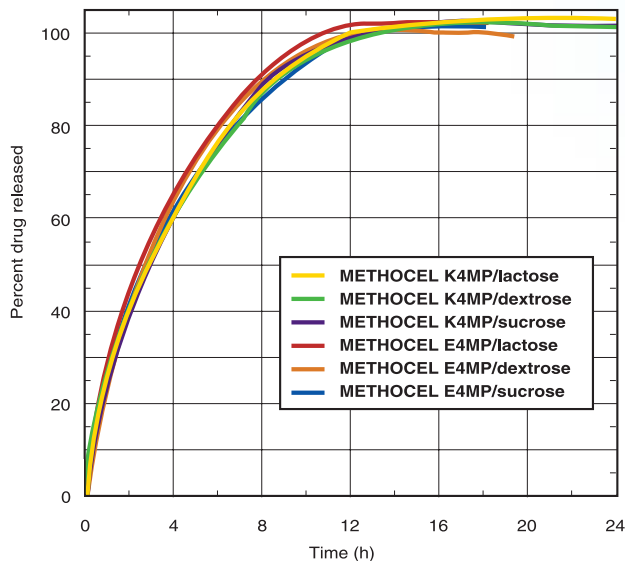
(30% METHOCEL K4MP or E4MP, 5% theophylline, 64.5% soluble filler, and 0.5% magnesium stearate)



A similar situation exists with the soluble drug naproxen sodium, Figure 13. Although the polymer is at a reasonable level, in both cases the amount of filler is relatively high, leading to gels which when hydrated have relatively high permeability. The formulations therefore produce similar release profiles despite the differences in drug solubility.

Figure 13: Effect of various soluble fillers on release of naproxen sodium

(30% METHOCEL K4MP or E4MP, 20% naproxen sodium, 49.5% soluble filler, and 0.5% magnesium stearate)



When the insoluble fillers dibasic calcium phosphate dihydrate, dibasic calcium phosphate anhydrous, and calcium sulfate were evaluated with theophylline, the release of theophylline from matrices containing METHOCEL K4M Premium CR and E4M Premium CR was again virtually the same for all three fillers (Figure 14). (The exception involved anhydrous dibasic calcium phosphate when used with METHOCEL K4M Premium CR).

The “average” release of theophylline from the matrices containing the insoluble fillers was somewhat longer than when the soluble fillers were used. When naproxen sodium was used as a model drug, the interesting results shown in Figure 15 were obtained. With both METHOCEL K4M Premium CR and E4M Premium CR, the release profiles resulting from the use of dibasic calcium phosphate dihydrate and anhydrous fillers were essentially identical. Naproxen sodium released from the matrices containing calcium sulfate at a considerably slower rate, but at a rate that was identical for both types of HPMC. The release of naproxen sodium from the phosphate-containing matrices was only slightly slower than from matrices containing the soluble sugars above.

One possible explanation for the slower than expected release of naproxen sodium is an interaction between this drug and HPMC; cloud point experiments indicate that naproxen sodium has a strong “salting in” effect on the polymer.

Figure 14: Effect of various insoluble fillers on release of theophylline

(30% METHOCEL E4MP CR or K4MP CR, 5% theophylline, 64.5% soluble filler, and 0.5% magnesium stearate)

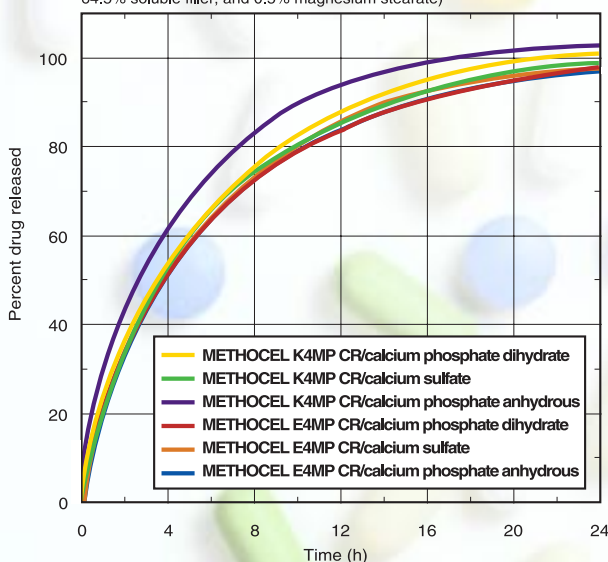
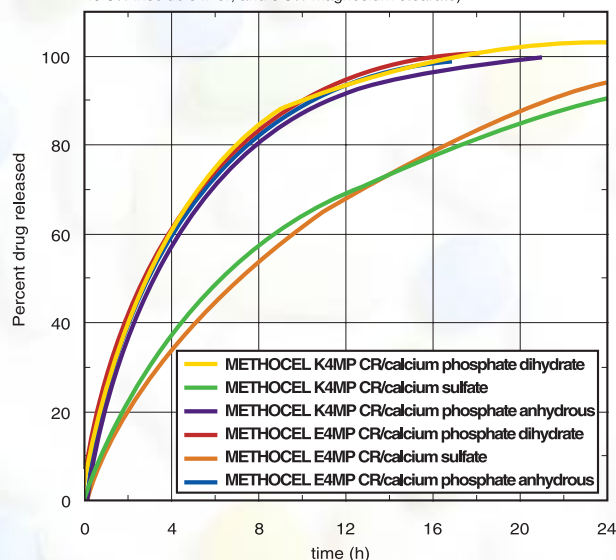


