ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 49 (2000) 177–182

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

Modeling of theophylline release from different geometrical erodible tablets

H.Y. Karasulu[a,*], G. Ertan[a], T. Köse[b]

[a]*Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ege, İzmir, Turkey*
[b]*Department of Computer Engineering, Faculty of Engineering, University of Ege, İzmir, Turkey*

Received 15 July 1999; accepted in revised form 11 November 1999

Abstract

The aim of this study is to reveal statistically how various geometrical shapes such as triangle, cylinder, half-sphere affect the release rate of the active substance called theophylline in erodible hydrogel matrix tablets. We have tried to indicate these changes in the release rate of theophylline by supporting our aim with the mathematical equations developed by Hopfenberg and Katzhendler et al. The model developed by Hopfenberg assumes that drug release occurs from the primary surface area of the device but Katzhendler et al. (I. Katzhendler, A. Hoffman, A. Goldberger, M. Friedman, Modelling of drug release from erodible tablets, J. Pharm. Sci. 86 (1997) 110–115), described a situation where the erosion rates of the tablet are different in the radial and axial directions. Hydrogel matrix tablets were prepared with hydroxypropylmethylcellulose (HPMC E_{50}) possessing different geometrical shapes as triangular, cylindrical and half-spherical using experimental design. When the dissolution results have been evaluated, it has been observed theophylline release from different geometrical erodible tablets fitted with that of the Katzhendler et al., equation. This equation which was suggested for cylindrical tablets was also used to interpret half-spherical and triangular tablets. According to the above stated equation, n has been determined as 4 for triangular tablets and 1.5 for half-spherical tablets and we have also suggested that, these n values could be used in the kinetic programs.

Keywords: Theophylline; Geometric shape; Erodible tablets; Hopfenberg equation; Katzhendler equation

1. Introduction

Compressed hydrophilic matrices are widely used as modified release dosage forms and hydroxypropylmethylcellulose (HPMC) frequently used as a polymer in these applications [1–3]. Erodible polymers have played an increasingly important role in the design of controlled-release drug delivery systems [4–6].

In erosion-controlled systems, the drug is dispersed uniformly throughout the hydrophilic polymer matrix. In many applications, especially for oral delivery, the drug-loaded hydrogels are usually stored in the dry, glassy state before usage due to stability and dosage form requirements [1,6–8]. When these systems are placed in water, they start to swell and the tablet thickness increases. Soon thereafter, polymer and drug dissolution begins to occur. The diffusion rate of the drug in the gel layer is slower than that of the polymer dissolution [1,7].

During the release process, the drug delivery in the erodible hydrophilic matrix is controlled by two mechanisms. While poorly soluble drugs are released solely by erosion of the gel, water-soluble drugs are released both by diffusion out of gelatinous layer and by erosion of the gel [1,7].

While it is known that geometric factors play an important role in altering the dissolution rate, no report has quantified the effect of tablet thickness or height on drug dissolution in gastro intestinal flow [9]. Drug release from surface-eroding devices with various geometries was first analyzed by Hopfenberg and a general mathematical equation was developed describing drug release from slabs, spheres and infinite cylinders [10].

For the model developed by Hopfenberg for slab, spherical and cylindrical matrices displaying heterogeneous erosion, the following relationship is applicable (Eq. (1))

$$M_t/M_\infty = 1 - \left[1 - k_0 t/C_0 a_0\right]^n \quad (1)$$

where M_t is the amount of drug released from the device in time t, M_∞ is the total amount of drug released when the device is exhausted, and k_0 is the erosion rate constant, C_0 is the uniform initial concentration of drug in the matrix, a_0 is the initial radius for a sphere or cylinder or the half-thick-

* Corresponding author. Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ege, 35100 Bornova, İzmir , Turkey.

0939-6411/00/$ - see front matter
PII: S0939-6411(99)00082-X

ness for a slab and n is the shape factor, 1 for a slab, 2 for a cylinder and 3 for a sphere.

The model assumes that the release kinetics are not influenced by time dependent diffusional resistances internal or external to the eroding matrix, i.e. the actual erosion process is the rate-limiting step. The model also ignores the contribution of the secondary surface area in the release process.

