HPMC-Matrices for Controlled Drug Delivery: A New Model Combining Diffusion, Swelling, and Dissolution Mechanisms and Predicting the Release Kinetics

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Purpose. The purpose of this study was to investigate the drug release mechanisms from hydroxypropyl methylcellulose (HPMC)-matrices, and to develop a new model for quantitative predictions of controlled drug delivery.

Methods. The dissolved mass of pure HPMC-matrices and the drug release rate from propanolol HCl-loaded HPMC-matrices were determined experimentally. Based on Fick’s second law of diffusion for cylinders, the transport of water and drug were modeled considering (i) both radial and axial diffusion, (ii) concentration-dependent drug diffusivities, (iii) matrix swelling and (iv) HPMC dissolution.

Results. Good agreement between theory and experiment (dissolved mass and drug release studies) was obtained, proving the validity of the presented model. The water and drug diffusivities are strongly dependent on the matrix swelling ratio. Diffusion, swelling, and dissolution are the governing mechanisms involved in the overall drug release process.

Conclusions. The practical benefit of the presented model is to identify the required shape and dimensions of drug-loaded HPMC-matrices in order to achieve desired release profiles, thus facilitating the development of new controlled drug delivery products. This will be demonstrated in a future study.

KEY WORDS: controlled release; diffusion; hydroxypropyl methylcellulose (HPMC); modeling; polymer dissolution; swelling.

INTRODUCTION

HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems (1). The transport phenomena involved in drug release from HPMC matrices are complex, because the micro- and macrostructure of HPMC exposed to water is strongly time-dependent. Upon contact with gastrointestinal fluid, HPMC swells significantly and finally dissolves. Numerous studies have been reported in the literature investigating the transport mechanisms and trying to predict the resulting drug release kinetics quantitatively.

Narasimhan and Peppas (2–4) developed mathematical models describing polymer dissolution quantitatively based on the theory of macromolecular disentanglement and chain retraction. They showed that the dissolution can be either disentanglement or diffusion controlled depending on the polymer molecular weight and the thickness of the diffusion boundary layer. Models for rubbery and glassy polymers were derived and the resulting dissolution kinetics and drug release rates were calculated.

Gao et al. (5–6) used a pulsed-field-gradient spin-echo NMR technique to determine the diffusivities in HPMC-gels. They found the drug and water diffusion coefficients to be exponentially dependent on the concentration of excipients, such as HPMC and lactose. These are excipients that are known as viscosity-inducing agents. In addition, they developed a novel optical imaging method to examine the dynamic swelling behavior of HPMC-based matrices in situ. The results show that the polymer concentration profiles and the gel layer thicknesses develop equally in both radial and axial directions, whereas the expansion of the matrix in the axial direction is more drastic than in the radial direction.

Pham and Lee (7) designed a new flow-through cell to provide well-defined hydrodynamic conditions during the experimental studies and to allow precise measurement 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. Rajabi-Siahboomi et al. (8) 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. Polymer concentration profiles within cylindrical HPMC matrices were also determined by Fyfe and Blazeck (9) using NMR spectroscopy and NMR imaging techniques. Ju et al. (10–12) developed a comprehensive mathematical model distinguishing between the “macromolecular overlap concentration,” above which polymer chain entanglement starts, and the “polymer disentanglement concentration,” below which polymer chains detach from the matrix and diffuse through the diffusion layer into the bulk solution. It is expected that the “polymer disentanglement concentration” is greater than the “macromolecular overlap concentration” because the extent of chain entanglement at the “macromolecular overlap concentration” is almost zero since it is the on-set concentration for entanglement. The extent of chain entanglement at the “polymer disentanglement concentration” is much higher. In addition,
they proposed an equation to calculate the “polymer disentanglement concentration” for HPMC as a function of molecular weight.

However, most of the published models make important assumptions. For example, they neglect polymer swelling (13), neglect polymer dissolution (14), or they reduce the mathematical analysis to transport in only radial direction, ignoring axial transport (11). Yet, no model has been proposed that takes into account diffusion (concentration-dependent, in radial and axial directions, considering water and drug), swelling (three-dimensional, with subsequent volume, concentration, and matrix composition changes) and polymer dissolution simultaneously. It was the aim of this study to develop such a model to get further insight into the transport mechanisms and to accurately predict the resulting drug release kinetics from HPMC-matrices.

