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Drug release kinetics from the gradient matrix system: Mathematical modelling

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Summary

A mathematical model is presented with which acetaminophen release curves from the gradient matrix system (GMS) with different geometries (slabs and spheres) can be described. Diffusion is considered the rate-controlling step in the release process. Position- and time-dependent diffusion coefficients account for the changes in the matrix structure due to the initial different loading concentrations and due to changes during the release process. Release of acetaminophen from slab model systems and from spherical systems can be adequately explained. Release curves of another model drug, mebeverine HCl, from planar GMS formulations are adequately predicted by the model.

Introduction

In previous papers (Van Bommel et al., 1989a, 1990) the gradient matrix system (GMS) has been presented. This controlled release device, prepared as planar and as spherical systems, allows for constant delivery of drug compounds during various periods of time.

The aim of the present paper is to develop a mathematical model that describes drug release from the GMS. Diffusion is assumed to be the rate-controlling release mechanism. Both dynamic changes in porosity and the effect of heterogeneously loading the matrix are taken into account. The effective diffusion coefficients are assumed to be time- and position-dependent. Estimates for the position-dependent effective diffusion coefficients have been derived from permeation experiments through leached-out films, initially containing different concentrations of either drug or excipient. The time-dependent functions for the effective diffusion coefficients have been estimated from release data of drug and excipient from homogeneously loaded slab matrix systems.

This model is used to describe and predict the

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effect of concentration gradients in the GMS on the drug release profiles. Calculated and experimentally observed release profiles from matrices with different geometries and different model drug compounds are evaluated.

The Model

In the model diffusion is assumed to be the rate-controlling step in the release process of drug and excipient out of the matrix. Hence, all drug/excipient is present as one diffusable phase. At the beginning of the release process water quickly enters the matrix. Due to mass transfer out of the matrix its structure changes. As was demonstrated previously, different loading concentrations of drug or excipient also change the ethylcellulose film structure (Van Bommel et al., 1989b). The permeation constants of both compounds through leached-out films were found to be a function of the initial loading concentration. These changes were included as a time- and position-dependent effective diffusion coefficient. In other words, a position-variable function was used to describe the potential changes in the effective diffusion coefficients, and a time variable was introduced to describe the actual changes as the release process proceeds.

Based on these considerations, the following well known diffusion equations were used to describe the mass transport of drug and excipient in the matrix (mass transport in x direction only):

$$\frac{\partial c_d}{\partial t} = \frac{\partial}{\partial x}\left(D_{e,d}(t,x)\frac{\partial c_d}{\partial x}\right) \tag{1}$$

$$\frac{\partial c_e}{\partial t} = \frac{\partial}{\partial x}\left(D_{e,e}(t,x)\frac{\partial c_e}{\partial x}\right) \tag{2}$$

where c_d and c_e are the concentrations of drug and excipient, respectively (kg m^{-3}); $D_{e,d}$ and $D_{e,e}$ are the time- and position-variable effective diffusion coefficients (m^2 s^{-1}).

The concentrations of drug and excipient in the releasing medium were calculated from Eqn 3:

$$V_B\frac{dc_{b,i}}{dt} = -A_m D_{e,i}\frac{\partial c_i}{\partial x}\bigg|_{x=d_m} \tag{3}$$

where $c_{b,i}$ is the concentration of acetaminophen or xylitol in the releasing medium (kg m^{-3}); c_i is the concentration of acetaminophen or xylitol in the matrix (kg m^{-3}); $D_{e,i}$ is the time- and position-dependent effective diffusivity of both compounds (m^2 s^{-1}); d_m is the layer thickness of the matrix (m); V_B is the volume of the releasing medium (m^3); A_m is the surface area of the matrix (m^2).

