International Journal of Pharmaceutics, 88 (1992) 99–109

IJP 02878

Swelling characteristics of hydrophilic matrices for controlled release New dimensionless number to describe the swelling and release behavior [1]

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(Received 18 February 1992)
(Accepted 4 April 1992)

Key words: Swelling; Controlled release; Matrix; Hydrophilic system; Release mechanism; Swelling interface number; Adimensional number; Releasing area

Summary

Drug release mechanisms of swellable systems for controlled drug administration were investigated The variations of the matrix relaxation and drug diffusion rates were quantified, by measuring the surface area exposed during matrix swelling and drug release as a function of impermeable coating coverage and location. Four different types of matrices, partially coated on various sides, were investigated in order to elucidate the role of the swelling behavior on the release from such delivery systems, especially in view of the three-dimensional nature of the swelling phenomenon. Dependence of the release kinetics on the matrix surface area was assesed. A new dimensionless number, the swelling area number, Sa, was defined for evaluating the significance of the relative rate of matrix swelling variation and drug diffusivity. The systems studied were produced by partial coverage of the release area of tablets by an impermeable coating.

Introduction

Swellable controlled release systems in the form of tablets are widely used for controlled drug administration, mainly due to their optimal performance and easy manufacturing.

The drug release mechanism of these hydrophilic systems occurs by water absorption, matrix swelling and subsequent drug diffusion through the outer gel layer.

However, the central role of the swelling behavior in the description of the performance of such delivery systems has not been adequately elucidated, especially in view of the three-dimensional nature of the swelling phenomenon.

In previous work, swellable compressed matrices coated with partially water-impermeable coatings were investigated (Colombo et al., 1990). These delivery systems exhibited drug release

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[1] Partially presented as the Colorcon Award Lecture at the 10th Pharmaceutical Technology Conference, April 16th, 1991, Bologna, Italy.

rates inversely proportional to the area of the applied impermeable coating. Drug release kinetics was related to the external surface matrix increase during swelling. In practice, the drug was released with varying kinetics, but always at the same rate per exposed (releasing) area. The advantage of this new manufacturing procedure is that the mechanism and rate of drug release can be changed by appropriate coating application. Thus, a variety of systems can be prepared by varying the location of the coating on the cylindrical matrix.

Given that the drug release behavior from these systems can be modulated by the extent of the coating applied, the aim of this work was to study the relationship between matrix swelling and drug release in a larger group of matrices, by partially coating various sides of the compressed matrix.

The objective of this contribution was to quantify the change of the matrix relaxation and drug diffusion rates, by measuring the surface exposed during polymer swelling and drug release as a function of coating coverage and location.

Experimental

Uncoated matrices containing hydroxypropyl methylcellulose as the swellable polymer (Methocel K100M, Colorcon, Orpington, U.K.), diltiazem as the drug (Profarmaco, Milan, Italy) and mannitol FU IX as the filler were prepared and coated according to the method of Colombo et al. (1990).

These compressed discs were coated with an impermeable coating in order to prepare the five systems illustrated in Fig. 1. These were coded as follows: case 0, uncoated matrix; case 1, matrix with one of the bases coated; case 2, matrix with two bases coated; case 3, matrix with the lateral surface coated; case 4, matrix with one base plus the lateral surface coated.

After coating, the matrices had the following

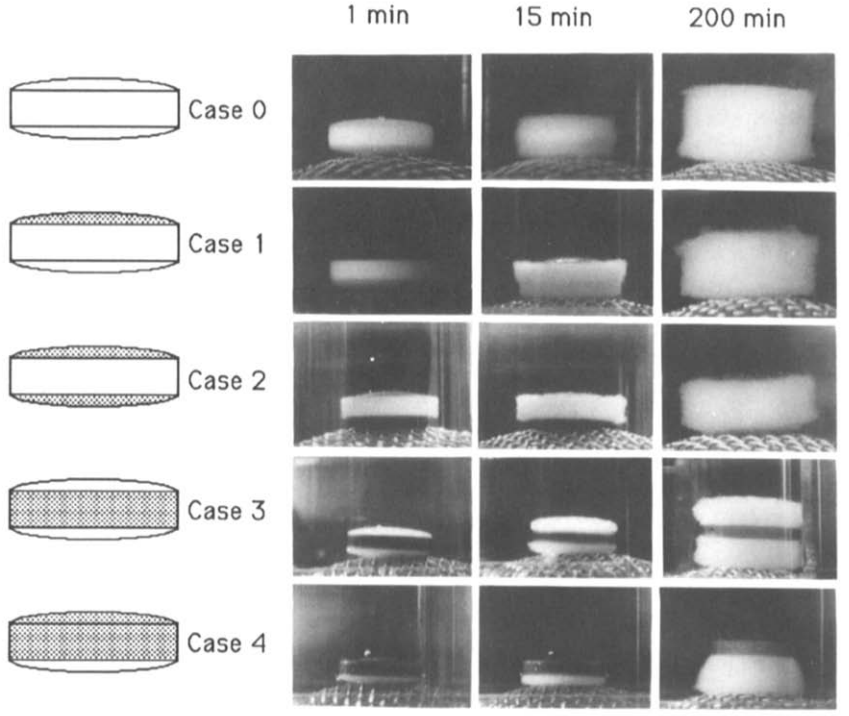

Fig 1. Swelling behavior of systems studied at different times

initial (uncoated) releasing areas: case 0, 1.143 cm^2; case 1, 0.754 cm^2; case 2, 0.365 cm^2; case 3, 0.778 cm^2; case 4, 0.389 cm^2.

Swelling and release experiments were performed as previously described by Colombo et al. (1990).

The diltiazem diffusion coefficient in the swollen polymer matrices was measured in a standard diffusional cell using equilibrium swollen matrices between the donor and receptor compartments.

Results and Discussion

Drug release rate and release mechanism

The release behavior was followed by taking photographs of various systems as a function of time. Fig. 1 shows the systems at different times of release experiments. The presence of the coating causes significant changes in the morphology of the swollen matrices, along with varying swelling kinetics. As the swelling kinetics of the prepared matrices can be altered by changing the coating location, drug release kinetics can be significantly different in the different cases.

Drug release kinetics determined from the release data from matrices of the five cases are shown in Fig. 2. The uncoated matrix (case 0) showed the highest amount of drug released at the same time, followed by matrices of case 3, case 1, case 2 and case 4. The same sequence was followed when comparing the uncoated area at the beginning of the release experiment, except for release from matrices of case 4 where, despite the greater exposed area than case 2, a slower release rate was observed.

The release curves for matrices of cases 2–4 were nearly linear with time after a short time from the beginning of the release experiment. The kinetics of drug release was analyzed by applying the empirical exponential equation, of-

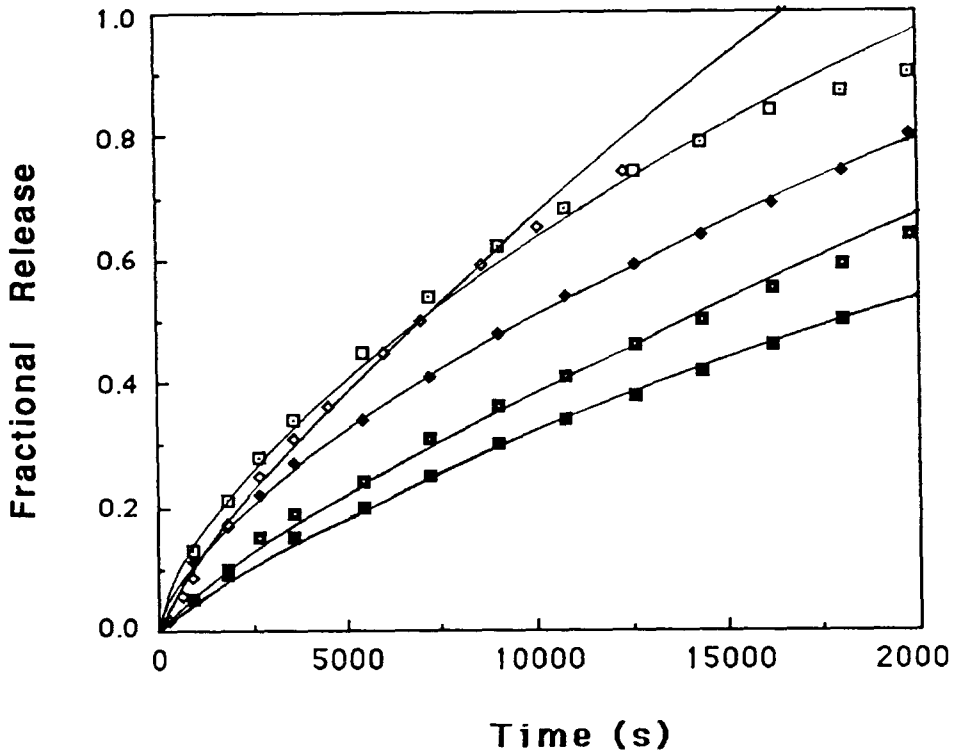

Fig. 2. Fractional diltiazem release from five systems prepared by coating vs time Case 0 (□), case 1 (♦), case 2 (■), case 3 (◇), case 4 (■). The theoretical curves were obtained by fitting the data to Eqn 1

ten used for identifying the release mechanism. In this equation, the drug fraction released is related to time according to the expression:

$$M_t/M_\infty = kt^n \quad (1)$$

Although, in order to compare the mechanistic information obtained from different samples the use of this equation requires detailed statistical analysis (Sinclair and Peppas, 1984), the calculated exponents n of Eqn 1 (Table 1) indicate that the release mechanism is anomalous for all cases, as would be expected for swellable matrices. Matrices of cases 2–4 exhibit values of the exponent n which indicate anomalous transport near case II transport. Thus, the presence of the coating alters the relationship between swelling and drug diffusion of the original uncoated matrix.

A more reliable and informative analysis can be obtained by considering that drug release in swellable matrices depends on two processes: (i) drug diffusion into the swollen polymer; and (ii) matrix swelling due to the penetrant. Calculation of the approximate contribution of the diffusional and relaxational mechanisms to the anomalous release process is carried out by fitting the data to the heuristic model proposed by Peppas and Sahlin (1989) for quantifying the two phenomena controlling the release from swellable matrix.

TABLE 1

Fitting of release data to Eqn 1

Case	Kinetic constant (k) ($\times 10^4$) (s^{-n})	Diffusional exponent (n) ($\pm$95% confidence limits)
0	19 0	0 66 $\pm$ 0.006
1	14.0	0.64 $\pm$ 0.02
2	2.6	0 79 $\pm$ 0.009
3	4 2	0 84 $\pm$ 0.007
4	2 9	0.76 $\pm$ 0.02

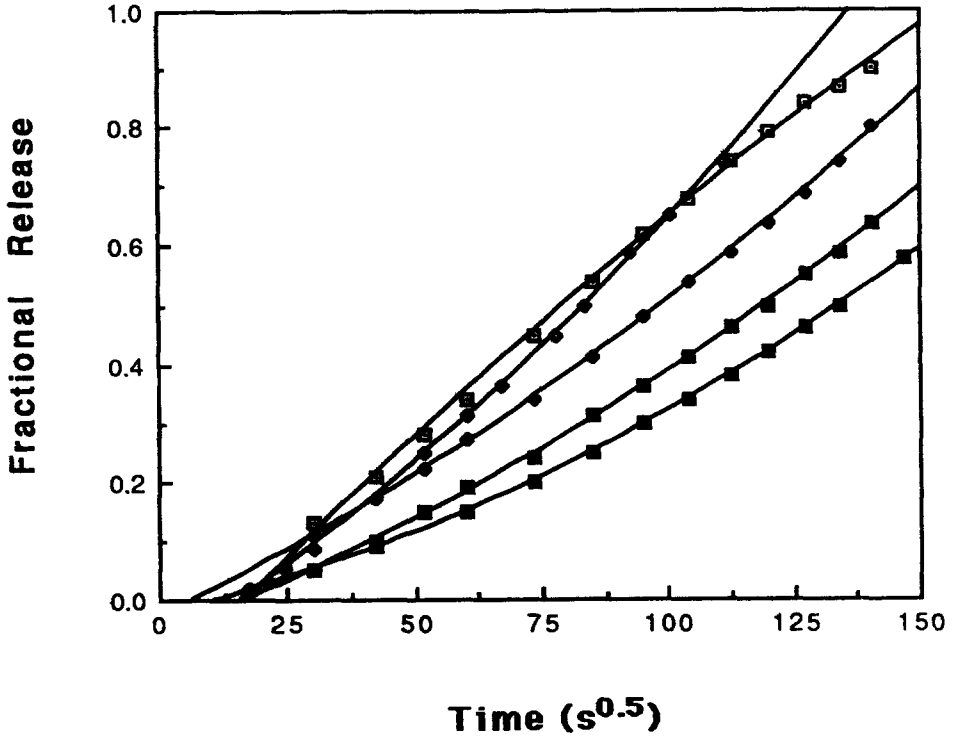

Fig. 3. Fractional diltiazem release from five systems prepared by coating vs square root of time. Case 0 (⊡), case 1 (◆), case 2 (◘), case 3 (◈), case 4 (■)

TABLE 2

Fitting of release data to a second-order polynomial expression [a]

Case	α	β	γ ($\times 10^6$)
0	−0.146	0 0089	−9.79
1	−0.027	0 0042	11.60
2	−0 059	0 0033	11.25
3	−0 091	0.0056	17 38
4	−0.024	0 0021	13.61

[a] $M_t/M_\infty = \alpha + \beta t^{1/2} + \gamma t$

The equation of the model is:

$$M_t/M_\infty = k_1 t^{1/2} + k_2 t \quad (2)$$

where the first term of the right-hand side represents the Fickian contribution, and the second term is the case II relaxational contribution.

From fitting of the data to this equation (Table 2), as shown in Fig. 3, the ratio of relaxational (R) and Fickian (F) contributions could be calculated:

$$R/F = k_2/k_1 t^{1/2} \quad (3)$$

The release curves of the five cases were analyzed according to Eqns 2 and 3. The values of the ratio of relaxational to diffusional contribution vs released fraction are presented in Fig. 4. This graph shows that the presence of a coating on the swellable matrix shifts the ratio of the two contributions towards an increase of the relaxational release mechanism. The release curve of a system according to case 4 exhibits a substantial contribution of the polymer swelling mechanism to drug release.

In order to ascertain the importance of the two mechanisms for drug release, the kinetics of drug release was alternatively evaluated by calculating the instantaneous release rate and plotting

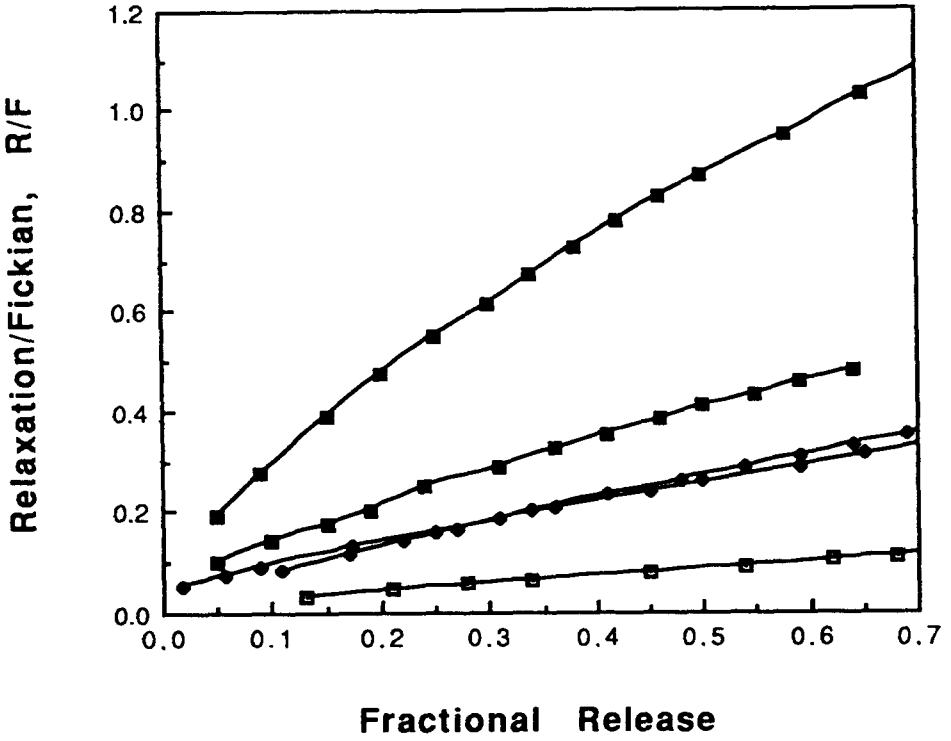

Fig. 4. Ratio of relaxational and diffusional contributions to overall release vs fractional diltiazem release from five systems. Case 0 (⊡), case 1 (♦), case 2 (◘), case 3 (◆), case 4 (■).

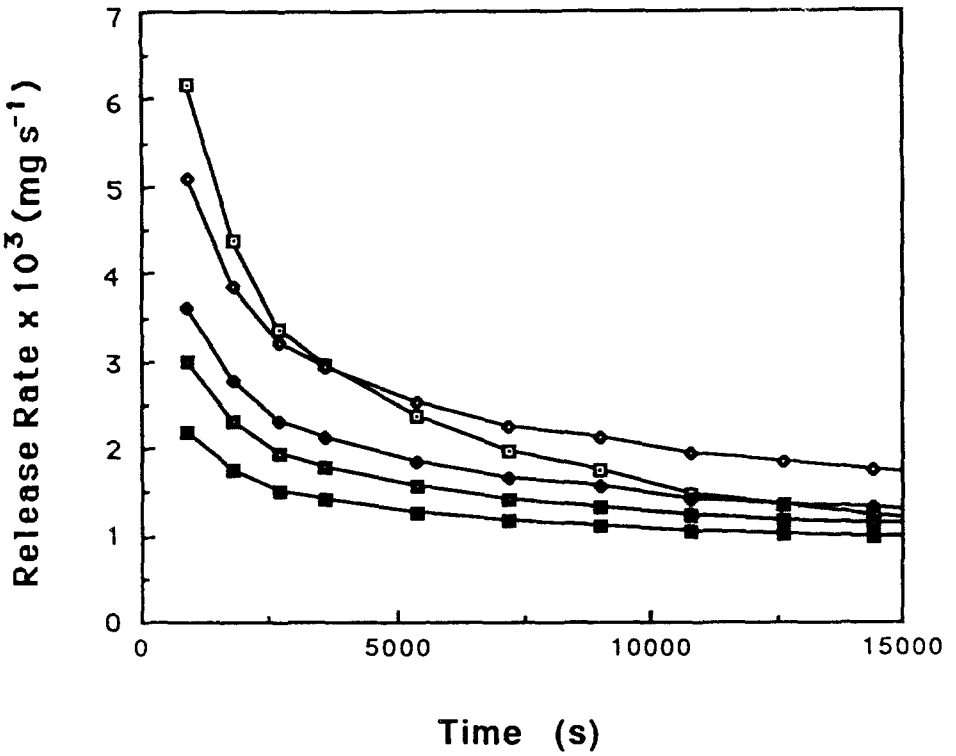

Fig 5 Instantaneous diltiazem release rate from the five systems prepared vs time Case 0 (⊡),case 1 (♦), case 2 (◘), case 3 (◈), case 4 (■)

it as a function of time (Fig. 5). The least variable release rate was exhibited by case 4 systems followed by case 2, case 1 and case 3 systems. The most variable release rate was shown by the case 0 system.

A comparison of Figs 4 and 5 indicates that systems possessing a significant coating (case 2 and case 4) exhibit drug release closer to linearity. Mechanistically, they show a substantial dependence of the drug released on polymer relaxation, especially case 4. In this case of the coating location, swelling is predominantly axial. Case 3 release kinetics is overestimated as anomalous transport by the value of exponent n, probably due to the low number of data points collected for this case, in comparison with others.

Releasing surface area produced during swelling

The releasing surface area increase of the five systems examined is plotted vs time and shown in Fig. 6. By taking the curve of the uncoated matrix as the reference curve, the rate of releasing area production of the four coated systems decreases according to the extent of coating of the matrix. These releasing area curves are analogous to the drug release curves (by comparison to Fig. 2), if one considers that, for the coated systems, the reduction of the quantity of drug released and area produced is dependent on the initially available releasing area.

In order to quantify the importance of matrix swelling on drug release, we plotted the amount of drug released vs the area of the system at the same time (Fig. 7). The linear relationship obtained indicates a direct dependence of the release on the amount of releasing area produced. It is interesting to note that increasing the coating of plain matrices led to a greater amount of drug released at the same value of the releasing area.

Finally, the results shown in Fig. 7 strongly suggest that drug release is linearly related to the

swelling behavior. Swelling kinetics, expressed as releasing area increase per time, governs the kinetics of drug release. This is also demonstrated by normalizing the instantaneous release rates by corresponding area values: the five different systems show practically the same drug release rate per unit area (Fig. 8), although the drug release kinetics are different.

Dimensionless analysis

The drug release kinetics and its exhibition of Fickian or case II drug transport can also mechanistically be analyzed using a novel dimensionless analysis. The physical conditions that determine the kinetics of drug release from swellable matrix were studied by Franson and Peppas (1983), who introduced the *swelling interface number*, Sw. This number compares the mobility of the solvent front relative to drug mobility, in the presence of polymer relaxation, and is defined as:

$$\mathrm{Sw} = \frac{v \cdot \delta(t)}{D} \tag{4}$$

where v is the velocity of the swelling front, $\delta(t)$ represents the time-dependent thickness of the swollen phase and D is the drug diffusion coefficient in the swollen phase. Values of Sw near unity indicate anomalous transport, whereas values much greater than 1 indicate Fickian diffusion and values much lower than 1 indicate case II transport.

As the systems prepared here are characterized by a major change of surface area, a new dimensionless number is proposed, in which the solvent front mobility is replaced by the matrix swelling expansion characteristics. The increase of the releasing area produced by the system during swelling is used as a measure of matrix expansion.

Thus, a new dimensionless number, the *swelling area number*, Sa, is defined as:

$$\mathrm{Sa} = \frac{1}{D} \cdot \frac{\mathrm{d}A}{\mathrm{d}t} \tag{5}$$

where $\mathrm{d}A/\mathrm{d}t$ is the rate of releasing area change

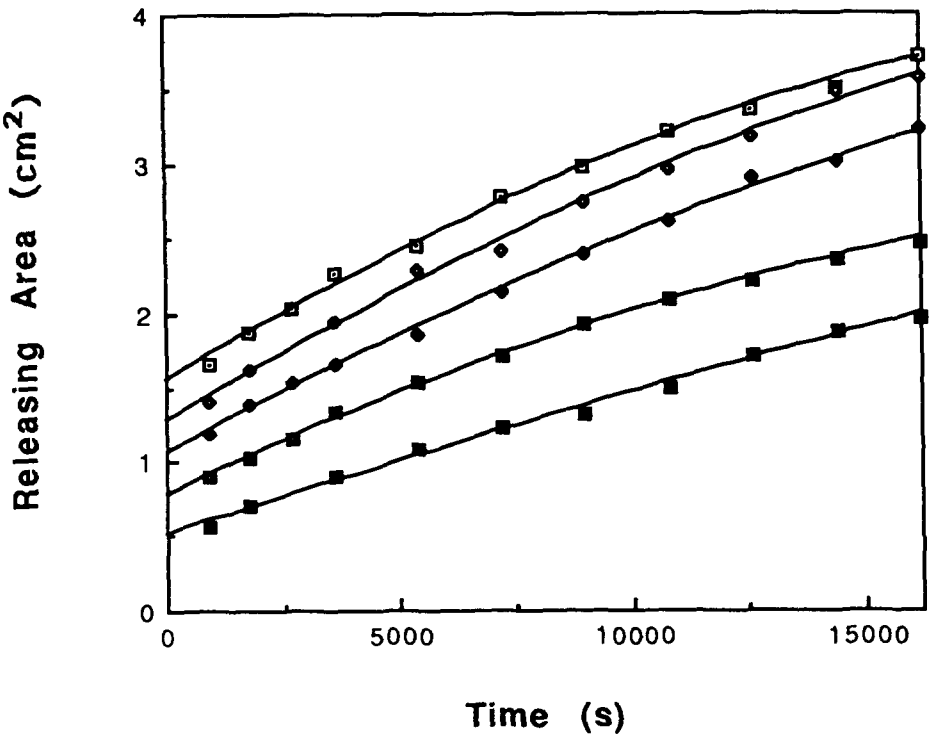

Fig 6 Releasing area vs time for the five systems Case 0 (⊡), case 1 (♦), case 2 (■), case 3 (◆), case 4 (■)

and D the drug diffusion coefficient in the swollen polymer. This dimensionless quantity is thus the ratio of the matrix surface area expansion rate to drug diffusivity and provides a measure of the relative contribution of three dimensional swelling and drug diffusivity on drug released.

For calculation of the swelling area number, the values of releasing area vs time were fitted to a second-order equation (Fig. 6 and Table 3). From the slopes of these curves the term dA/dt was determined. The diffusion coefficient was measured as described in Experimental. Diltiazem permeation was measured and diffusion coefficients were calculated by applying the non-constant source model with pseudo-steady-state conditions (Baker and Lonsdale, 1974). The value was calculated as 6.2×10^{-6} cm^2/s.

For realistic comparison of the importance of matrix front mobility and drug transport, samples with Sa numbers at the same value of fractional drug released were compared. The swelling area numbers for the five cases proposed are shown in Fig. 9.

For each case studied here, the decrease of the swelling area number with time is justified by the decrease of the matrix expansion during the time-swelling history of the system. The order of decrease of swelling area number for the cases tested here is the same as for the drug release rates. Initially, the highest dimensionless number corresponds to case 3 followed by case 0 systems; the same systems showed the highest initial releasing area rates. These are followed by case 1 and case 2. Systems of case 4 showed the lowest and least variable swelling area number, due to the lowest releasing area production rate.

As the release kinetics approaches linear time dependence when the releasing area production

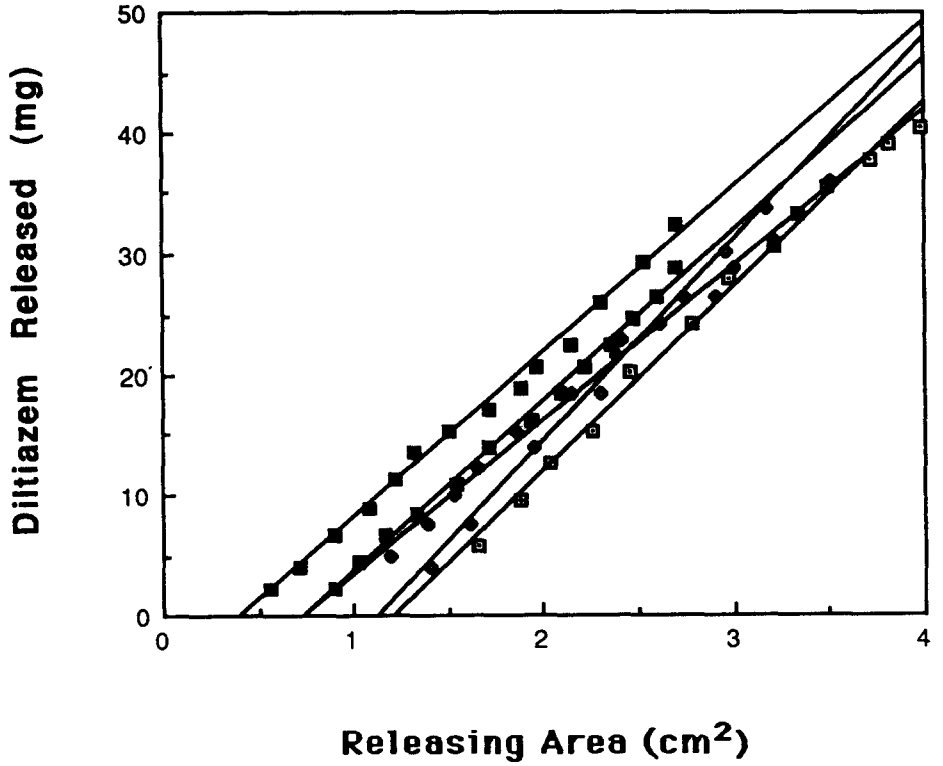

Fig. 7 Relationship between diltiazem release and releasing area for the five systems prepared Case 0 (⊡), case 1 (♦),case 2 (■), case 3 (◆), case 4 (■)

TABLE 3

Fitting of releasing area to the second-order polynomial equation (Eqn A4)

Case	α'	β' ($\times 10^4$)	γ' ($\times 10^9$)
0	1 555	1 882	−3.422
1	1 061	1 701	−2 348
2	0 784	1.505	−2.779
3	1.275	1 895	−2.898
4	0.513	1.010	−0.588

rate decreases, one could expect that additional impermeable coating could reasonably lead to an essentially constant drug release rate. These results indicate that the increase of the releasing area of the swellable matrix (i.e., matrix expansion) is the true variable controlling drug release.

Moreover, during the swelling process, if the matrix expansion rate, dA/dt, drops to a value similar to the drug diffusion coefficient, the release is practically constant. Thus, heterogeneous hydrophilic matrices can approach the release behavior of reservoir systems.