EXPERIMENTAL SECTION

Materials

The following chemicals were obtained from commercial suppliers and used as received: propranolol HCl (Sigma Chemical Co., St. Louis, MO), hydroxypropyl methylcellulose (Methocel® K15M Premium Grade) (Colorcon, Nordmann Rassmann GmbH & Co., Hamburg, Germany).

Methods

Pure HPMC-tablets (200 mg, 13 mm diameter) were prepared by compressing the polymer powder manually (Specac Hydraulic Press P1N 25.011, Specac Limited, Kent, UK; compaction force = 50 kN, holding time = 15 s). Propranolol HCl-containing HPMC-matrices (5% w/w drug loading, 5 mm diameter) were prepared by compressing a homogeneous mixture of the drug and polymer powders using a tableting machine (Korsch, EK 0, Berlin, Germany).

The USP XXIII rotating paddle method [37°C, 50 rpm, 900 mL 0.1 M phosphate buffer (pH 7.4) USP XXIII] was used to study the dissolution of pure HPMC-tablets and the drug release from propranolol HCl-containing HPMC-matrices. At predetermined time intervals, pure HPMC-tablets were withdrawn from the medium and oven-dried at 105°C to constant mass. For the drug release studies, 2 mL samples (which were replaced with fresh medium) were withdrawn at predetermined time intervals, filtered and assayed spectrophotometrically (λ = 290 nm).

MATHEMATICAL ANALYSIS

Release Mechanism

The proposed new model takes into account a series of transport phenomena occurring during drug release.

(i) At the beginning of the release process, there are steep water concentration gradients at the polymer/water interface, resulting in water imbibition into the matrix. To describe this process adequately, it is important to consider (a) the cylindrical geometry of the device, (b) both axial and radial directions of the mass transport, and (c) the significant dependence of the water diffusivity on the matrix swelling ratio. 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 (self-diffusion coefficient).

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

(iii) With increasing water content the drug diffusivity increases and the drug diffuses out of the device.

(iv) The polymer itself dissolves, resulting in time-variant matrix composition, matrix dimensions and diffusion pathways.

All these processes have to be taken into account simultaneously.

Model Assumptions

The new model is based on a series of assumptions:

(i) Matrix swelling is ideal throughout the device: The sum of the volumes of water, drug and polymer in the system are always equal to the total volume of the system; there is no volume contraction upon mixing.

(ii) Perfect sink conditions are maintained.

(iii) Water imbibing in axial/radial direction leads to a volume increase in axial/radial direction that is proportional to the relative surface area in this direction.

(iv) The concentration-dependence of the diffusivities of water and drug is time-invariant.

(v) The drug is dissolved instantaneously in the release medium. However, the model can be modified (considering the presence of solid and dissolved drug within the system) to be applicable to poorly water-soluble drugs, too.

Diffusion

The mathematical description of water and drug diffusion is based on Fick’s second law for cylindrical devices, taking into account axial and radial mass transfer with concentration-dependent diffusivities (15):

\[
\frac{\partial c_k}{\partial t} = \frac{1}{r} \left( \frac{\partial}{\partial r} \left( D_k \frac{\partial c_k}{\partial r} \right) + \frac{\partial}{\partial \theta} \left( \frac{D_k}{r} \frac{\partial c_k}{\partial \theta} \right) \right) + \frac{\partial}{\partial z} \left( r D_k \frac{\partial c_k}{\partial z} \right)
\]

(1)

Here, \( c_k \) and \( D_k \) are the concentration and diffusion coefficient of the diffusing species (\( k = 1 \): water; \( k = 2 \): drug), respectively, \( r \) denotes the radial coordinate, \( z \) the axial coordinate, \( \theta \) the angle perpendicular to both axis [Fig. 1(a)], and \( t \) represents time.

As there is no concentration gradient of any component with respect to \( \theta \), this equation can be transformed into:

\[
\frac{\partial c_k}{\partial t} = \frac{\partial}{\partial r} \left( D_k \frac{\partial c_k}{\partial r} \right) + \frac{\partial}{\partial z} \left( r D_k \frac{\partial c_k}{\partial z} \right)
\]

(2)

According to the free volume theory of diffusion, a Fujita-type (16) exponential dependence of the diffusivities of water and drug, \( D_1 \) and \( D_2 \), is considered: