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Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)

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Abstract

The objective of this article is to review the spectrum of mathematical models that have been developed to describe drug release from hydroxypropyl methylcellulose (HPMC)-based pharmaceutical devices. The major advantages of these models are: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, thus facilitating the development of new pharmaceutical products. Simple empirical or semi-empirical models such as the classical Higuchi equation and the so-called power law, as well as more complex mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously are presented, and their advantages and limitations are discussed. Various examples of practical applications to experimental drug release data are given. The choice of the appropriate mathematical model when developing new pharmaceutical products or elucidating drug release mechanisms strongly depends on the desired or required predictive ability and accuracy of the model. In many cases, the use of a simple empirical or semi-empirical model is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories must be applied. The present article is a comprehensive review of the current state of the art of mathematical modeling drug release from HPMC-based delivery systems and discusses the crucial points of the most important theories.

Keywords: Controlled drug delivery; HPMC; Hydrophilic matrices; Hydroxypropyl methylcellulose; Modeling; Release mechanism

Contents

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1. Introduction

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems [1,2]. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [3,4]. Then, the incorporated drug diffuses out of the system.

For the design of new controlled drug delivery systems which are based on HPMC and aimed at providing particular, pre-determined release profiles, it is highly desirable: (i) to know the exact mass transport mechanisms involved in drug release; and (ii) to be able to predict quantitatively the resulting drug release kinetics. The practical benefit of an adequate mathematical model is the possibility to simulate the effect of the design parameters of HPMC-based drug delivery systems on the release profiles [5]. In the ideal case, the required composition (type and amount of drug, polymer and additives) and geometry (size and shape) of the new controlled drug delivery system designed to achieve a certain drug release profile can be predicted theoretically. Thus, the number of necessary experiments can be minimized and the development of new pharmaceutical products significantly facilitated.

Diffusion, swelling and erosion are the most important rate-controlling mechanisms of commercially available controlled release products [6]. Diffusion can be described using Fick's second law [7–9]. There are various ways to apply the respective equations [10]. First of all, the considered geometry is important. Assuming one-dimensional transport in thin films results in rather simple mathematical expressions, but this approach is only valid for flat, planar devices. In the case of HPMC-based drug delivery systems three-dimensional, cylindrical geometries (tablets) are more relevant, but mathematically more difficult to treat. In addition, it is necessary to decide whether to assume constant or non-constant diffusivities. The mathematical treatment of constant diffusivity problems is much simpler, but only valid in the case of polymers that do not significantly swell upon contact with water (e.g., ethylcellulose). For HPMC tablets, the drug diffusion coefficients are strongly dependent on the water content of the system [11]. Here, the assumption of constant diffusivities leads to less realistic mathematical models. Depending on the degree of substitution and chain length of the HPMC type used, polymer dissolution might be observed during drug release. This will complicate the solution of Fick's second law of diffusion, leading to moving boundary conditions. In addition to the physicochemical properties of the polymer also the characteristics of the drug have to be considered. For example, drug dissolution has to be taken into account in case of poorly water-soluble drugs.

Depending on the complexity of the resulting system of mathematical equations describing diffusion, swelling and/or dissolution processes, analytical and/or numerical solutions can be derived. Analytical solutions have the major advantage of being more informative. The involved design and physicochemical parameters still appear in the equations.

In the case of explicit analytical solutions, we can obtain direct relationships between the dependent and independent variables. In the case of implicit analytical solutions, this dependence is not as obvious. However, compared to numerical solutions, it is still much easier to get an idea of the effect of certain independent variables on particular dependent variables. Thus, it is highly desirable to derive explicit analytical solutions. Unfortunately, this is only possible in the case of rather simple forms of the diffusion equations, e.g., assuming constant diffusivities. In general, physically more realistic models are mathematically more complex and very often it is difficult to find analytical solutions of the respective set of equations [12]. Three important methods to derive exact mathematical solutions can

be distinguished: (i) the method of reflection and superposition; (ii) the method of separation of variables; and (iii) the method of the Laplace transform. For a discussion of the advantages and disadvantages of these methods the reader is referred to other literature (e.g., [7,13,14]). Also a description of the principles of numerical analysis is beyond the scope of this review, but excellent textbooks are available (e.g., [7,13–15]). In contrast to analytical solutions, only approximate solutions are derived. The resulting error can be controlled using various different methods. Generally, cumbersome mathematical calculations are required to reduce the approximation error to an acceptable level (e.g. $<0.1\%$). The development of digital computers dramatically decreased the time necessary to perform the calculations, so that nowadays numerical methods have become economic even for routine use.