Following the analysis, Hopfenberg and Katzhendler et al. developed a general mathematical model, which is aimed at describing drug release from an erodible matrix in the form of a tablet [5]. It is assumed that the matrix swelling is slower when compared with the erosion process or that the matrix swelling occurs prior to the release of drug from the matrix. They also described a situation where the erosion rates of the tablets are different in the radial and axial directions.

When analyzing the kinetics of drug release from erodible tablets, Katzhendler et al. refer to two coordinates: a, radial and b, axial as shown in Eq. (2).

$$M_t/M_\infty = 1 - \left(1 - k_a t/C_0 a_0\right)^2 \left(1 - 2k_b t/C_0 b_0\right) \quad (2)$$

where k_a is the radial erosion rate constant, k_b is the axial erosion rate constant and a_0 and b_0 are the tablets' initial radius and thickness, respectively.

Eq. (2) describes the fractional amount of drug release from surface erodible tablets. When $k_a \cong k_b$ Eq. (2) could be described by the following expression in Eq (3)

$$M_t/M_\infty = 1 - \left(1 - k_0 t/C_0 a_0\right)^2 \left(1 - 2k_0 t/C_0 b_0\right) \quad (3)$$

In this paper we have aimed at showing the effect of the geometrical shape on the release rate of the effective substance by using mathematical equations developed by Hopfenberg and Katzhendler and others. The shape factor n, defined in the equation developed by Hopfenberg, has not been defined for the other geometric shapes such as square, half-sphere, triangle, oblong, etc. Thus, we hope our study will be able to fill such a gap which has been ignored by Hopfenberg. We have also evaluated Eq. (1) and additionally Eq. (3) to describe the release rate of theophylline from triangular, cylindrical and half-spherical hydrogel tablets, which were prepared with HPMC E_{50}. The reason why we have used Eq. (3) is that, we have assumed that the radial and the axial surface erosion rates could have been accepted as equivalent. At the end of the study, this assumption of ours has been proven to be true experimentally. That is $k_a \cong k_b$.

2. Materials and methods

2.1. Materials

Theophylline (Dolder Ltd., Switzerland), hydroxypropylmethylcellulose (HPMC E_{50}) (Colorcon, UK), dibasic calcium phosphate (Merck, Germany), and magnesium stearate (Merck, Germany) were used.

2.2. Preparation of tablets

In the preparation of matrix tablets, experimental design was used for both different factors and levels. All tablets contain 300 mg theophylline, and magnesium stearate constitutes 0.1% of the final tablet weight as a lubricant. The effects of the following variations in tablet formulae on dissolution rates were examined.

1. Geometric shape of tablet: three different geometrical shapes (triangular, cylindrical and half-spherical) have been used as tablet shapes.
2. Polymer ratio: in formulation prepared with HPMC E_{50} two different drug -polymer ratios (1:0.5, 1:1) have been used.
3. Percentages of diluent: each tablet has contained three different percentages of dibasic calcium phosphate as a diluent (0, 20, 40% on the polymer and drug mixture).

In the experimental design performed by using different factors and levels, effects of factors on t_{50} values obtained as a result of dissolution studies for all formulations were evaluated by analysis of variance (ANOVA) with $3 \times 2 \times 3$ factorial design.

2.3. Tableting

Three different tablet molds have been prepared for the compression of the tablets. These molds are made of stainless steel and have been subjected to process of hardening. These tablets have been pressed under the pressure of 5 tons force for 10 s under a hydraulic press (Perkin–Elmer) by direct compressing method.

These tablets have been compressed by using:

1. Punch and matrix in the shape of an equilateral triangle, each side of which is 1.66 cm with a flat surface in the compressing of triangular shaped tablets
2. Punch and matrix in the shape of a cylinder, the radius of which is 1.3 cm with a flat surface in compressing of cylindrical shaped tablets
3. A matrix whose bottom is concave shaped and a flat punch whose diameter is 1.45 cm for the preparation of spherical cup tablets.

2.4. Dissolution studies

Dissolution testing was carried out at 37°C in the USP XXII paddle apparatus (method II) at 50 rev./min using 900 ml of water as the dissolution medium over a period of 12 h. The amount of drug released was determined using a Shimadzu (UV-160A, UV-Visible) spectrophotometer at 272 nm. Dissolution studies were performed in triplicate for each batch of tablets. A 95% confidence interval for mean of percent releases obtained in all formulations have been calculated by using Student's t-distribution with help of GENSTAT 5 program.

2.5. Erosion studies

Erosion studies were conducted together with dissolution studies. At the same designed times used in the release studies, the tablets were removed from the vessels and dried at 37°C until a constant weight was obtained. The percentage of tablet eroded was calculated from the weight loss of tablets.

The erosion studies required three tablets per point, and this study has been completed by using 18 tablets per formula. Erosion rate constants (k_0) have been calculated using least squares analysis for three different geometrical shaped tablets.

2.6. Determination of n

The value of n has been determined by trial and error (iterative fitting) method by replacing erosion rate constants (k_0) using Microsoft Excel 5.0, which were calculated for three geometrical shaped tablets, in Eq. (3). This equation has been processed for cylindrical shaped tablets by Katzhendler and others [5].

2.7. Modeling of drug release

The estimated amount of drug released from the device in time t and the observed results have been compared to one another using Eqs. (1) and (3). These calculated results and observed values have been interpreted by considering residuals $[(\sum \mathrm{Res}d^2)/(n-2)]$ and determination coefficient (r^2).

2.8. Plotting of target profile

For the theophylline matrix tablets, target profile of the active substance was plotted by using Eq. (4) [11].

$$k_r^0 = k_d x C_p x V_d \quad (4)$$

where k_r^0 (34.692 mg/h) is the zero order rate constant, k_d (0.098 h^{-1}) is the drug elimination rate constant, C_p (10 μg/ml) is the peak concentration of drug released and V_d (35.4 l) is the apparent volume of distribution.

3. Results and discussion

The cumulative amount of theophylline released versus time for three different geometric shapes and two different drug polymer ratios are summarised in Fig. 1. Confidence interval calculated for percent releases obtained in all formulations and percent release values suggested by Parab et al. [12] for theophylline matrix tablets have been compared to each other (Table 1). As a result of this comparison the percentages of the release rates, obtained out of triangular tablet containing only a drug:polymer ratio of 1:1 and 40% diluent, agree with the results suggested by Parab et al. [12] and besides, they have shown a release profile similar to the target profile of theophylline (Fig. 1).

In addition to this, the variance analysis of all tablets having the same weight (0.841 ± 0.001) and same formulation (1:1 + 40%) has been carried out by using t_{50} values obtained as a consequence of the release rate studies in order to be able to show the effect of the geometrical shape on the release rate of the active substance more clearly. Variance analysis results obtained with the help of GENSTAT 5 program are given in Table 2. As these are obtained from ANOVA results, the main effects of each factor and their interactions were also found to be significant ($P < 0.001$). Thus geometrical shape, polymer ratio and also diluent percentage have been found to be as important factors affecting the dissolution rate. By stabilising polymer ratio and diluent percentage, we have investigated only the effect of geometrical shape on the release rate.

The erosion rate constant k_0, determination coefficient r^2 and degree of significance P obtained for each geometric shape are summarised in Table 3. The erosion rate constants (k_0) of the triangular, cylindrical and half-spherical tablets which were calculated by studying their erosion rates are different from one another. When the release profile of the tablets have been observed, the following results in decreasing order have been obtained: The fastest release has been determined in the triangular tablet, then in the half-spherical and the slowest is in the cylindrical tablet. These results are in accordance with the erosion rate constants.