Different forms for the time dependency of the effective diffusivity are possible (e.g. Lee, 1987). Here, the diffusivity was assumed to be exponentially related to the concentrations present in the matrix at time t:

$$D_{e,d} = D^0_{e,d}\exp\left(-\alpha\frac{c_d(t)+c_e(t)}{C_{0,d}+c_{0,e}}\right) \tag{4}$$

$$D_{e,e} = D^0_{e,e}\exp\left(-\beta\frac{c_d(t)+c_e(t)}{c_{0,d}+c_{0,e}}\right) \tag{5}$$

where $D^0_{e,d}$ and $D^0_{e,e}$ are the initial, position-variable effective diffusion coefficients of drug and excipient (m^2 s^{-1}); c_d and c_e are the concentrations of drug/excipient in the matrix at time t (kg cm^{-3}); $c_{0,d}$ and $c_{0,e}$ are the initial position-dependent loading concentrations in the matrix (kg m^{-3}); α and β are adjustable parameters.

The initial loading concentrations of drug and excipient in the GMS are position-dependent. As was stated previously, the structure of the ethylcellulose matrix will change due to these different concentrations. The dependency of the matrix structure on the initial position-variable loading concentrations of drug and excipient was included in the effective diffusivity. Estimates for the position variable part were based on permeation experiments of each compound through leached-out ethylcellulose films, initially containing either acetaminophen or xylitol (Table 1). Four regression functions (Y^i_j, i, j = drug or excipient) were derived from the permeability data to describe the effect of loading concentrations on the effective diffusivities in the ethylcellulose films. The effective diffusivity ranged from the diffusivity of drug/excipient through unloaded ethylcellulose films to the effective diffusivity of the compounds in water as the upper value. Finally, the position-

TABLE 1

Permeability constants for acetaminophen (ACE) and xylitol (XYL) through ethylcellulose films with different concentrations of additives initially present in the film

Initial loading in EC films (% w/w of EC)	$P(m^2/s)$ ($\times 10^{-14}$)	
	ACE	XYL
0 ACE	2.0 (0.5) [a]	5.8 (0.5)
0 XYL	2.0 (0.5)	5.8 (0.5)
20 ACE	12.5 (2.0)	10.0 (1.2)
20 XYL	10.0 (2.0)	14.0 (2.0)
30 ACE	25.3 (1.0)	–
30 XYL	15.5 (0.5)	–
40 ACE	31.3 (1.1)	62 (4)
40 XYL	22.5 (1.2)	39 (3)
50 ACE	89.0 (2.3)	–
50 XYL	54.3 (2.5)	–

–, not determined;
[a] SD.

dependent diffusivities of drug and excipient ($D^0_{e,i}$, see Eqns 4 and 5) in the three-component GMS were derived by linear interpolation of the regression functions (Y^i_j) based on the mass fractions of both compounds at each position in the matrix:

$$D^0_{e,d} = D_{0,d}\left[Y^e_d + g_d\left(Y^d_d - Y^e_d\right)\right] \quad (6)$$

$$D^0_{e,e} = D_{0,e}\left[Y^d_e + g_e\left(Y^e_e - Y^d_e\right)\right] \quad (7)$$

where $D_{0,d}$ and $D_{0,e}$ are the diffusion coefficients in unloaded ethylcellulose films ($m^2\ s^{-1}$); g_d and g_e are the mass fractions (by weight of ethylcellulose) of acetaminophen and xylitol, respectively; Y^d_d and Y^e_d are the regression functions for the change in permeability of acetaminophen due to leached-out drug or excipient, respectively, and Y^d_e and Y^e_e are the regression functions for the change in permeability of xylitol due to leached-out drug or excipient, respectively.

The boundary and initial conditions are: the concentrations of drug or excipient (c_i) in the matrix are set to a given initial loading concentration.

$0 \le x \le d_m$:

$$t = 0:\ c_i = c_i(x,0) \quad (8)$$

no diffusion at core interface.

$t \ge 0$:

$$x = 0: \frac{\partial c_i}{\partial x} = 0 \quad (9)$$

infinite sink conditions at $x = d_m$.

$$x = d_m:\ c_i = c_{b,i} \sim 0 \quad (10)$$

Experimental

Materials

All materials were used as received. The properties of acetaminophen, xylitol and ethylcellulose have been described elsewhere (Van Bommel et al., 1989a, 1990). Mebeverine hydrochloride (Duphar BV, Weesp, The Netherlands) was used as a second model drug compound. It is a highly water-soluble compound ($C_{s,37°C}$ = 83% w/w), used for treatment of irritable bowel syndrome.

Preparation of the matrix systems

For preparing the acetaminophen-containing matrix systems, both slabs and spheres, spraying techniques were used. In short, ethanolic solutions of ethylcellulose with variable concentrations of drug and excipient were sprayed on either flat tablet surfaces or on spherical core material in two different types of coating equipment. The GMS devices were prepared as three-step gradient systems, by spraying consecutively three solutions on the core material. Details on the spraying procedures have been described elsewhere (Van Bommel et al., 1989a, 1990). The same method was used for preparation of the slab matrix systems containing mebeverine HCl.

Film thickness was measured using a Minitest 1000S^R thickness gauge (Elektro-Physik, D-Köln).

Determination of drug release and permeation rate

The release of acetaminophen from the slab matrices was determined using an automated procedure in a modified USP XXI dissolution test apparatus. Acetaminophen release from the spherical systems was assessed in a USP XXI

dissolution test apparatus 2 with spectrophotometric determination of the amount of drug released in the dissolution medium. The experimental set-up is described in greater detail in previous papers (Van Bommel et al., 1989a, 1990).

Mebeverine HCl release was determined in the same experimental set-up ($\lambda = 264$ nm; $A_1^1 = 259$).

For determination of the xylitol release rate, samples were taken at appropriate time intervals during the dissolution experiment (USP XXI apparatus 2). An HPLC method was used to assess the xylitol concentration. The samples were diluted (1 : 1) with acetonitrile and chromatographed on two Hypersil APS-2^R, 3 μm columns, 5.0 cm $\times$ 4.6 mm and 15.0 cm $\times$ 4.6 mm. As mobile phase a (11 : 39 v/v) mixture of sodium phosphate solution (1.15%) and acetonitrile was used. Detection was performed by UV-absorption measurements at 190 nm.

All release studies were performed at least in triplicate. The relative standard deviation for the data points was $\leq 5\%$ for acetaminophen and mebeverine experiments, and $\leq 10\%$ for xylitol.

Permeation experiments were performed as described previously (Van Bommel et al., 1989b). For acetaminophen and xylitol the permeation constants through empty ethylcellulose films and through leached-out films were determined. Mebeverine permeation was determined through unloaded films only. All experiments were performed at least in six-fold.

Numerical methods

The coupled partial differential equations describing the instationary diffusion of drug and excipient were solved numerically by the method of orthogonal collocation on finite elements (Villadsen and Michelsen, 1978; Finlayson, 1980). As basis functions piecewise third degree Jacobi polynomials were chosen, with inclusion of the element boundaries as interpolation points. Continuity of concentration and of flux was imposed at the boundaries between elements. The time integration of the ensuing system of ordinary differential equations was carried out by Gear's method for stiff systems (Gear, 1971).

At the interface between matrix and solvent steep concentration gradients occurred, especially for very early times. Here the degree of the interpolating polynomial was increased in order to maintain the accuracy of the calculation.

The number of elements and size of the time step in the integration routine were varied until no significant change in accuracy was observed. The typical computation time on a VAX 8810 was 1 min CPU.

Results and Discussion

Model parameters

The model was developed first for planar matrix systems. The position-dependent parts of the effective diffusion coefficients of acetaminophen and xylitol were estimated from the independent permeation experiments as described in the previous sections. The effective diffusion coefficients through unloaded ethylcellulose films, $D_{0,d}$ and $D_{0,e}$ (Eqns 6 and 7), were calculated from the permeation data and equal to 0.3×10^{-14} and 25×10^{-14} m^2 s^{-1}, respectively (Van Bommel et al., 1989b).

With the position-variable part now known, the time-dependency of the effective diffusivities was determined (Eqns 4 and 5). Data from matrices with different loading concentrations of either acetaminophen or xylitol were used to calculate the values of the parameters α and β by regression with least-squares analysis. Thus, α and β were determined at 2.12 and 0.0, respectively. In these time-dependent functions, amongst other things, interaction differences between the compounds and the polymer were incorporated. Therefore, α and β were considered as compound-related parameters.

As an example, in Figs 1 and 2 experimental and best-fitting release curves for three selected matrix systems, plotted as cumulative amount of acetaminophen or xylitol released vs time, are shown.

Clearly, xylitol release was very fast with regard to the total release times of acetaminophen. The accuracy of the experimentally obtained release data for xylitol at early times was rather low. Therefore, the time-dependent function was not

incorporated in the effective diffusivity of xylitol, hence $\beta = 0$.

The concentration of acetaminophen in the matrix decreased at a much slower rate. As the release process continued, the concentration diminished, resulting in the well-known time-dependent release rate for matrix systems.

All parameters in the model were now set to their estimated values based on independent experiments with only one additive in the ethylcellulose matrix. Validation of the model and determination of its predictive power in the three-component systems was done by evaluating matrices with different concentration gradients of both compounds, different geometries and two different model drug compounds.

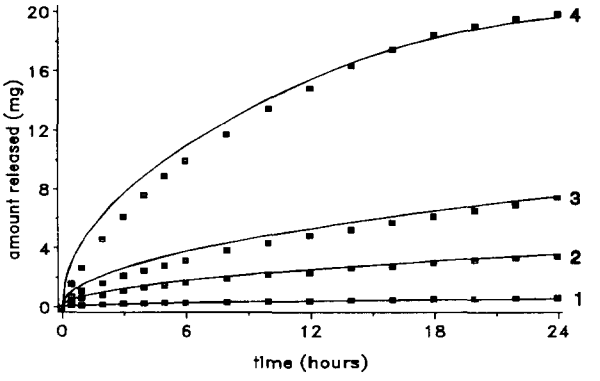

Fig. 1. Cumulative acetaminophen release from slab matrix systems homogeneously loaded with various concentrations of drug (concentrations are % w/w of EC): 10% (curve 1); 40% (curve 2); 75% (curve 3); 100% (curve 4). Lines represent calculated release curves. Symbols represent experimental data.

Validation of the model

For validation of the model, calculated release profiles of a number of slab matrix systems loaded with both drug and excipient, were compared with experimental findings. All formulations under investigation were sprayed as three-step matrix systems. The compositions of all spraying solutions are summarized in Table 2.

As an example, in Fig. 3 computed and experi-

TABLE 2

Composition of matrix systems [amounts (g) of all compounds in each spraying solution (approx. 100 ml) are given (ACE, acetaminophen; XYL, xylitol; EC, ethylcellulose; MEB, mebeverine HCl)]

System	Fig.	Inner layer			Middle layer			Outer layer			Total amount of ACE [a]	Total film thickness (μm)
		ACE	XYL	EC	ACE	XYL	EC	ACE	XYL	EC		
A	3	2.0	1.0	2.0	1.0	2.0	2.0	0.5	0.0	2.0	7.1 mg	156 (10) [e]
B	3	3.33	0.5	3.33	1.33	1.67	3.33	0.5	3.0	3.33	12.1 mg	270 (12)
C	4	3.33	0.5	3.33	2.08	1.75	3.33	0.33	3.25	3.33	12.5 mg	270 (10)
D	4	1.91	1.83	3.33	1.91	1.83	3.33	1.91	1.83	3.33	12.4 mg	262 (10)
E	7a	3.0	0.0	2.0	2.0	1.0	2.0	1.0	2.0	2.0	16.2 mg	292 (10)
F	7a	3.0	0.0	2.4	2.0	1.0	2.4	1.0	2.0	2.4	17.4 mg	330 (15)
G	7b	3.0	0.0	2.0	2.0	1.0	2.0	1.0	2.0	2.0	17.8 mg	352 (12)
H	8	3.0	0.0	2.0	2.0	1.0	2.0	1.0	2.0	2.0	15.8% [b]	95 (9)
J	8	3.0	0.0	2.4	2.0	1.0	2.4	1.0	2.0	2.4	15.3% [b]	90 (11)
		MEB	XYL	EC	MEB	XYL	EC	MEB	XYL	EC	Total MEB [c]	
K	5	3.0	0.0	2.4	2.0	1.0	2.4	1.0	2.0	2.4	17.8 mg	310 (15)
L	6	9.2	0.0	8.5	4.5	2.3	8.9	1.7	5.1	9.0	16.4 mg [d]	290 (15) [d]
M	6	4.5	0.0	3.8	2.0	1.0	4.1	0.75	2.25	4.3	10.0 mg	190 (10)
N	6	7.5	0.1	4.9	3.0	1.4	5.0	1.0	3.1	5.1	11.5 mg [d]	220 (15) [d]