It is the scope of this article to review the most important mathematical models which have been developed to describe drug release from HPMC-based pharmaceutical systems. Simple and very comprehensive theories are presented and their advantages and limitations are discussed. For a better understanding of the described theories, first the most relevant physicochemical properties of HPMC and the major principles of the overall drug release mechanisms from HPMC-based delivery systems are presented. Due to the substantially high number of variables, no effort was made in this review to present a uniform picture of the different systems of notation defined by the respective authors. The original nomenclatures are used and only some cases are modified by using more common abbreviations to avoid misunderstandings.

2. Physicochemical characterization of HPMC

HPMC is a propylene glycol ether of methylcellulose; its chemical structure is illustrated in Fig. 1. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom. The physicochemical properties of this polymer are strongly affected by: (i) the methoxy group content; (ii) the hydroxypropoxy group content; and (iii) the molecular weight. The USP distinguishes four different types of HPMC, classified according to their

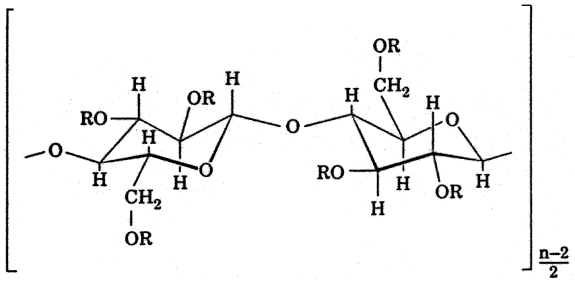

Fig. 1. Chemical structure of HPMC. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom.

relative $-OCH_3$ and $-OCH_2CH(CH_3)OH$ content: HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy-groups, the last two numbers the percentage of hydroxypropoxy-groups, determined after drying at 105°C for 2 h. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 1. In addition, the USP describes a method to determine the apparent viscosity of an aqueous 2% solution of the polymer using a suitable viscosimeter of the Ubbelohde type. This apparent viscosity serves as a measure for the average chain length of the polymer. The measured value must lie within the 80.0 to 120.0% range of the viscosity stated on the label for HPMC types of 100 mPa s or less, and within the 75.0 to 140.0% range for HPMC types of higher viscosity.

Interestingly, Dahl et al. [16] reported broad variations concerning important characteristics of seven batches HPMC 2208 with a labeled viscosity of 15,000 mPa s, provided by two different manufacturers. All samples had similar viscosities, except one batch which was outside the USP specifications. The methoxy-group content was uniformly high and

Table 1
USP specifications for different types of HPMC, classified according to their degree of methoxy- and hydroxypropoxy-substitution

Substitution type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

three batches fell outside the USP limits of 19.0 to 24.0%. The hydroxypropoxy-group content (although within the USP specifications of 4.0 to 12.0%), varied relatively more than the methoxy group content. These variations lead to significant differences concerning the resulting release rate of naproxen from compressed matrix tablets in vitro. The authors concluded that each batch (even from the same manufacturer) should be carefully controlled and that the specifications of the USP and other pharmacopoeas might have to be reinforced.

The glass transition temperature, T_g, of a polymer is an important characteristic constant, in particular with respect to applications in the field of controlled drug delivery. Below the T_g the mobility of the macromolecules is very low. The material is in its glassy state resulting in extremely small diffusion rates [10]. In contrast, above the glass transition temperature the mobility of the polymer chains is markedly increased (rubbery state), leading to much higher mass transfer rates of water and drug. Thus, we must know the T_g of the polymer when modeling drug release from controlled delivery systems. A good summary of work that has been done to determine the T_g of HPMC has been provided by Doelker [17]. He compares the results of various researchers [18–26] and lists values ranging from 154 to 184°C (Table 2). Various techniques have been used to determine the glass transition temperature: differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermomechanical analysis (TMA), torsional braid analysis (TBA) and dynamic mechanical analysis (DMA). Different methods often lead to different T_g-values, and usually only the results achieved with one special method can be compared directly. In addition, the variation of the degree of substitution and the molecular weight plays a role in the observed variance of the T_g. Furthermore, a 57°C-value was reported by Conte et al. [26], which seems to correspond to a low-energy secondary transition. The relevance of this low-temperature transition is yet unknown, but could be of significance in the diffusion of oxygen and water.

Numerous studies have been reported in the literature investigating the drug release kinetics from HPMC-based delivery systems [27–31]. Various techniques have been used to elucidate the physical processes involved. For example, Melia and coworkers [32–35] characterized the water mobility in the gel layer of hydrating HPMC matrices using NMR imaging. It has been shown that there is a diffusivity gradient across this layer and that it is affected by the degree of substitution of the polymer. Also Fyfe and Blazek [36] investigated the HPMC hydrogel formation by NMR spectroscopy pointing out the complications due to the presence of trapped gas [37]. Recently, they studied the release behavior of two model drugs, triflupromazine–HCl and 5-fluorouracil from HPMC tablets [38]. The tablet swelling was restricted to one dimension and distributions of the water and model drugs were obtained by ^{1}H and ^{19}F imaging. The distributions of triflupromazine–HCl and HPMC paralleled each other and the drug was only released at the eroding edge of the tablet where the HPMC concentration dropped below 10%. In contrast, 5-fluorouracil was released much more rapidly from the tablet and appeared to escape by diffusion from regions as high as 30% HPMC. They also developed a system for performing NMR imaging experiments on drug delivery devices within a flow-through dissolution apparatus, USP Apparatus 4 [39].