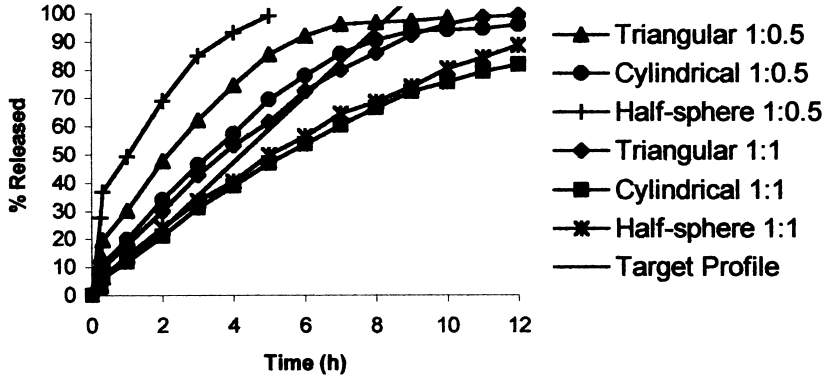

Fig. 1. The release rates and target profiles of the different shaped theophylline matrix tablets containing HPMC-E_{50} and 40% dibasic calcium phosphate as a diluent.

Table 1
Confidence interval space values obtained as the result of releasing rate studies for geometric shaped tablets and the comparison of these values with the Parab's standard [12]

Tablet shape	Drug:polymer ratio	Time (h)	Released (%)	SD	Confidence interval 95%	Parab et al. Standard (%) min–max	Suitability
Triangle	1:1 + %40	2	30	0.458	28.8–31.1[a]	25–40	
		4	53.3	1.044	50.7–55.8[a]	40–60	+
		8	85.9	0.794	83.9–87.8[a]	70–90	
Cylinder	1:1 + %40	2	21.1	0.361	20.2–21.9	25–40	
		4	38.9	0.7	37.1–40.6	40–60	–
		8	66.4	0.436	65.3–67.4	70–90	
Half-sphere	1:1 + %40	2	24	0.656	22.3–25.6	25–40	
		4	40.3	0.458	39.1–41.4	40–60	–
		8	68.4	0.3	67.6–69.1	70–90	
Triangle	1:0.5 + %40	2	47.8	0.557	46.4–49.1	25–40	
		4	74.4	0.557	73.0–75.7	40–60	–
		8	96.9	2.26	91.2–102.5	70–90	
Cylinder	1:0.5 + %40	2	34.1	0.608	32.5–35.6	25–40	
		4	57.3	0.6	55.8–58.7	40–60	–
		8	90.4	0.794	88.4–92.3	70–90	
Half-sphere	1:0.5 + %40	2	69.0	0.436	67.9–70.0	25–40	
		4	93.2	0.458	92.0–94.3	40–60	–
		8	–	–	–	70–90	

[a] $P > 0.05$.

Figs. 2–4 demonstrate that the experimental data obtained from the whole surface of the tablets are in accordance with the calculated values obtained by Eq. (3). If Eq. (1) is used, the predicted and observed values of cylindrical tablet are like those in Fig. 5. When Figs. 2–4 have been studied, it has been seen that the values calculated by using Eq. (3) are in accordance with the observed values, but when Fig. 5 has been studied, it has been observed that the values calculated for cylindrical tablets by using Eq. (1) are completely different from the observed values.

The present work demonstrates that the rates of dissolution and erosion of matrices prepared from a hydrophilic polymer depend on device geometry. Some attempts have been made to regulate the dissolution of drug matrices by controlling their geometry and it is known that geometric factors play an important role in the dissolution rate [1,10,12–16]. Rose-

Table 2
The findings of 3 × 2×3 variation analysis carried out using t_{50} values for hydrogel matrix tablets including dibasic calcium phosphate as a diluent in different ratios prepared with HPMC E_{50}: effect of the independent variables, geometric shape (a), polymer ratio (b) and diluent (c)

Source	SS	DF	MS	F	P
Main effects	25.927	5	5.185	641.777	0.000
Geometric shape (a)	2.083	2	1.041	128.888	0.000
Polymer ratio (b)	19.630	1	19.630	2429.497	0.000
Diluents (%) (c)	4.215	2	2.107	260.806	0.000
Two-way interactions	4.564	8	0.570	70.607	0.000
a × b	1.146	2	0.573	70.916	0.000
a × c	2.933	4	0.733	90.764	0.000
b × c	0.458	2	0.242	29.986	0.000
Three-way interactions	3.259	4	0.815	100.852	0.000
a × b × c	3.259	4	0.815	100.852	0.000
Explained	33.751	17	1.985	245.715	0.000
Residual	0.291	36	0.008		0.000
Total	34.042	53	0.642		0.000