Figure 15: Effect of various insoluble fillers on release of naproxen sodium

(30% METHOCEL E4MP CR or K4MP CR, 20% naproxen sodium, 49.5% insoluble filler, and 0.5% magnesium stearate)



In contrast to the performance of the soluble naproxen sodium and the slightly soluble theophylline, Figure 16 shows the effects of fillers on the release of the insoluble drug alprazolam. Use of the soluble fillers sucrose, dextrose, and lactose led to one grouping of similar release profiles, while the use of the insoluble fillers dibasic calcium phosphate dihydrate, dibasic calcium phosphate anhydrous (data not shown in Figure 16), and calcium sulfate led to a second grouping, but of significantly slower release profiles. Use of blends of soluble lactose and insoluble dibasic calcium phosphate dihydrate produced release profiles of an intermediate duration. The use of blends of fillers illustrates another option available to the pharmaceutical formulator in tailoring the desired release profile of the controlled-release dosage form.

Figure 17 illustrates the effects of replacing the soluble filler lactose with the insoluble filler dibasic calcium phosphate dihydrate. The level of drug, polymer, and the total quantity of filler were constant throughout. There was essentially no difference in release profiles for formulations that were predominantly lactose, up to and including the formulation containing equal proportions of the two fillers.

Only when the dibasic calcium phosphate dihydrate level was greater than 75% or greater of the filler fraction did the release slow down. The addition of soluble filler increases porosity, which results in faster diffusion and an increased rate of erosion. Even a small amount of soluble filler will have an effect.



Figure 16. Effect of soluble and insoluble fillers on release of alprazolam

(40% METHOCEL K4MP, 2.5% alprazolam, 20% microcrystalline cellulose, 36.5% filler, 0.5% silicon dioxide, and 0.5% magnesium stearate)

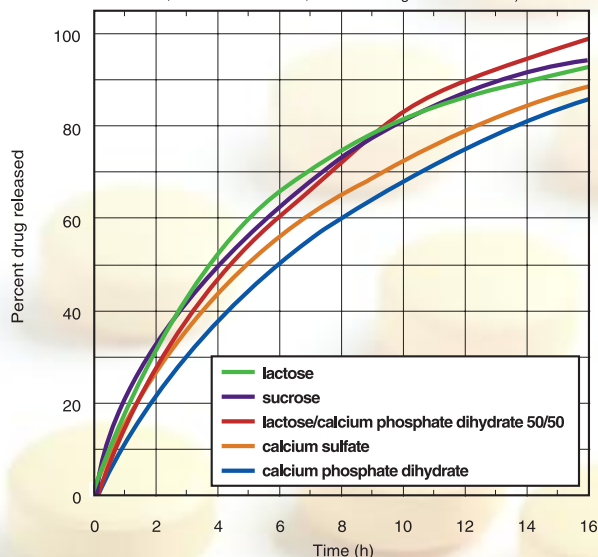
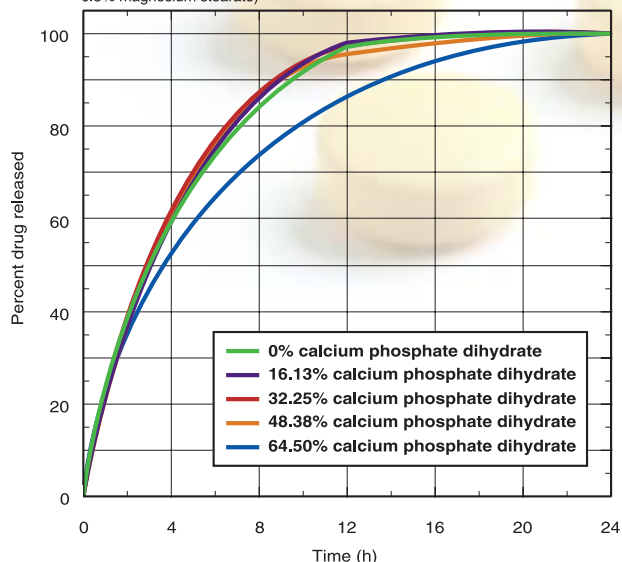


Figure 17: Effect of replacing soluble filler (lactose) with insoluble filler (calcium phosphate dihydrate) on release of theophylline.

