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Modeling of drug release from partially coated matrices made of a high viscosity HPMC

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Abstract

A mathematical model able to describe the release kinetics of two model drugs (Diprophylline and Theophylline) from partially coated hydroxypropylmethylcellulose (HPMC, Methocel® K4M) matrices is presented. As solvent interaction with the system and drug release can only take place in one direction, the physical frame to be modeled turns out simpler. The model was developed starting from the established equation describing drug dissolution and taking into account the resistance to drug release given by the presence of a growing gel barrier around a matrix system.

The model fits the release data obtained from both series of hydrophilic matrices containing increasing amounts (from 0.2 to 0.8 mass ratio) of the two xanthine derivatives. Differences were found in drug release rate according to the different solubility of the actives. Interestingly, however, there is no further reduction in the outer gel layer permeability when the polymer mass fraction exceeds a certain value, with both Theophylline and Diprophylline systems. Results confirm the importance of the fraction of the glassy/rubbery interface held by the active substance in defining the release rate from hydrophilic systems.

Keywords: Modeling; Hydroxypropylmethylcellulose (HPMC); Hydrophilic matrix; Release mechanism

1. Introduction

Hydrophilic polymer-based modified-release dosage forms are very popular for their flexibility with respect to drug release kinetics. Matrices, in particular, are widely proposed as they can be prepared by means of relatively easy, well known and inexpensive processes such as casting, extrusion and tableting (Ranga Rao and Padmalatha Devi, 1988).

When hydrophilic matrices interact with aqueous media (water, buffers, physiological fluids, etc.), both the polymer hydration (glassy/rubbery transition) and the dissolving of soluble components take place. Dissolution of the drug at the tablet surface causes a burst effect in the release profile of the system. This is more or less pronounced depending on the drug solubility and the polymer hydration rate (Huang and Brazel, 2001). The release kinetics working after the initial burst is heavily governed by the gel layer thickness,

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which in turn depends on the relative position of the eroding front (separating the release environment from the gel and generally moving outwards) and the swelling front (separating the dry glassy tablet core from the gel layer and moving inwards) (Colombo, 1993). Additionally, in the case of sparingly soluble drugs, a third front, the diffusion front, can appear between the outer portion of the gel layer, where the drug is completely dissolved, and the inner one, where undissolved drug particles still exist (Lee and Kim, 1991; Tahara et al., 1995; Colombo et al., 1999a).

Delivery of drug from hydrophilic matrices is known to be affected by many factors such as the polymer swelling and erosion behavior, the drug dissolution characteristics, the drug/polymer ratio and the tablet shape (Harland et al., 1988; Conte et al., 1988; Colombo et al., 1999b). Using partially coated matrices made of a high viscosity hydroxypropylmethylcellulose (HPMC, Methocel® K4M) a new parameter was previously defined by our group, crucial for the interpretation of drug release kinetics from these kind of systems (Lombardi et al., 1998; Zema et al., 1998). It deals with the surface area up to the drug at the swelling front, i.e. the fraction of the glassy/rubbery interface available for the active substance to come in contact with the solvent. This parameter depends on the initial characteristics of the system (weight, shape, formulation, true density of the components) and varies continuously during the release process because of the front movements (dimensional changes of the swollen matrix). Because an impermeable coating is applied on all the tablet surfaces except one base, glassy matrix layers can be considered to subsequently interact with the solvent. Every layer can be regarded as a slab, uniformly swelling. Here, solvent penetration and drug release take place only in one direction (Colombo et al., 1990, 1996). As the swelling front area and composition remain almost constant, the physical frame to be modeled is less complex.

In the present work a new mathematical model of semi-empirical nature, but founded on reasonable assumptions is therefore presented, leading to an analytical solution and able to describe drug release from partially coated HPMC tablets of different composition.