[a] Total initial amount of acetaminophen in matrix (mg).
[b] Total initial amount of acetaminophen (% w/w) in spherical GMS units.
[c] Total initial amount of mebeverine HCl in matrix (mg).
[d] Theoretical layer thickness and loading of mebeverine HCl in matrix.
[e] SD.

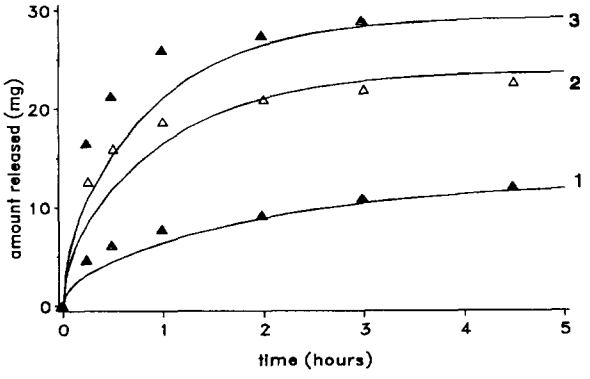

Fig. 2. Cumulative xylitol release from slab matrix systems homogeneously loaded with various concentrations of excipient (concentrations as % w/w of ethylcellulose): 40% (curve 1); 75% (curve 2); 100% (curve 3). Lines represent calculated release curves. Symbols represent experimental data.

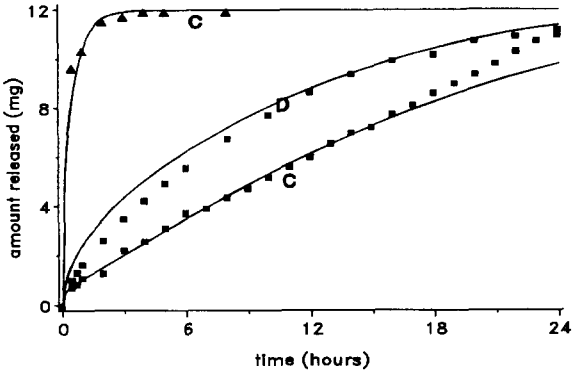

Fig. 4. Cumulative release of acetaminophen (■) and xylitol (▲) from various slab matrix systems: (C) gradient system; (D) homogeneous system: For composition of matrix systems see Table 2. Lines represent calculated release curves. Symbols represent experimental data.

mental release curves are plotted (cumulative amount of acetaminophen released in the dissolution medium) as a function of time. The drug release curve from a system with a high total drug loading (curve B) was adequately described by the model. Clearly, for the system with low loading concentrations in the outer layer (curve A) the initial release rate of drug was underestimated. The initial burst of acetaminophen release from the slabs was not followed by the model. This might be caused by a dragging of acetaminophen by the quickly released xylitol. Since the concentration of xylitol in the matrix rapidly decreased, the effect was only observed in the first stage of the drug release process.

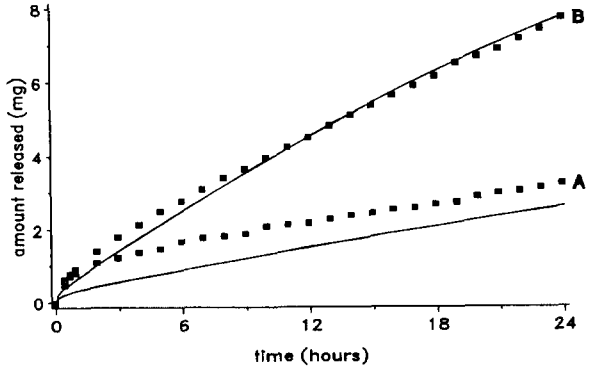

Fig. 3. Cumulative release of acetaminophen from various slab matrix systems: (A) barrier system; (B) gradient system. For composition of matrix systems, see Table 2. Lines represent calculated release curves. Symbols represent experimental data.