(5% theophylline, 30% METHOCEL K4MP, 64.5% total filler, 0.5% magnesium stearate)



In addition to the effects of fillers presented above, this area has been studied extensively by many other researchers. Ford et al. studied the effect of various levels of spray-dried lactose and calcium phosphate on promethazine HCl release at two different drug/polymer levels.²³ Ford states that at low levels, the solubility of the filler has a small or no effect on rate of drug release. However, differences in filler solubility can become apparent when filler levels are relatively low if the dosage is relatively high and the HPMC content is relatively low.

By contrast, in Rekhi et al., filler composition is either second or first in significance at 4, 6, and 12 h time points in a statistically designed experiment.²⁴ All of the formulas had between 61% and 25% filler. This tends to disprove the statement that filler solubility is important only at high filler levels (most investigators say greater than 50%). The type of filler (soluble vs. insoluble) was an experimental variable, so its statistical significance is meaningful. One can see an increase in drug release at the 4, 6, and 12 h time points by changing from insoluble to soluble filler. This was ascribed to a “reduction in tortuosity and/or gel strength of the polymer.” The authors state that they see a marked divergence of the effects of filler at greater than 50%, attributing this to a difference in tortuosity resulting from the difference in solubility.

In a paper by Sung et al. on adinazolam mesylate (> 50 mg/mL solubility), HPMC/spray-dried lactose ratio was found to be an important variable, as was HPMC viscosity grade.²⁵ With METHOCEL K4M Premium, there was a systematic variation in both drug release and polymer release as HPMC/spray-dried lactose was varied from 80:17 to 20:77 (five ratios). It is interesting to note that there was little difference in HPMC release rate between the 80:17 and the 65:32 HPMC/spray-dried lactose ratios, but as the ratio was further decreased, the slope of the percent released vs. time curve quickly increased.

The same paper by Sung et al. examined other aspects of HPMC performance worth noting here. In separate experiments on molecular weight of the polymer, they saw the usual trend in drug release rates: K100 LV >> K4M > K15M ≈ K100M Premium. However, in the case of polymer release, there was no indication of a “limiting HPMC viscosity.”

Sung et al. note that swelling and erosion are not accounted for in the Higuchi development; nevertheless, they assert that good $t^{1/2}$ fits are indicative of diffusion control. If drug and polymer release are superimposable, then erosion control may be assumed. If they are not, then diffusion contributes at least partially.

It is interesting to note that the mathematical modeling work of Ju et al. predicts that the difference between drug and HPMC release should decrease with a decrease in the “equivalent molecular weight” of the matrix.²⁶ This is seen both qualitatively and quantitatively in the case of METHOCEL K100 Premium LV. The effect of filler solubility and filler level on the “polymer critical disentanglement concentration” is also likely to be important.

Effects of Binders

Direct Compression

The preparation of hydrophilic matrix tablets using METHOCEL cellulose ethers is most easily accomplished by directly compressing a dry mixture of drug, HPMC, and other excipients. HPMC has good compaction characteristics;

however, some formulations may require a binder to increase tablet strength.

One useful excipient for direct compression is microcrystalline cellulose (MCC). It is now available in a wide variety of grades, differing in parameters such as mean particle size, particle size distribution, density, and moisture. Newer materials consist of

MCC co-processed with other excipients. As a result, there exists a range of flow properties and compressibilities for MCC products that results in differing tablet strengths and manufacturing constraints, which potentially could affect drug dissolution.

To test the effect of MCC on drug release, a model formulation was developed containing 5% theophylline, 30% METHOCEL K4MP, and total filler level of 64.5%. The initial formulation contained dibasic calcium phosphate dihydrate as the filler. The other formulations contained 6% and 12.9% MCC (90 μm avg. particle size) with the remainder of the 64.5% filler level being dibasic calcium phosphate dihydrate.

The release profiles for these formulations are shown in Figure 18. The formulation with 12.9% MCC (90 μm) had the slowest release. MCC may function in some formulations as a binder and/or disintegrant, depending on the level. MCC exhibits disintegrating properties at levels as low as 10%.²⁷ In this formulation, the highest

level of MCC was most likely acting as a strong tablet binder to decrease tablet porosity, and thus slow drug release.

The effects of particle size distribution and/or density of MCC on the release of a slightly soluble, low dose drug from a matrix tablet containing METHOCEL K4M Premium were examined. The amount of MCC in the dosage form was kept constant at the realistic level of 10% w/w. In all cases, very strong tablets with low friability were obtained; the trend in tablet hardness followed the compressibility of the individual MCC grades. Tablet thickness variation was also quite low, with no trend that could be associated with the MCC grade. As shown in Figure 19, neither MCC particle size nor the MCC density had a significant effect on drug release in this model formulation.

Granulation

Direct compression is not always feasible for hydrophilic matrix formulations containing METHOCEL products. In these cases, wet and dry granulation technologies can provide better product flow on tablet presses, overall improved tablet physical characteristics, uniform drug content within the dosage form, and fewer industrial hygiene constraints.

Wet granulation processes include low-shear, high-shear, and fluid-bed processes. One study compared the effects of low-shear and high-shear processes with direct compression on a controlled-release matrix tablet containing HPMC and a high-dose, highly water-soluble drug.²⁸ Drug release was not

influenced by the method of tablet manufacture (wet granulation vs. direct compression) or the level of water used during wet massing of the granulation. Tablets with good hardness and low friability values were produced using either low-shear or high-shear granulation techniques.

Figure 18. Effect of level of microcrystalline cellulose on release of theophylline from tablets containing METHOCEL K4MP

(30% METHOCEL K4MP, 5% theophylline, varying levels of microcrystalline cellulose (90 μm avg. particle size), balance calcium phosphate dihydrate, 0.5% magnesium stearate)

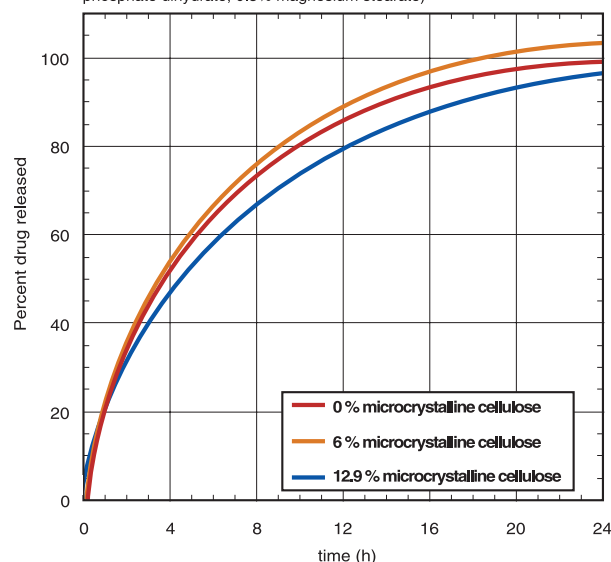
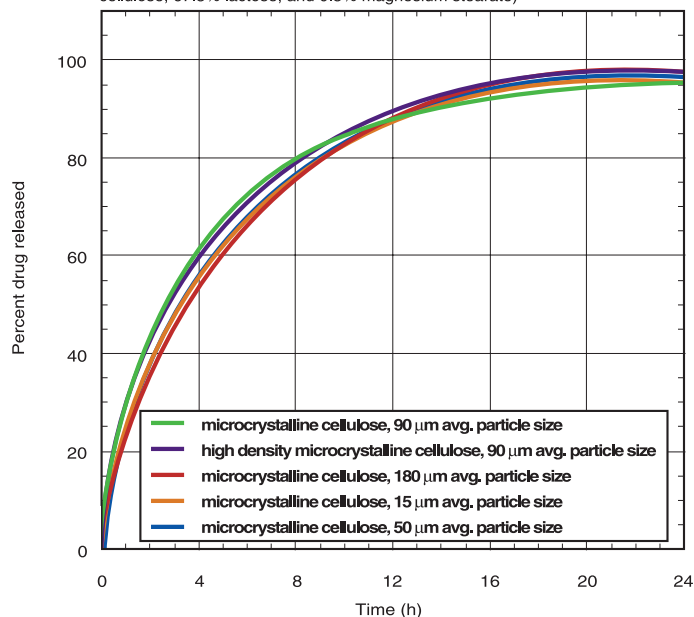


Figure 19. Effect of microcrystalline particle size and/or density on release of promethazine HCl from tablets containing METHOCEL K4MP

(20% METHOCEL K4MP, 2% promethazine HCl, 10% microcrystalline cellulose, 67.5% lactose, and 0.5% magnesium stearate)



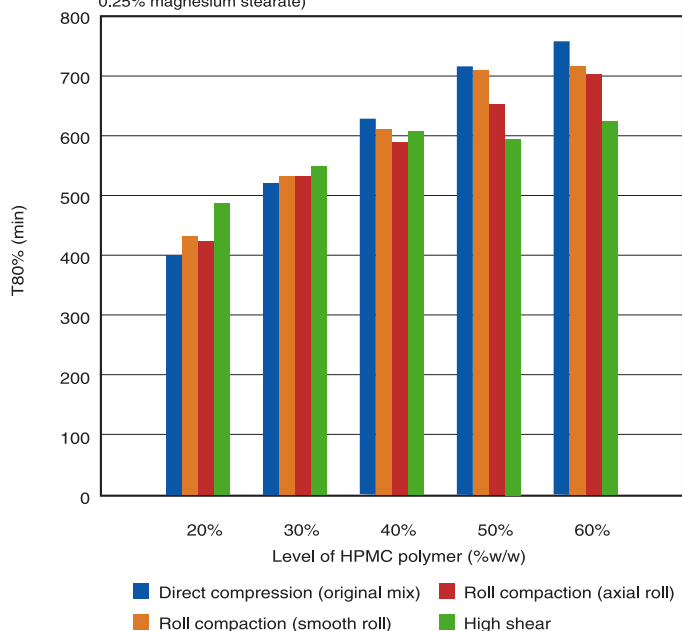


Roll compaction is a dry granulation process that provides high-volume production of granules and good control of final particle bulk density and flow properties.^{29,30} Roll compaction offers an alternative means of improving flow by granulating a formulation that is difficult to wet granulate. Sheskey and Hendren found that roll compaction equipment variables had little effect on tablet physical properties or drug release.³¹ Actual drug release was similar for all three methods (direct compression vs. roll compaction vs. high shear), although the T80% values for roll compaction were closer to those of direct compression than were the values for high-shear granulation (Figure 20). T80% represents the time required for 80% drug release from the tablet.