2. Modeling

The need for further studies on drug release from HPMC-based drug delivery systems, to provide tools for the selection of the best formulation, resulted in many attempts to model the complex phenomena. These results were summarized in a recent review (Siepmann and Peppas, 2001). Most advanced and very powerful models are based on the extension of the mass conservation law, originally born for continuous media, to a heterogeneous medium such as a tablet (Zhou and Wu, 1997; Wu and Zhou, 1998; Siepmann et al., 1999a,b; Siepmann and Peppas, 2000a). Looking for manageable expressions for the correlation and/or analysis of release data, some authors decided on the simplification of the physical frame to be modeled (Lee, 1980; Harland et al., 1988; Ford et al., 1991; Peppas and Colombo, 1997).

Taking the whole background into proper account, we started from the main idea of generalizing the classical equation describing the dissolution of a solid drug:

$$\frac{dC}{dt} = -\frac{DA}{Vh}(C_s - C) \quad (1)$$

where t is time, C and C_s are drug concentration and solubility in the dissolution medium, respectively, D is the diffusion coefficient in the dissolution medium, A is the surface area at the solid/liquid interface, V is the medium volume and h is the stagnant layer thickness. D/h can be indicated as the dissolution rate constant K. Bearing in mind that the global diffusional resistance of a multi-layered membrane is given by the sum of the resistance of each layer (Flynn et al., 1974), Eq. (1) can be modified to describe drug release from a hydrophilic matrix by properly incorporating the diffusion step of the drug through the gel layer:

$$\frac{dC}{dt} = -\frac{\varphi_d A}{V}\frac{C_s - C}{(1/K) + R} \quad (2)$$

where φ_d is the drug volume fraction and R is the gel layer resistance ($1/R$ can also be defined as gel permeability, P). The global resistance to drug release is given by the sum of the dissolution phenomenon resistance ($1/K$) and the resistance to drug diffusion through the gel layer (R). Since the solid/liquid interface in a swollen system matches the swelling front, $\varphi_d A$ represents the above mentioned parameter surface area

up to the drug at the swelling front (Lombardi et al., 1998). Eq. (2) also holds for drug release in non sink conditions due to the presence of the $(C_s - C)$ term and has the advantage of degenerating into Eq. (1) for tablets made of drug only ($\varphi_d = 1$; $R = 0$). Additionally, this approach becomes particularly simple when dealing with the partially coated systems we used due to the fact that the swelling front area A can be considered practically constant.

Drug diffusion rate through a gel layer can reasonably be correlated to the layer thickness, so on the basis of experimental data regarding the temporary evolution of the gel thickness (Cappello et al., 1994; Wan et al., 1995; Colombo et al., 1999a) we defined:

$$R = B(1 - \exp^{-bt}) \tag{3}$$

where B represents the asymptotic value of R and b rules the kinetics of R variation. Both B and b are model parameters to be determined by data fitting.

Due to its empirical nature, Eq. (3) can properly account for other phenomena contributing to the diffusional resistance such as the influence of radial transport. The drug is released prevalently in the axial direction (one-way diffusion) but not exclusively because of the particular shape the gel layer acquires with time (mushroom shaped gel layer).

Finally, we introduced a third parameter f (whose value ranges between 0 and 1) to account for the lower ability of the drug to dissolve in a swollen system compared to pure solvent (Levich, 1962):

$$\frac{dC}{dt} = -\frac{\varphi_d A}{V} \frac{C_s - C}{(1/fK) + B(1 - \exp^{-bt})} \tag{4}$$

Considering $M = CV$, the solution of the resulting Eq. (4), performed by usual techniques (Demidovic, 1975), leads to:

$$M = VC_s(1 - (\exp^{bt}(1 + BfK(1 - \exp^{-bt})))^{-A\varphi_d/bV(B+1/(fK))}) \tag{5}$$

where M is the amount of drug released by time t. It should be noted that Eq. (5) holds as long as a glassy portion of the matrix exists. This means, for our systems, that it holds until the swelling front reaches the coating on the bottom of the tablet.