To further test the validity of the model the release curves of various slab systems were evaluated. In Fig. 4 their experimental and calculated release curves are shown. For these systems the model adequately described the effect of applying concentration gradients in the matrix on the release process. Almost linear release profiles with time were predicted for the GMS, in contrast to the homogeneous system which showed a decreasing release rate with time.

The above demonstrates that the model could be used to predict release profiles of acetaminophen from various types of planar matrix systems. For systems with a very low drug loading concentration in the outer layer the model would have to be adapted.

Next, the predictive power for matrices with other geometries and for other drug compounds was studied. The mathematical model was developed for the situation where the dissolution step in the release process is negligible. This prerequisite is presumably fulfilled for matrix systems loaded with highly water-soluble compounds. Mebeverine HCl, a highly water-soluble compound, was chosen as an alternative to acetaminophen. Slab matrix systems, homogeneously and heterogeneously loaded with mebeverine HCl, were prepared as described in the experimental section.

It was assumed that the change in film structure (tortuosity) due to different loading concentrations of mebeverine was the same as the changes observed in acetaminophen films. Hence, the same two regression functions Y_d^d and Y_d^e), derived for the permeation change of acetaminophen, were used in the case of mebeverine HCl. The permeation constant of mebeverine HCl through an unloaded ethylcellulose film was experimentally determined. From these experiments $D_{0,d}$ was estimated to be 0.95×10^{-14} m^2 s^{-1}. Hence, the position-dependent function for the effective diffusion coefficient, $D_{e,d}^0$ (Eqn 6), was similar to that of acetaminophen, except for the diffusion coefficient in unloaded films, $D_{0,d}$.

The interaction between mebeverine and ethylcellulose was incorporated in the effective diffusivity by $D_{0,d}$, as discussed above, and by the time-dependent function according to Eqn 4. Similar to the estimation of α and β for acetaminophen- and xylitol-containing matrices, the compound-related parameter (γ) for mebeverine-containing systems was estimated from the best-fitting calculated curves to experimentally obtained release data of homogeneously loaded slabs. A value of γ of 1.60 was found.

Both calculated and experimental release curves of mebeverine from a slab GMS prepared with an identical concentration gradient as for acetaminophen are shown in Fig. 5. Contrary to what was found with acetaminophen in a gradient matrix with the same initial loading, no constant release

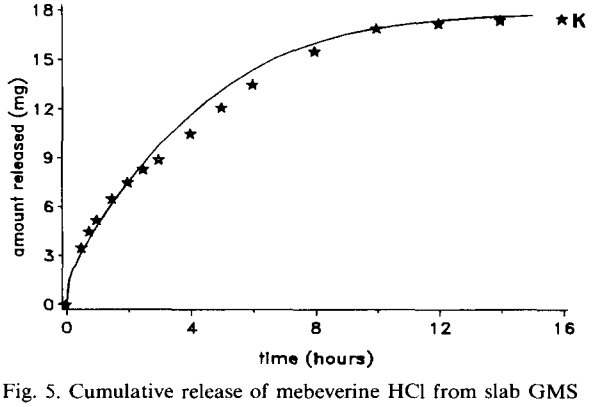

Fig. 5. Cumulative release of mebeverine HCl from slab GMS (K). For composition see Table 2. Line represents calculated release curve. Symbols represent experimental data.