Although the model systems discussed in the examples above did not show any effects from method of manufacture, every formulation is unique and requires experimentation to optimize formulation properties.

Figure 20. Effect of manufacturing method and level of HPMC on T80% values for release of theophylline.

(30% METHOCEL K4MP, 10% theophylline, 59.75% lactose, 0.25% magnesium stearate)



Effects of other Excipients

Lubricants

Lubricants are added to reduce sticking to the punch faces and to allow easy ejection of the tablet during tablet formation. Magnesium stearate, a boundary-type lubricant, is the lubricant of choice because its plate-like crystalline structure readily deforms in shear during the mixing and compaction process,

thereby coating the powder and tooling surfaces. The obvious concern here is that overlubrication could lead to coating of this hydrophobic material on the surfaces of the tablet and thereby retard release. This would be not only a function of lubricant level, but also a function of blend time with the lubricant since increased mixing can lead to increased shearing of the magnesium stearate particles.

Sheskey et al. found that magnesium stearate levels from 0.2 to 2.0% and blend times of 2 to 30 minutes had only a slight impact on drug-release rates.³² Other formulation variables such as filler type and drug solubility had a much greater impact on drug release. They also found that tablets containing lubricant plus unmilled dibasic calcium phosphate anhydrous were harder and had significantly better friability patterns than those prepared using spray-dried lactose, regardless of drug type or mixing conditions. These results may be because dicalcium phosphate has a “brittle fracture” mechanical property, which allows for the formation of new clean surfaces available for bonding during the tablet compression state. As expected, tablet ejection forces were influenced to the greatest extent by the level of lubricant in the formulation.



Release Modifiers

Modifying Internal pH

For drugs with pH dependent solubility, an obvious strategy to alter the dissolution profile is to modify the microenvironment near the drug to increase solubility. Meddeb and co-workers showed that addition of NaHCO_3 to HPMC matrix tablets of furosemide dramatically increased release rates.³³

Ju and his co-workers at Upjohn have examined the modification of gel matrix pH for a number of acidic and basic drugs.³⁴ The drugs were incorporated into HPMC matrices of METHOCEL K4M Premium and showed variation in release rate as a function of media pH. Release rate was modulated by the addition of acidic and basic modifiers such as citric acid, *p*-toluenesulfonic acid, glycine, and tris-hydroxymethyl aminomethane (THAM). In general, pH-induced decreases in drug solubility leading to slower release could be overcome by the addition of the appropriate acidic or basic modifier to the matrix. It was implied that drug-polymer interactions and drug structure were also important.

Ventouras and Buri examined this concept with vincamine HCl hemihydrate, drotaverine HCl, and quinidine sulfate dihydrate.^{35,36} The solubility and release of these drugs were strongly affected by media pH. METHOCEL K100 Premium was the rate-controlling polymer. The base formula consisted of 50% HPMC and 15% drug; the balance comprised normal fillers with succinic, tartaric, and oxalic acids as pH compensating additives. A pH microelectrode (diameter approx. 10 μm) verified that the pH was 3.5 to 4.5 in the interior of the tablet,

6.8 a few microns from the surface, and 7.2 at the surface. There was no clear relationship between the magnitude of the effect on drug release and the pK_a of the different acids. While the authors correctly note that the dissolution profile is the net effect of a number of factors, altering the pH within the gelled medium (the tablet) did exert a favorable effect on drug dissolution. The solubility of the drug in the gel is important, and it may be possible to minimize the effects of pH along the GI tract.

Modifying Drug Solubility

The use of cyclodextrins to encapsulate and enhance the solubility of insoluble drugs is an active area of pharmaceutical research. Cyclodextrins may be used in conjunction with HPMC. For example, Conte and co-workers have shown that diazepam encapsulated in hydroxypropyl β -cyclodextrin is released at a fairly constant rate from matrices.³⁷

Modifying Drug Release with Other Polymers

Other natural or semisynthetic polymers may be used in some circumstances to modify the drug-release profile. The two most commonly used polymers are sodium carboxymethylcellulose and sodium alginate. Sodium alginate is protonated at low pH and contributes to gel structure, but is in a more soluble and erodible form at higher pH. Mixtures of HPMC and sodium alginate have been used with drugs that have a pH-dependent solubility in order to obtain a more pH-independent release.³⁸

Combinations of HPMC and sodium carboxymethylcellulose (NaCMC) have been extensively studied for many years. With certain water-soluble drugs, a blend of appropriate grades of HPMC and NaCMC may minimize the release of drug during the initial phase of the release profile. This tends to “flatten” the shape of the release profile, i.e., produce a more “zero order” release.^{39,40} The explanation for this effect is not clear; many researchers have cited a synergistic interaction between HPMC and NaCMC.⁴¹

However, the studies of the rheology of solutions containing both polymers are contradictory, and other studies of the erosion rate of polymer blends do not show synergistic effects.^{42,43} For some soluble drugs, drug release is faster than the observed polymer erosion, while for others it is slower.⁴⁴ The molecular weight of the NaCMC seems to be important in neutral/basic environments, whereas in acidic environments (where the NaCMC is protonated) the MW does not appear to be crucial.⁴⁵ While NaCMC alone as the rate-controlling polymer is not practical because of accelerating release rates and poor stability, its use in conjunction with HPMC may be beneficial.

Drug/HPMC/Excipient Interactions

The interaction of HPMC with other molecules present in the formulation or in the medium is complex. A number of recent studies have shown this for even the simplest case, the interaction of HPMC and water. The effects of interactions can be accentuated by the conditions that exist within a hydrophilic

matrix tablet, from the fully hydrated outer surface through various states of partial hydration to the dry inner core. In these partially hydrated regions, the “concentration” of the drug, other excipients, water, and species from the medium may be relatively high, creating a condition favorable to interaction with HPMC. The hydration and gelation of HPMC under these conditions are only now beginning to be understood. One approach is to consider these interactions as resulting from specific binding of smaller molecules to HPMC, from so-called “generic effects” resulting from disruption of solvent (water) structure and solvent dilution, or from a combination of the two.

Interactions between drugs and HPMC that negatively impact polymer hydration are relatively rare. Perhaps the best-studied example is diclofenac Na; Rajabi-Siahboomi, Melia, and others have studied this at the University of Nottingham. It was observed that a tablet comprising 70% METHOCEL K4M Premium, 15% diclofenac Na, and 15% lactose disintegrated in 5 min. when exposed to 0.12M phosphate buffer, pH 7.4. Placeboes containing lactose and/or calcium phosphate had not disintegrated after 300 min. Furthermore, disintegration time was greater than 60 min. if the phosphate concentration was 0.09M or less, was 30 minutes at 0.10M, but was only 3 minutes at 0.16M. Solvent uptake was slightly increased (relative to water) by the presence of either diclofenac Na or phosphate (0.12M), but was dramatically increased by the presence of both. Particle swelling, measured by video microscopy, was most dramatically decreased by the presence of both the drug and phosphate ions. When dissolution testing on the tablets was performed in 0.12M phosphate buffer, very rapid drug release occurred at 37°C (due to tablet disintegration), very limited control of the release was observed at 31°C, but very good sustained release was obtained at 23°C.

These results prompted Rajabi-Siahboomi et al. to examine the structure of diclofenac Na more closely. This was done by measuring the effect on the cloud point of an HPMC solution that also contained compounds equivalent to various substructures of diclofenac Na. It was found that the substructure that most affected the hydration of HPMC was the 2,6-dichloroaniline moiety. The combination of diclofenac Na and phosphate acts to inhibit hydration and swelling of HPMC, thereby retarding gel layer formation. This allows solvent to percolate to the interior of the tablet, leading to disintegration. The identification of a specific active moiety chiefly responsible for this effect points to the possibility of developing structure-activity relationships.

Charge, in and of itself, is probably not important in drug-HPMC interactions. Too much insoluble material in the formulation can inhibit polymer-polymer interaction and gelation by presenting a simple physical barrier. This can be prevented by ensuring that a reasonable HPMC level is present in the formulation—a condition that also contributes to formulation robustness.



Effects of Tablet Dimensions

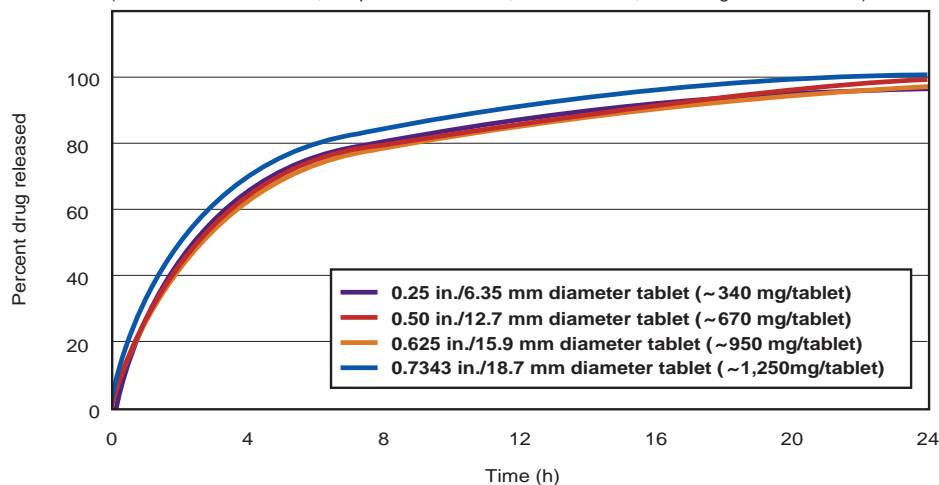
It is widely accepted that the release from HPMC matrix tablets occurs by one of two means, either diffusion of dissolved drug or release due to matrix erosion. Higuchi proposed that the amount of drug release of a soluble drug uniformly dispersed in a homogenous matrix is proportional to the unit area of exposed matrix surface.⁴⁶ Ford et al. found that the release rates for tablets containing different levels of drug but the same ratio of HPMC to drug were similar when normalized to initial tablet surface area.⁴⁷ Later, Ford et al.²³ provided data that indicated that a linear relationship exists between the drug-release rate, as determined by fitting the data to the Higuchi square-root time equation,⁴⁸ and tablet surface area.