Ford and coworkers [40–42] used DSC techniques to study the distribution and amount of water in

Table 2
Reported glass transition temperatures for HPMC (adapted from Doelker [17], with permission from Springer–Verlag)

Material	Method	T_g (°C)	Ref.
HPMC Type 2910			
Methocel® E15	TMA	172–175[a]	[18]
Pharmacoat® 606	DSC	177	[19]
Pharmacoat® 606	DSC	155	[20]
Pharmacoat® 606	DSC	180	[21]
Pharmacoat® 606	DTA	169–174	[21]
Pharmacoat® 606	TBA	153.5, 158.5	[21]
Pharmacoat® 606	DSC	155.8	[22]
Pharmacoat® 606	TMA	163.8, 174.4	[22]
Pharmacoat® 603	DMA	160	[23]
Pharmacoat® 606	DMA	170	[23]
Pharmacoat® 615	DMA	175	[23]
Pharmacoat® 606	DMA	154	[24]
HPMC Type 2208			
Methocel® K4M	DSC	184	[25]
Methocel® K4M	DSC	(57)	[26]

[a] The values obtained by TMA in the penetration mode have been reported by the authors as softening temperatures.

HPMC gels. Water loosely bound to the polymer was detected as one or more events appearing at the low-temperature side of the main endotherm for the melting of free water in the DSC scans. The HPMC molecular weight, HPMC substitution type, gel storage time, and added drug influenced the appearance of these melting events [43,44]. Pham and Lee [28] designed a new flow-through cell to provide well-defined hydrodynamic conditions during the experimental studies and to allow precise measurements of dissolution and swelling front positions versus time. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release were found to increase with either higher levels of drug loading or lower viscosity grades of HPMC. Gao and Meury [45] developed an optical image analysis method to examine the dynamic swelling behavior of HPMC-based matrix tablets in situ. In addition to providing precise determinations of the apparent gel layer thickness and the tablet dimensions, this method is also capable of estimating the HPMC concentration profile across the gel layer. They used this technique to characterize the effect of the HPMC/lactose ratio and HPMC viscosity grade (molecular weight) on the swelling of the matrix [46]. For all formulations tested it was found that (i) swelling is anisotropic with a preferential expansion in the axial direction; and (ii) swelling is isotropic with respect to the gel layer thickness and composition in both, axial and radial directions.

The modification of the surface area of HPMC tablets in order to achieve a desired release rate has been studied by Colombo et al. [47,48]. Different surface portions of an HPMC matrix tablet were covered with an impermeable coating. They investigated the drug release mechanisms and studied the influence of the type of coating on the resulting release rate. In order to facilitate the industrial production, the manual film-coating process can be avoided using press-coating techniques [49].

3. Overall drug release mechanism from HPMC-based systems

The overall drug release mechanism from HPMC-based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. The following phenomena are involved:

(i) At the beginning of the process, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. To describe this process adequately, it is important to consider (i) the exact geometry of the device; (ii) in case of cylinders, both, axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient on the matrix swelling ratio [50,51]. In dry systems the diffusion coefficient is very low, whereas in highly swollen gels it is of the same order of magnitude as in pure water. Water acts as a plasticizer and reduces the glass transition temperature of the system. Once the T_g equals the temperature of the system, the polymer chains undergo the transition from the glassy to the rubbery state.

(ii) Due to the imbibition of water HPMC swells, resulting in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system.

(iii) Upon contact with water the drug dissolves and (due to concentration gradients) diffuses out of the device.

(iv) With increasing water content the diffusion coefficient of the drug increases substantially.

(v) In the case of poor water-solubility, dissolved and non-dissolved drug coexist within the polymer matrix. Non-dissolved drug is not available for diffusion.

(vi) In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon drug depletion.

(vii) Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly. In certain cases this phenomenon is negligible, for example if all drug has already been released before polymer dissolution becomes important.

As a result of conditions (i), (ii), (iv), (vi), and (vii) the mathematical description of the diffusional processes requires strongly time-dependent terms.

From the aforementioned possible phenomena it is obvious that there is no universal drug release mechanism that is valid for all kinds of HPMC-based systems. In contrast, there are many devices that

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