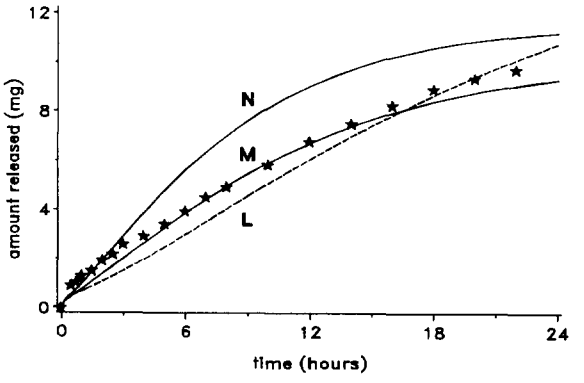

Fig. 6. Predicted and experimental (system M) release curves of mebeverine HCl from various slab matrix systems. For composition of systems see Table 2. Symbols represent experimental values. Lines represent calculated curves.

over the whole time interval was observed, neither experimentally nor mathematically. The calculated curve correlated well with the experimental data.

With the aim of obtaining linear mebeverine HCl release profiles several different loadings were tried mathematically. The model predicted that changing the concentration profiles or total loading in the matrix would result in linear release curves with time. In Fig. 6 some of these calculated curves are plotted. For system M the release profile was experimentally obtained. The experimental release data from system M showed a satisfactory resemblance with the calculated curve.

The GMS with spherical geometry

The effect of changing the geometry of the systems on the predictive power of the model was investigated. Spherical systems were prepared as described previously (Van Bommel et al., 1990). The diffusion equations were adapted for spherical geometry. Because no conceptual changes were made in the model, the adjusted equations are not repeated here.

Different spraying solvents were used for preparing the planar and the spherical matrices. Slabs were sprayed from ethanolic solutions, whereas the spheres were prepared from ethanol/water mixtures. Water was necessary to prevent premature crystallization of xylitol during spraying. Unlike the experimental set-up to prepare the slabs, with the spraying apparatus for the spherical sys-

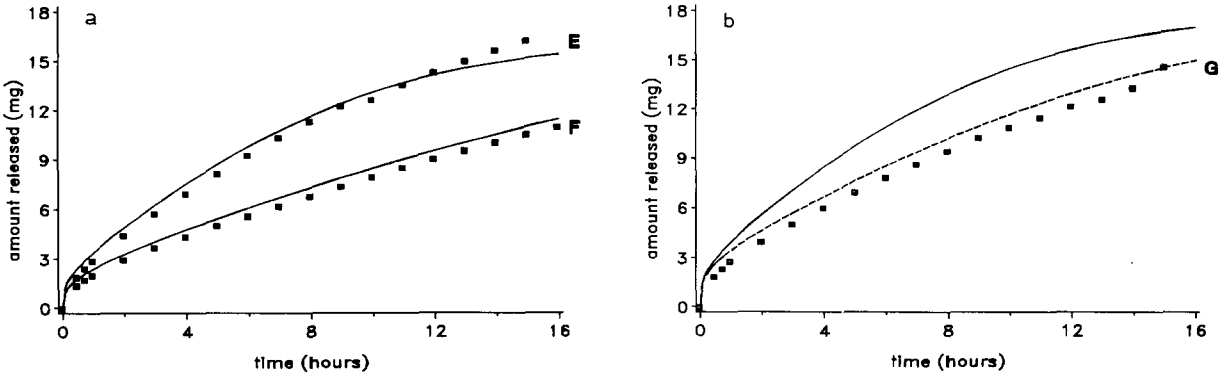

Fig. 7. (a) Cumulative release of acetaminophen from slab GMS, sprayed under standard conditions (E and F). For composition see Table 2. Lines represent calculated curves. Symbols represent experimental data. (b) Cumulative release of acetaminophen from slab GMS (system G), sprayed with water/ethanol mixtures. For composition see Table 2. Lines represent calculated curves: (———) slab model parameters; (- - - - -) adjusted model parameters. Symbols represent experimental data.

tems this crystallization from purely ethanolic solutions could not be prevented.

The type of solvent used for preparation of ethylcellulose films has a marked influence on the film structure (Haas et al., 1952; Rosilio et al., 1988; Arwidsson and Nicklasson, 1989). To investigate the influence of changing spraying conditions on the release profiles, slabs were prepared with either the normal spraying solvent or with the water/ethanol mixture. In Fig. 7a and b calculated and experimental drug release curves from these slab systems are shown.