Rekhi et al. examined the effect of surface area on the release of metoprolol tartrate from matrix tablets containing METHOCEL K100 Premium LV.⁴⁹ A standard concave tablet and a caplet shape tablet were used to examine the effect of surface area on metoprolol tartrate release. The surface areas for the standard concave and caplet shape tablets were 3.7 and 4.8 cm², respectively, and the release for the caplet shape tablet was faster due to its larger surface area. They normalized the release profile for the caplet shape with respect to the caplet tablet surface area and obtained a calculated release profile similar to the concave shape. They also proposed another means of using tablet surface area to manipulate release profiles for different tablet dimensions by controlling the dose/surface area ratio. The release profile for a tablet containing 100 mg of metoprolol tartrate and having a surface area of 0.568 sq. in. (366.5 sq. mm) was similar to those of a tablet containing 50 mg and surface area of 0.284 sq. in. (183.2 sq. mm)

Lapidus and Lordi modified Higuchi's square root equation to describe the release of soluble drugs from matrix controlled-release tablets.⁵⁰ This equation indicates that drug release is proportional to surface-area-to-volume ratio available for release. Gao et al. state that application of this equation allows one to predict drug-release rate by using the surface-area-to-volume ratio of the dry tablet.⁵¹ Therefore, we used a model formulation containing 2% promethazine HCl, 20% METHOCEL K4M Premium CR, and the remainder dibasic calcium phosphate dihydrate to examine the effect of surface-area-to-volume ratio on theophylline release. Four different round, flat-faced tablets with diameters of 6.35, 12.7, 15.9, and 18.7 mm were used. The surface-area-to-volume ratio of each tablet was kept constant by varying the total tablet weight. The release profiles are shown in Figure 21. Within a particular tablet shape, in this case a round flat-faced tablet, controlling surface-area-to-volume ratio offers a formulator the flexibility of obtaining similar drug release for different size doses of the same formulation.

Figure 21. Effect of constant tablet surface area/volume on release of promethazine HCl.

(20% METHOCEL K4MP, 2% promethazine HCl, 77.5% lactose, 0.5% magnesium stearate)



Reworkability

During the manufacture of solid dosage forms, some tablets may not meet the final quality specifications. They may exhibit capping and lamination or may be outside hardness or weight variation limits. One method of recovery is to rework or reprocess the drug product. Such reprocessing is described in the Federal Register,⁵² FDA guidelines,⁵³ and the literature.⁵⁴

A study on the reworkability of controlled-release tablets investigated the effects of reprocessing on tablet properties and drug release for tablets containing 50 to 100% reprocessed material.⁵⁵ Three model drug compounds were used: ascorbic acid, chlorpheniramine maleate, and meclizine dihydrochloride.

Reworked tablets exhibited good physical characteristics, with friability values at less than 0.6% weight loss. Drug release of the three model drugs was not significantly affected (<12%) by compression force, type of rework procedure, presence of additional lubricant, or level of reworked material.

Formulations containing HPMC polymers for controlled-release activity physically withstand the mechanical processes involved in a reworking procedure used to manufacture a solid dosage form. This unique characteristic provides additional product formulation and manufacturing flexibility for the formulator.

Formulating for Robustness

A robust formulation is one that is resistant to small changes in raw materials or manufacturing processes. For example, a robust formulation should not exhibit a significant change in drug-release rate when a different lot of a raw material is used, provided the raw material is within approved specifications. Formulators and suppliers can work together to be sure that specifications are realistic both for manufacturing a raw material and developing a drug formulation. Other suggestions for producing a robust formulation include:

- Use appreciable amounts of HPMC polymer (30-40%)
- Investigate three lots of raw materials
- Use experiment design to look for interactions of variables
- Keep the formulation as simple as possible
- Conduct simple screening tests (i.e., disintegration, etc.) to measure the integrity of the tablets



Dissolution Conditions

Apparatus

The USP describes four types of dissolution apparatus primarily used for solid oral dosage forms. Apparatus 1 and Apparatus 2 are the most widely used; Apparatus 3 and Apparatus 4 were added to the USP in 1990 after researchers in Europe found them particularly useful for characterizing controlled-release products.

The rotating basket method was adopted in 1970. Now referred to as Apparatus 1, it uses an approximately 2.54-cm diameter x 3.5-cm stainless-steel, 40-mesh wire basket rotated at a constant speed between 25 and 150 rpm.⁵⁶ Because of problems with some dosage forms occluding the mesh, baskets are available in a wide variety of mesh sizes.

The paddle method, or Apparatus 2, is similar to Apparatus 1 except that a paddle is substituted for the rotating basket.⁵⁶ Dimensions and tolerances of the paddle are critical for ensuring consistent results. In particular, there must not be significant “wobble” while the paddle is rotating. Deaeration is recommended for both Apparatus 1 and 2.

When using Apparatus 2, small variations in the position of the tablet within the dissolution vessel can have a significant effect on the recorded dissolution profile. Therefore, it is important to ensure that the tablet is placed into position as reproducibly as possible. The tablet should be allowed to drop to the bottom of the vessel before the paddle begins to rotate and should be centered if possible. A tablet that sticks to the side of the vessel

will produce a significantly different drug release. If the tablet floats, a “sinker device” of some type should be used. This may be as simple as a few turns of wire or as sophisticated as a gold-coated wire mesh cylinder threaded at one end to allow for introduction of the tablet. The sinker device should allow for swelling of the tablet, should be inert in the dissolution medium, and its use must be appropriately validated.

Apparatus 3, or the reciprocating cylinder apparatus, encloses the dosage form in a transparent cylinder capped on each end with a screen.⁵⁶ The cylinder is reciprocated up and down in medium contained by a glass tube in a water bath. The cylinder can move from one vessel to another, enabling a smooth transition between different pH environments. The advantages of Apparatus 3 reportedly include superior dissolution of formulations containing poorly soluble drugs^{57,58} and lack of sensitivity to dissolved gases in the media.⁵⁹ According to Jorgensen and Bhagwat, the main difficulty with Apparatus 3 is its lack of automation.⁶⁰

The flow-through cell technique (Apparatus 4) pumps the dissolution medium through a flow-through cell immersed in a water bath. Because fresh medium is continuously flowing across the sample, pH changes are easily accomplished, and the method is applicable to poorly soluble drugs.⁶¹ According to Jorgensen and Bhagwat, a drawback to Apparatus 4 is the large volume of dissolution medium required, approximately 60 L for a typical test.⁶⁰





Most controlled-release systems are sensitive to agitation; the greater the agitation the faster the release profile of the drug product. Ideally, a controlled-release product should not be overly sensitive to agitation in order to allow for variable *in vivo* conditions. The rotation of the basket or paddle in Apparatus 1 and 2, the agitation rate of the reciprocating cylinders of Apparatus 3, and the flow rate in Apparatus 4 are typically adjusted to yield at least 80% dissolved by the end of the specified dosing interval as suggested in the current FIP guidelines.⁶²

Media Selection

Ideally, *in vitro* dissolution media and conditions should be as close as possible to actual physiological conditions. Realistically, this objective can be difficult to reach. The time required for a dosage form to release the drug in the body depends on many factors, including food recently consumed by the patient. Usually water or a buffer solution is recommended for the dissolution medium,⁵⁶ although water has some drawbacks as a medium—pH and other properties depend on the water source and may vary during the dissolution run as the dosage form dissolves.⁶³ Testing is typically performed at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

Surfactants can be helpful for dissolution testing of drugs with poor water solubility. Jorgensen and Bhagwat note that good *in vivo-in vitro* correlations (IVIVC) have been obtained with surfactant-containing media, although they mention that the addition of small amounts of antifoaming agents also may be necessary, particularly when using Apparatus 3.⁶⁰

pH and Ionic Strength

Varying the pH and ionic strength of the medium can improve the predictive value of dissolution testing as well as reveal sensitivities presented by the drug and the controlled-release system. Test conditions could conceivably encompass the entire physiological pH range, from pH 1 to 7.5. In practice, the range of media pH will depend on the drug and controlled-release system characteristics and on apparatus limitations. Varying pH is difficult using Apparatus 1 and 2; it is relative easy when using Apparatus 3 and 4.

Deaeration

Deaeration of dissolution media has been the subject of a number of investigations spanning numerous laboratories. Results have been mixed. In general, it is recommended that the effect of media deaeration on drug release be investigated for a given set of dissolution vessels, dissolution type, and dissolution media. If there is no effect, deaeration need not be performed. If there is an effect, the formulator should incorporate it into the prescribed dissolution method.

There are a number of deaeration techniques in use. The most common involve helium sparging, room-temperature vacuum filtration, and elevated temperature ($45\text{--}50^{\circ}\text{C}$) vacuum filtration through a suitable membrane or glass filter (usually $0.45\ \mu\text{m}$).



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