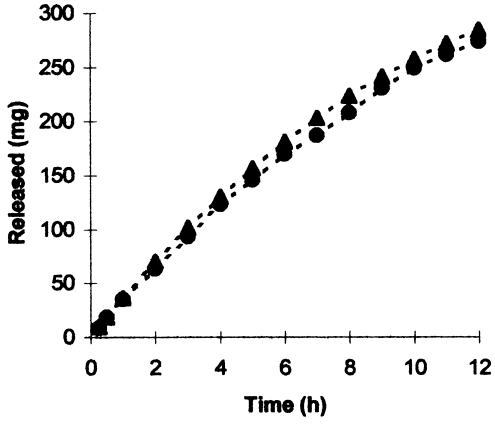

Fig. 2. Release profiles of theophylline from whole cylindrical tablet surface containing 40% dibasic calcium phosphate and 1:1 theophylline-HPMC E_{50} ratios: (▲) predicted values calculated according to Eq. (3), (●) observed data ($r^2 = 0.998$, $[(\sum \mathrm{Res}d^2)/(n-2) = 108.5]$).

Table 3
The effect of geometrical shape on erosion constant (k_0) obtained by fitting the experimental data of the formulation containing 40% dibasic calcium phosphate and 1:1 theophylline-HPMC E_{50} ratio to Eq. (3) (mean ± SD)

Tablet shape	Tablet dimensions a_0 (cm)	Tablet thickness b_0 (cm)	Erosion constant k_0	Regression coeff: r^2	Degree of significance: P
Triangle (half of side length)	0.83	0.46	0.184 ± 0.0034	0.993	0.000
Cylinder (radius)	0.65	0.45	0.140 ± 0.0029	0.924	0.000
Half-sphere (radius)	0.725	0.57	0.172 ± 0.0028	0.915	0.000

man and Higuchi [14] developed equations for drug release from both planar and cylindrical surfaces. Roseman [15] showed that the fraction of drug release from a matrix with a planar surface was linear with the square root of time. Roseman, also showed that the initial portion of a similar plot for a matrix of cylindrical shape was similar to that of the planar case. However, as more drug was released, the slope for the fraction versus square root of time plot decreased. Ford et al. [1] demonstrated the influences of tablet shape and size on the time release rates of promethazine hydrochloride tablets compressed to the same weight and formula. Cobby et al. [16] found that the release profiles could be described by a nonlinear expression for both cylindrical and biconvex tablets, even though the rate of drug release varied noticeably with tablet shape. These studies particularly put forward how the geometric shape factors affect the known dissolution kinetics.

For the first time, drug release from surface-eroding devices with various geometries was analyzed by Hopfenberg [10]. Many years later, Katzhendler et al. [5] developed a general mathematical model (Eqs. (2) and (3)) where in both radial and axial erosion rate constants of the tablets were taken into account.

Three limiting cases should be considered regarding the erosion rate constants of the tablet according to Katzhendler et al.

1. $k_a \gg k_b$ ($a_0 \approx b_0$, $b_0 \approx a_0$): The tablet's radius declines at a higher rate compared with the tablet's thickness. The theoretical drug release approximates that of a cylinder and Eq. (2) reduces to $M_t/M_\infty = 1 - (1 - k_a t/C_0 a_0)^2$.
2. $k_b \gg k_a$ ($a_0 \approx b_0$, $a_0 \approx b_0$): The Tablet's thickness declines at a higher rate compared with the tablets radius. The theoretical drug release approximates that of a flat disk, and Eq. (2) reduces to $M_t/M_\infty = 2k_b t/C_0 b_0$.
3. $k_a \gg k_b$ ($a_0 \approx b_0$, $a_0 \gg b_0$, $b_0 \gg a_0$): The rate of drug release could be described by a single rate constant as expressed in Eq. (3).