In Fig. 7a all model parameters were kept constant at the previously determined values. The calculated data from systems sprayed under standard conditions (systems E and F) correlated very well with the experimental curves, demonstrating the validity of the model.

A poor fit was observed for the system prepared with the water/ethanol mixtures (Fig. 7b, line). Clearly, the film structure had changed, thereby changing the effective diffusivity of the compounds through the matrix. Hence, the value for the initial effective diffusivity of acetaminophen ($D_{0,d}$), accounting for the effect of matrix structure on the overall effective diffusivity, was changed and now set at 0.2×10^{-14} m^2 s^{-1}. The time-dependent part of the effective diffusivity was kept constant, because no change in interaction between the drug and the polymer was anticipated. Recalculation of the release curves from system G resulted in a good correlation (Fig. 7b, broken line).

In Fig. 8 calculated and experimental release curves of acetaminophen from spherical systems are shown. The composition of the spraying solutions was the same as the slab systems (see Table 2). The adjusted value for $D_{0,d} = 0.2 \times 10^{-14}$ m^2 s^{-1} was used for the calculations. Good correlations were observed for both gradient systems.

From these results it is concluded that the simple slab system is in principle a good model for spherical geometries. Care must be taken to use the same solvent (mixtures) for preparation of the

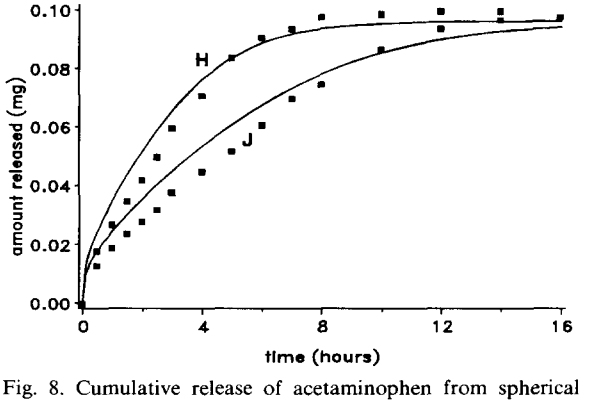

Fig. 8. Cumulative release of acetaminophen from spherical GMS formulations (H and J). For composition of the systems see Table 2. Lines represent calculated release curves, using 'adjusted model parameters'. Symbols represent experimental data.

systems. Although manufactured in different equipment, the use of a similar spraying technique minimized the potential differences in film structure between slabs and spheres. This offfers an advantage over the often used solvent-casting method for preparing slab systems. The latter is quite a different way of preparing films, which may result in non-predictive slab systems for sprayed spherical devices (Allen et al., 1972; Aulton, 1982). For example, sedimentation of the added compounds during preparation of the films may occur, thereby introducing unwanted inhomogeneities.

For both geometries, the model adequately describes the effect of applying concentration gradients in the ethylcellulose matrix on the release profiles of acetaminophen. More work is needed to further confirm the predictive power of the mathematical model under various conditions.

Conclusions

A mathematical model has been developed to describe the release of water-soluble compounds, like acetaminophen and mebeverine HCl, from both planar and spherical matrix systems. With the model the effects of applying concentration gradients of acetaminophen and xylitol in the matrix can be adequately predicted. Almost linear release profiles can be obtained for both the planar and spherical type of matrix. For prediction of mebeverine release from planar matrix systems only minor changes in the model are needed. These adjustments can be readily obtained from simple, spraying experiments. Thus, with the restrictions of the basic assumption that diffusion is the sole mechanism in the release process, extension of the applicability of the model for other drug compounds is possible.

In the development of a multiple unit controlled release device prepared as spherical systems, the use of a slab model system in the formulation stage can offer marked advantages compared to spherical units: both less time and less material is needed to produce the slab systems. Based on release data and modelling parameters obtained for slab systems, the release characteristics of spherical GMS particles can be mathematically manipulated and properly adjusted. Care should be taken to choose the correct solvent systems, so that slabs indeed are indicative for spherical systems. With these restrictions the mathematical model based on slabs is applicable for other geometries.

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