3. Experimental

3.1. Materials

Model drugs: Diprophylline (Rhone-Poulenc Chimica, Milan, Italy), M_w 254.2, water solubility 212.0 mg/ml at 37 °C, true density 1.51 g/cm^3; Theophylline monohydrated (Boehringer Ingelheim, Firenze, Italy), M_w 198.2, water solubility 11.2 mg/ml at 37 °C, true density 1.36 g/cm^3. Hydrophilic polymer: hydroxypropylmethylcellulose, Methocel® K4M (Colorcon, Orpington, UK), true density 1.20 g/cm^3. Coating polymer: cellulose acetate propionate, CAP482 (Eastman-Kodak, Kingsport, UK).

3.2. Methods

3.2.1. Matrices preparation

Drug and polymer in different ratios were mixed in Turbula apparatus (Bachofen AG Maschinenfabrik, Basel, CH) for 10 min. In Table 1 formulations are reported in terms of mass fractions. Mixtures were compressed (direct compression) with a single die tabletting machine (Korsch, EKO, Berlin, D) fitted with flat-faced punches. The obtained cylindrical tablets (diameter: 10 mm; height: ≈3 mm; weight: 300 mg) were coated on all surfaces except one base by immersion in CAP 15% acetone solution.

3.2.2. Release test

Release tests (six replicates) were performed in distilled water (37 °C, $V = 900$ cm^3) using USP 26 apparatus II with the paddle rotating at 100 rpm. The

Table 1
Tablet formulations in terms of mass fractions (X): d, drug; p, polymer; D, Diprophylline; T, Theophylline

Code	X_d	X_p
D_{28}	0.2	0.8
D_{46}	0.4	0.6
D_{64}	0.6	0.4
D_{73}	0.7	0.3
D_{82}	0.8	0.2
T_{28}	0.2	0.8
T_{46}	0.4	0.6
T_{64}	0.6	0.4
T_{73}	0.7	0.3
T_{82}	0.8	0.2

amount of drug released was determined by UV spectrophotometer (Spectracomp 602, Advanced Products srl, Milan, Italy) set at 270 and 273 nm for the determination of Theophylline and Diprophylline, respectively.

3.2.3. Intrinsic dissolution test

Compacts of pure drug were prepared by means of a hydraulic press (applied pressure: 1.5 tons, diameter: 10 mm) and coated with CAP as previously described. Dissolution tests were performed in the USP 26 apparatus II under the same experimental conditions used for the release test. The amount of drug dissolved (mg/cm^2) is plotted as a function of time; the slope of the linear curve obtained by the best fitting of the data (within 5 min of dissolution) represents drug intrinsic dissolution rate (mg/cm^2 min).

4. Results and discussion

Release data were obtained from partially coated HPMC matrices containing increasing amounts of active substance (0.2–0.8 mass fraction X_d) as reported in Table 1. By using xanthine derivatives, Diprophylline (D) and Theophylline (T), as model drugs, differences owing to drug molecular size should be minimized.

Preliminarily, the values of some of the model parameters were determined. The drug dissolution rate constant is strongly dependent on the hydrodynamic conditions (Levich, 1962). Therefore, K values introduced in the model were calculated from the intrinsic dissolution rate data determined under the same experimental conditions in which release tests were performed. Theophylline is less soluble but its dissolution rate constant (K_T) results three times higher than that of Diprophylline (K_D); $K_T = 0.210$ and $K_D = 0.067$ cm/min. This result suggests easier diffusion through the stagnant layer for Theophylline. In a HPMC matrix system, the dissolution of the incorporated drug is also influenced by the penetration of the medium through a growing gel layer. In this way the K value should be corrected by an f parameter to reflect this condition. Eq. (5) was first fitted to the experimental data to determine the value of the parameter f; a second fitting was then performed by setting the value of f to the mean of the values previously found, $f_T = 0.24 \pm 0.05$ and $f_D = 0.10 \pm 0.03$. The

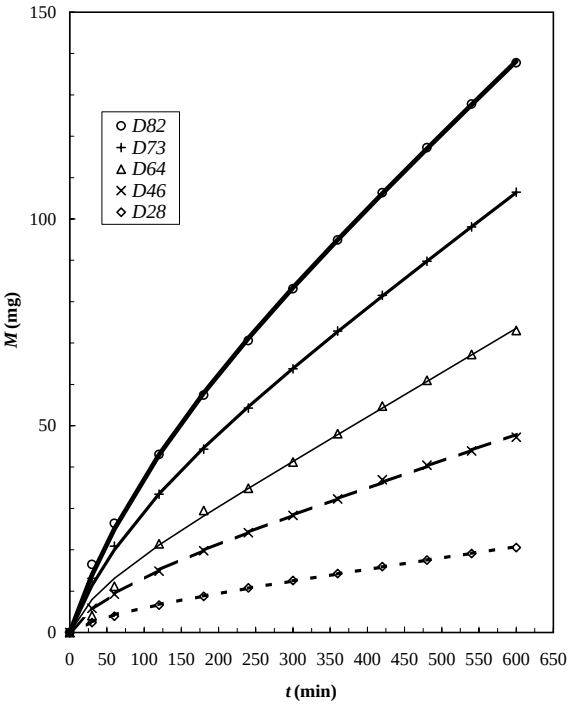

Fig. 1. Comparison between model best fitting (lines) and experimental Diprophylline release data (symbols). Percent standard deviation of data ≤ 12.

presence of a swollen gel barrier affects to a greater extent the Diprophylline dissolution performance, because of its higher solubility. This results in a 10-fold increase of the difference between the dissolution rate constants of the two model drugs ($fK_D = 4.2 \times 10^{-3}$ and $fK_T = 45.1 \times 10^{-3}$ cm/min).

Figs. 1 and 2 show model best fitting (lines) to the amount of drug released (symbols) from the binary matrices containing Diprophylline (D_{28}, D_{46}, D_{64}, D_{73} and D_{82}) and Theophylline (T_{28}, T_{46}, T_{64}, T_{73} and T_{82}), respectively. The accuracy of fit was evaluated by means of the coefficient of determination r^2 and the F analysis. The values of the model's parameters (B and b) and of the statistical parameters r^2 and F obtained are reported in Table 2.

Whatever the drug/polymer ratio considered, a good agreement between model best fitting and experimental data was found. This implies that the model is able to accurately describe both the initial burst phase of the release profiles and the following almost linear trend. It is clearly evident that Eq. (5) properly

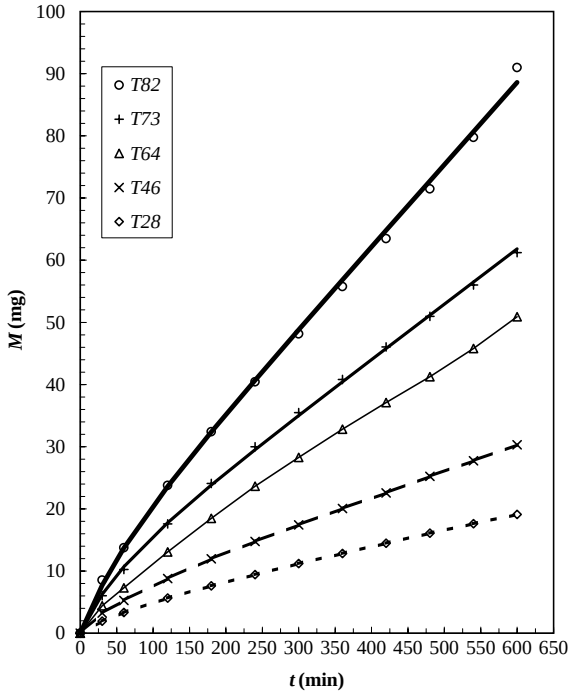

Fig. 2. Comparison between model best fitting (lines) and experimental Theophylline release data (symbols). Percent standard deviation of data ≤ 12.

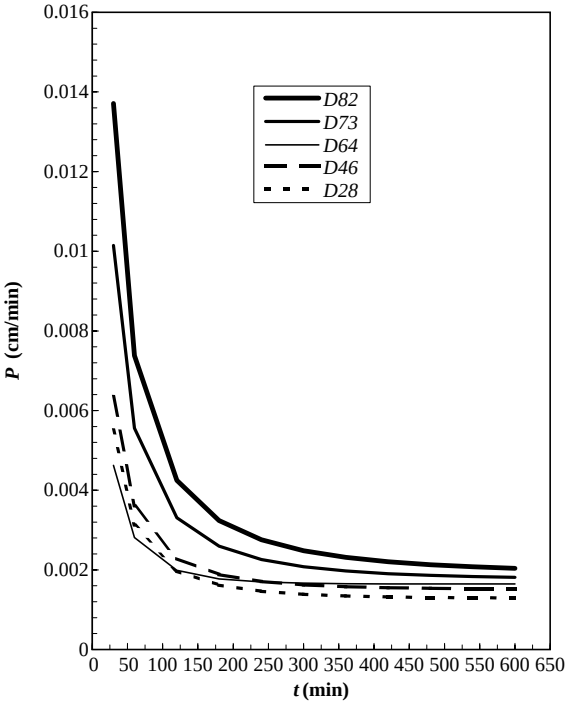

Fig. 3. Calculated gel permeability P relative to Diprophylline-containing matrices.

takes into account all the phenomena governing drug release from this kind of delivery systems. Empirical assumptions and simplifications introduced in the model proved effective.

The fitting results were plotted in terms of gel permeability, $P = 1/R$, calculated according to Eq. (3), versus time; in Figs. 3 and 4 P profiles relevant to matrices containing Diprophylline and Theophylline, respectively, are reported.

Table 2
Values of the free fitting parameters (±S.D.) and values of the determination coefficient (r^2) and F-statistic (F)

Code	B (min/cm)	b (1/min)	r^2	F
D_{28}	776 ± 19	$(8.9 \pm 0.5) \times 10^{-3}$	0.999	20299
D_{46}	659 ± 22	$(9.1 \pm 0.6) \times 10^{-3}$	0.999	22657
D_{64}	608 ± 19	$(14.6 \pm 1.6) \times 10^{-3}$	0.998	7952
D_{73}	563 ± 21	$(6.4 \pm 0.5) \times 10^{-3}$	0.999	19943
D_{82}	514 ± 25	$(5.1 \pm 0.4) \times 10^{-3}$	0.999	26588
T_{28}	40 ± 1	$(7.0 \pm 0.4) \times 10^{-3}$	0.999	60113
T_{46}	51 ± 1	$(13.5 \pm 0.5) \times 10^{-3}$	0.999	22112
T_{64}	42 ± 1	$(20.0 \pm 2.0) \times 10^{-3}$	0.999	27183
T_{73}	44 ± 1	$(11.6 \pm 0.7) \times 10^{-3}$	0.999	23666
T_{82}	29 ± 1	$(12.3 \pm 1.8) \times 10^{-3}$	0.999	11137

Compared to Diprophylline-containing systems with the same polymer content, gel permeability to Theophylline always turns out much higher (up to over 20 times) than was expected on the basis of the ability of the two model drugs to diffuse, i.e. calculated dissolution rate constant K and diffusion coefficient in water reported in the literature (Harland et al., 1988; Grassi et al., 2001). In the matrices containing Theophylline, the drug with the higher dissolution rate constant, the swelling and diffusion fronts probably move with different rates, the latter siting at an increasing distance from the first, to the detriment of the dissolved drug gel region that becomes thinner (Bettini et al., 2001). Accordingly, as many solid drug particles remain between the two fronts, a perfectly connected structure cannot be formed, thus compromising the overall resistance to erosion. Macroscopically, the weakening of the gel structure and length reduction of the homogeneous

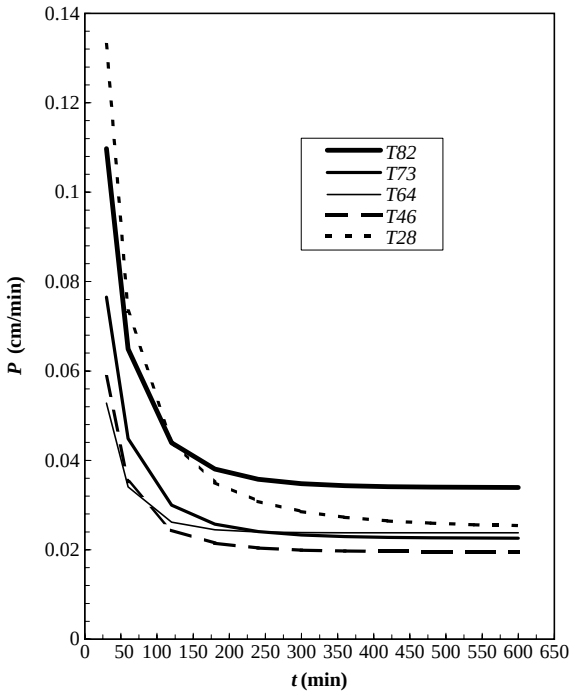

Fig. 4. Calculated gel permeability P relative to Theophylline-containing matrices.

zone through which diffusion has to take place, both reflect in an increased gel permeability.

The P trend for D_{28}, D_{46} and D_{64} matrices is very similar; calculated gel permeability results higher for the remaining formulations, progressively decreasing from D_{82} to D_{73} (Fig. 3). Analogously, T_{46}, T_{64} and also T_{73} after the burst phase, give rise to very similar P profiles, while the matrix with less polymer (T_{82}) generates a more permeable gel layer (Fig. 4). On the contrary, a different behavior was observed for the system with the highest content of polymer, in accordance with data recently reported by Siepmann and Peppas (2000b); T_{28} P profile, in fact, starts highest, then advancing close to T_{82} profile.

P is a function of gel thickness, which in turn is generally described to depend on the relative amount of polymer. Assuming that polymer reaches instantaneously its equilibrium degree of swelling upon contact with the release environment, P should decrease when the polymer fraction X_p rises. Nevertheless, gel thickness is also influenced by the tendency of the rubbery system to erode (Ju et al., 1997). The solvent concentration in the gel layer of a swollen matrix necessarily follows a gradient from a fluid free zone (tablet glassy portion) to a completely swollen zone where the polymeric chain disentanglement gives rise to polymer dissolution (erosion front). While the gel thickness increases, the eroding surface area extends. Gel permeability therefore results from the combination of the phenomena governing gel growth and gel erosion with their different kinetics. On the basis of our results we can say that when X_p exceeds a threshold value the excess of polymer does not seem to contribute anymore to decrease P. Interestingly, for these systems the only parameter changing in the model is $\varphi_d A$, so the surface area up to the drug at the swelling front becomes the factor actually governing the release kinetics. In fact, maintaining the model parameters B and b determined by the D_{28} data fitting, i.e. assuming for all the systems same evolution of the gel layer, the variation of $\varphi_d A$ leads to model predictions (lines)

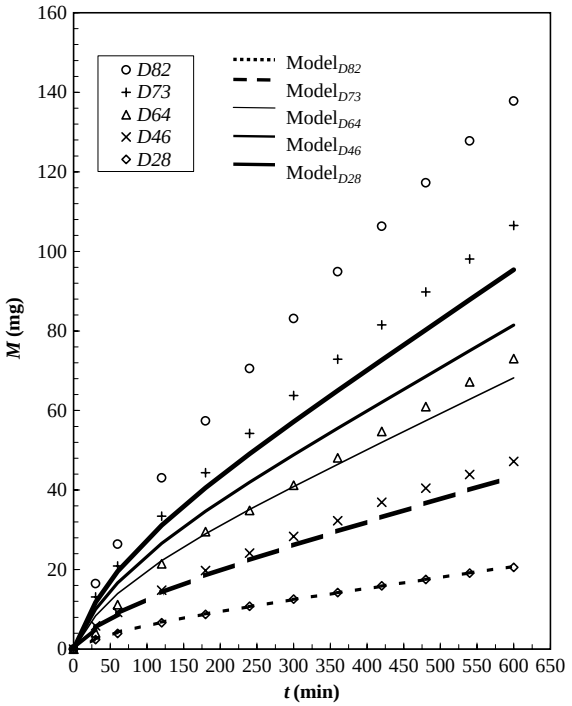

Fig. 5. Comparison between experimental Diprophylline release data (symbols) from D_{28}, D_{46}, D_{64}, D_{73}, D_{82} matrices and model prediction (lines) obtained by maintaining the parameters B and b of the best fitting on the D_{28} release data. Percent standard deviation of data ≤ 12.

able to well describe the experimental data (symbols) of D_{46}, D_{64} and, obviously, D_{28} formulations, not of D_{73} and D_{82} formulations (Fig. 5).

In the case of the less soluble drug Theophylline, the gel layer composition and structure should be taken into account. The dependence of gel permeability on the thickness has already been stated as well as the fact that the presence of solid particles can reduce the entanglement of polymeric chains thus lowering gel resistance (Adler et al., 1999). Nevertheless, the permeability of the Theophylline-containing systems is also affected by the presence of an excess of drug remaining undissolved, unable to be delivered by diffusion, in the homogeneous gel zone located between the swelling and the dissolution front. Only in the case of T_{28} formulation, containing the relatively smaller amount of drug, the main part of Theophylline, while approaching the swelling front, is likely to promptly dissolve and effectively diffuse throughout the gel. This is the reason why the fitting parameters obtained from release data of the formulation with the highest content of polymer determine a *P* profile higher than for all the other systems.

5. Conclusions

In this work a semi-empirical mathematical model is presented able to describe drug release from hydrophilic matrices made of a high viscosity HPMC. The model has been developed starting from release data obtained from particularly simple systems with practically constant swelling front area. However, it could still be valid when dealing with uncoated matrices showing temporal variations in the swelling front area.

The model demonstrates to be able to accurately describe the release profiles of Diprophylline and Theophylline from partially coated matrices containing increasing amounts of Methocel® K4M, thus supporting the validity of the hypothesis made to derive it. By plotting the fitting results in terms of gel permeability, some issues were focused: (i) resistance to both dissolution and diffusion processes due to the presence of a gel layer results higher for the more soluble drug; (ii) the physical frame and release performance of the matrices containing the less soluble drug are probably affected by the presence of undissolved particles within the gel; and (iii) within a range of hydrophilic polymer content, release kinetics seems to mainly be affected by the drug volume fraction (φ_d) rather then the amount of HPMC. This result, in particular, has a potential relevance on manufacturing of prolonged-release matrix systems as part of the polymer could be substituted with a different material showing improved technological properties without affecting drug release kinetics.

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References

Adler, J., Jayan, A., Melia, C.D., 1999. A method for quantifying differential expansion within hydrating hydrophilic matrices by tracking embedded fluorescent microspheres. J. Pharm. Sci. 88, 371–377.

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A., Colombo, P., 2001. Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. J. Control. Release 70, 383–391.

Cappello, B., Del Nobile, M.A., La Rotonda, M.I., Mensitieri, G., Miro, A., Nicolais, L., 1994. Water soluble drug delivery systems based on a non-biological bioadhesive polymeric system. Il Farmaco 49, 809–818.

Colombo, P., 1993. Swelling-controlled release in hydrogel matrices for oral route. Adv. Drug Dev. Rev. 11, 37–57.

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangalli, M.E., Peppas, N.A., La Manna, A., 1990. Drug release modulation by physical restrictions of matrix swelling. Int. J. Pharm. 63, 43–48.

Colombo, P., Bettini, R., Santi, P., De Ascentiis, A., Peppas, N.A., 1996. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. J. Control. Release 39, 231–237.

Colombo, P., Bettini, R., Peppas, N.A., 1999a. Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. J. Control. Release 61, 83–91.

Colombo, P., Bettini, R., Castellani, P.L., Santi, P., Peppas, N.A., 1999b. Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropylmethyl cellulose matrices containing a soluble drug. Eur. J. Pharm. Sci. 9, 33–40.

Conte, U., Colombo, P., Gazzaniga, A., Sangalli, M.E., La Manna, A., 1988. Swelling-activated drug delivery system. Biomaterials 9, 489–493.

Demidovic, B., 1975. Esercizi e Problemi di Analisi Matematica. Editori Riuniti, Rome, Italy.

Flynn, G.L., Yalkowsky, S.H., Roseman, T.J., 1974. Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci. 63, 479–509.

Ford, J.L., Mitchell, K., Rowe, P., Armstrong, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1991. Mathematical modelling of drug release from hydroxypropylmethyl cellulose matrices: effect of temperature. Int. J. Pharm. 71, 95–104.

Grassi, M., Colombo, I., Lapasin, R., 2001. Experimental determination of the theophylline diffusion coefficient in swollen sodium-alginate membranes. J. Control. Release 76, 93–105.

Harland, R.S., Gazzaniga, A., Sangalli, M.E., Colombo, P., Peppas, N.A., 1988. Drug/polymer matrix swelling and dissolution. Pharm. Res. 5, 488–494.

Huang, X., Brazel, C.S., 2001. On the importance and mechanisms of burst release in controlled drug delivery—a review. J. Control. Release 73, 121–136.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1997. Diffusion coefficients of polymer chains in the diffusion layer adjacent to a swollen hydrophilic matrix. J. Pharm. Sci. 86, 1293–1298.

Lee, P.I., 1980. Diffusional release of a solute from a polymeric matrix: approximate analytical solutions. J. Membr. Sci. 7, 255–275.

Lee, I.P., Kim, C.J., 1991. Probing the mechanism of drug release from hydrogels. J. Control. Release 16, 229–236.

Levich, V.G., 1962. Physicochemical Hydrodynamics. Prentice-Hall, Englewood Cliffs, NJ, pp. 39–73.

Lombardi, C., Zema, L., Sangalli, M.E., Maroni, A., Giordano, F., Gazzaniga, A., 1998. Influence of drug/polymer ratio on the release from heterogeneous high viscosity HPMC matrices. Proc. World Meet. APGI/APV 2, 335–336.

Peppas, N.A., Colombo, P., 1997. Analysis of drug behavior from swellable polymer carriers using the dimensionality index. J. Control. Release 45, 35–40.

Ranga Rao, K.V., Padmalatha Devi, K., 1988. Swelling-controlled release systems: recent developments and applications. Int. J. Pharm. 48, 1–13.

Siepmann, J., Peppas, N.A., 2000a. Hydrophilic matrices for controlled drug delivery: an improved mathematical model to predict the resulting drug release kinetics (the 'sequential layer model'). Pharm. Res. 17, 1290–1298.

Siepmann, J., Peppas, N.A., 2000b. A new mathematical model to predict drug release from hydrophilic matrices: the "sequential layers" model. Proc. Int. Symp. Control. Release Bioact. Mater. 27, 55–56.

Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropylmethyl cellulose (HPMC). Adv. Drug Del. Rev. 48, 139–157.

Siepmann, J., Kranz, H., Bodmeier, R., Peppas, N.A., 1999a. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics. Pharm. Res. 16, 1748–1756.

Siepmann, J., Podual, K., Peppas, N.A., Bodmeier, R., 1999b. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. J. Pharm. Sci. 88, 65–72.

Tahara, K., Yamamoto, K., Nishihata, T., 1995. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropylmethyl cellulose 2910. J. Control. Release 35, 59–66.

Wan, L.S.C., Heng, P.W.S., Wong, L.F., 1995. Matrix swelling: a simple model describing extent of swelling HPMC matrices. Int. J. Pharm. 116, 159–168.

Wu, X.Y., Zhou, Y., 1998. Finite element analysis of diffusional drug release from complex matrix systems. II. Factors influencing release kinetics. J. Control. Release 51, 57–71.

Zema, L., Sangalli, M.E., Pavesi, P., Vecchio, C., Giordano, F., Gazzaniga, A., 1998. Influence of formulation variables on drug release from hydrophilic matrices: effect of the partial replacement of the polymer with an inert excipient. Proc. World Meet. APGI/APV 2, 333–334.

Zhou, Y., Wu, X.Y., 1997. Finite element analysis of diffusional drug release from complex matrix systems. I. Complex geometries and composite structures. J. Control. Release 49, 277–288.