In Eq. (2), two different types of erosion rate constants have been used as k_a and k_b, while in Eq. (3) k_a has been taken equal to k_b ($k_a \cong k_b$). When the experimental data are applied to in Eq. (3), it has been seen that the calculated values have been in accordance with our observed values. Thus, it has been found out that k_a equal to k_b in our study as well. For this reason, we have not used Eq. (2). To sum up, when we used Eq. (3) we have seen that both calculated and observed values have been in accordance with one another (Figs. 2–4).

In conclusion, in this study we have tried to show how the geometrical shape of the tablet could change the release profile of the drug. According to this statement, the release rate of the active substance out of erodible hydrogel matrix tablets having different geometrical shapes has been found out to be the highest on triangular tablets and successively in order of decreasing amounts on half-spherical and cylindrical tablets. This also leads us to believe that, the reason why tablets having the same weight and formulation, and pressed under the same pressure have got different release rates is

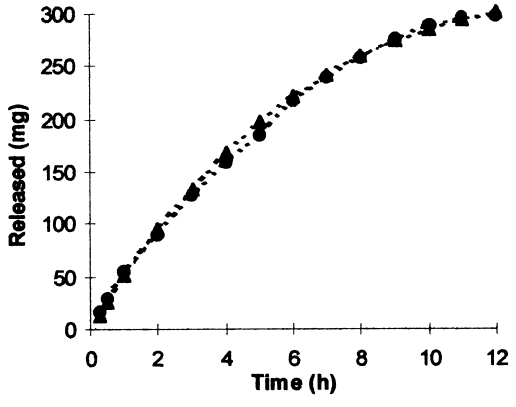

Fig. 3. Release profiles of theophylline from whole triangular tablet surface containing 40% dibasic calcium phosphate and 1:1 theophylline-HPMC E_{50} ratios: (▲) predicted values calculated according to Eq. (3), (●) observed data ($r^2 = 0.997$, $[(\sum \mathrm{Resd}^2)/(n-2) = 32.5]$).

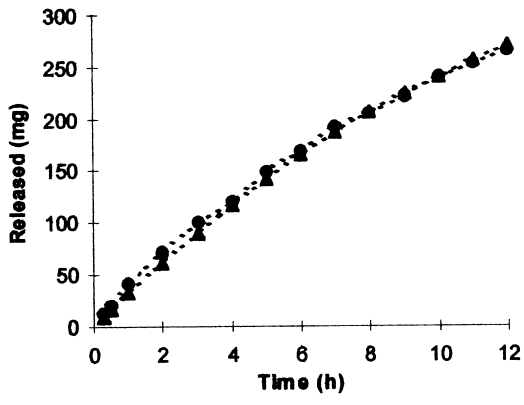

Fig. 4. Release profiles of theophylline from whole half-spherical tablet surface containing 40% dibasic calcium phosphate and 1:1 theophylline-HPMC E_{50} ratios: (▲) predicted values calculated according to Eq. (3), (●) observed data ($r^2 = 0.998$, $[(\sum \mathrm{Resd}^2)/(n-2) = 44.80]$).

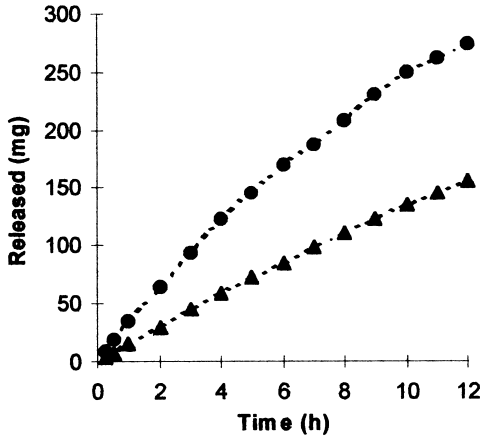

Fig. 5. Release profiles of theophylline from whole cylindrical tablet surface containing 40% dibasic calcium phosphate and 1:1 theophylline-HPMC E_{50} ratios: (▲) predicted values calculated according to Eq. (1), (●) observed data ($r^2 = 0.994$, $[(\sum \mathrm{Res}d^2)/(n-2) = 7505.5]$).

that the geometries of the tablets are different. We have also tried to explain this change by calculating n for the triangular, cylindrical and half-spherical tablets respectively as 4, 2 and 1.5 by using Eq. (3). This is the first time the n values were calculated according to Eq. (3) and the validity of calculations was also proved practically. Hopfenberg has defined the n values of the sphere as 3 and we found the n value of the half-sphere as 1.5 so there is an agreement of these n values. As a result, the n value existing at Hopfenberg and Katzhendler equations may be used as 1 for slab, 1.5 for half-sphere, 2 for cylinder, 3 for sphere, 4 for triangle in the computer programs where combined kinetic models used for the linerization of release profiles exist. In addition, the n values of the other geometrical shapes should be investigated.

References

[1] J.L. Ford, M.H. Rubinstein, F.M. Caul, J.E. Hogan, P.J. Edgar, Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets, Int. J. Pharm. 40 (1987) 223–234.

[2] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliott, J.E. Hogan, C. Rostron, The influence of the particle size of hydroxypropylmethylcellulose K15M on its hydration and performance in matrix tablets, Int. J. Pharm. 100 (1993) 1175–1179.

[3] G. Xu, H. Sunada, Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets, Chem. Pharm. Bull. 43 (1995) 483–487.

[4] X. Xu, P.I. Lee, Programmable drug delivery from an erodible association polymer system, Pharm. Res. 10 (1993) 1144–1152.

[5] I. Katzhendler, A. Hoffman, A. Goldberger, M. Friedman, Modeling of drug release from erodible tablets, J. Pharm. Sci. 86 (1997) 110–115.

[6] T.D. Reynolds, S.H. Gehrke, A.S. Hussain, L.S. Shenouda, Polymer erosion and drug release characterization of hydroxypropylmethylcellulose matrices, J. Pharm. Sci. 87 (1998) 1115–1123.

[7] P.I. Lee, Kinetics of drug release from hydrogel matrices, J. Cont. Rel. 2 (1985) 277–288.

[8] N. Shah, G. Zhang, V. Apelian, F. Zeng, M.H. Infeld, A.W. Malick, Prediction of drug release from hydroxypropylmethylcellulose (HPMC) matrices: Effect of polymer concentration, Pharm. Res. 10 (1993) 1693–1695.

[9] M.S. Gordon, D.J. Ellis, B. Molony, J. Shah, P. Teitelbaum, In vitro dissolution versus in vivo evaluation of four different aspirin products, Drug Dev. Ind. Pharm. 20 (1994) 1711–1723.

[10] H.B. Hopfenberg, In controlled release polymeric formulations, in: D.R. Paul, F.W. Haris (Eds.), ACS Symposium Series, Vol. 33, American Chemical Society, Washington, DC, 1976, pp. 26–31.

[11] A. Goodman-Gilman, L.S. Goodman, T.W. Rall, F. Murad, Goodman and Gilman's The Pharmacological basis of Therapeutics, 7th ed., Pergammon Press, New York, 1985.

[12] P.V. Parab, C.K. Oh, W.A. Ritschel, Sustained release from precirol (glycerol palmito-stearate) matrix, effect of mannitol and hydroxypropylmethylcellulose on the release of theophylline, Drug Dev. Ind. Pharm. 12 (1986) 1309–1327.

[13] G. Ertan, E. Karasulu, D. Demirtaş, M. Arıcı, T. Güneri, Release characteristics of implantable cylindrical polyethylene matrices, J. Pharm. Pharmacol. 49 (1997) 229–235.

[14] T.J. Roseman, W.I. Higuchi, Release of medroxyprogesterone acetate from a silicone polymer, J. Pharm. Sci. 59 (1970) 353–357.

[15] T.J. Roseman, Release of steroids from a silicone polymer, J. Pharm. Sci. 61 (1972) 46–50.

[16] J. Cobby, M. Mayersohn, G.C. Walker, Influence of shape factors on kinetics of drug release from matrix tablets I: theoretical, J. Pharm. Sci. 63 (1974) 725–737.