This phenomenon was previously observed with swellable minimatrices, where an increasing superficial crosslinking of the polymer forming the matrix gradually altered the drug release behavior of the matrix towards that of a pseudo-reservoir system (Colombo et al., 1985). The same behavior was observed when studying the release mechanism of coated swellable minimatrices, in which the coating did not control directly the drug release (Gazzaniga et al., 1991).

Conclusions

From the data obtained here we can conclude that in swellable matrices the release kinetics can be changed towards linearity through slowing down the matrix swelling by adjusting the external matrix surface. The amount of drug released

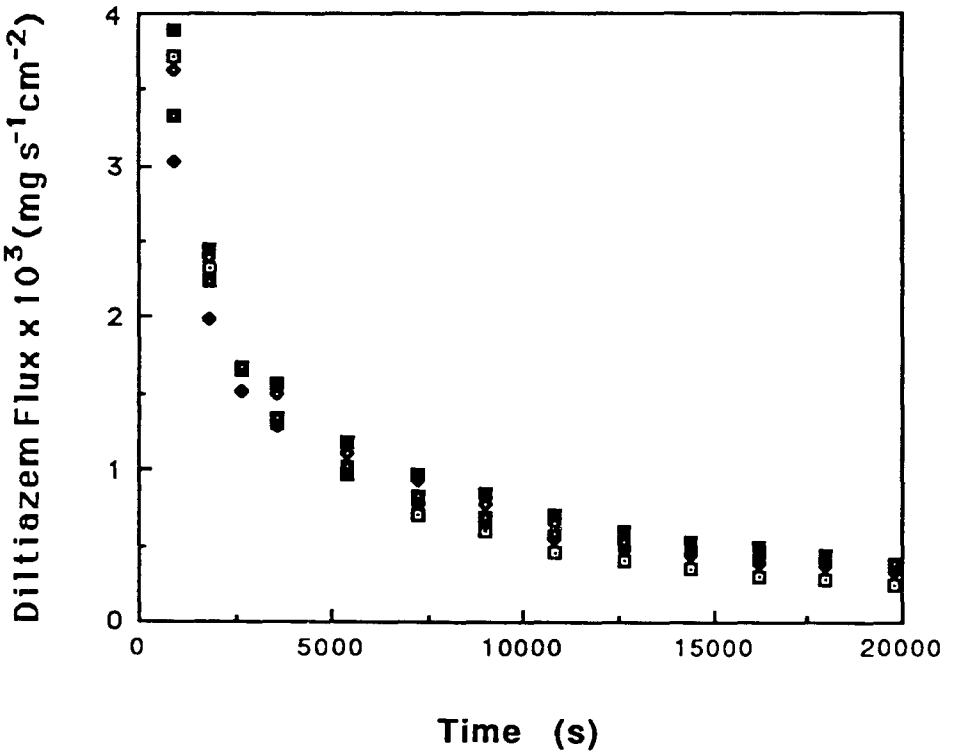

Fig. 8. Diltiazem flux vs time for the five systems prepared. Case 0 (⊡), case 1 (◆), case 2 (■), case 3 (◈), case 4 (■).

is linearly dependent on the releasing area of the matrix; the release mechanism is more anomalous as the rate of matrix swelling decreases.

In pharmaceutical swellable systems drug release kinetics depends on swelling kinetics. Kinetically, drug release from swellable matrices can be more reliably described by a second-order equation in which polymer chain relaxation and drug diffusion influence the release behavior. When the importance of the relaxation contribution is increased, the release kinetics approaches linear behavior.

The swelling area number is similar to the swelling interface number, but the evaluation of matrix expansion by releasing area production rate renders it easier to use. The swelling area number constitutes a means for formulation and evaluation of the significance of the relative rates of matrix swelling variation and drug diffusivity.

Acknowledgements

This work was supported in part by grant no. INT-90-19184 from the National Science Foundation of the U.S.A. and by grant no. 91.03524 CT03 of the Consiglio Nazionale delle Ricerche (Italy) through their U.S.A.-Italy programs. Partial support was obtained by CNR grant no. 90.00545 CT03.

Appendix 1

Relation of swelling area and swelling interface numbers

The swelling interface number, Sw, is a dimensionless number that was defined by Franson and Peppas (1983) to describe the anomalous release behavior of swellable systems. Defined according

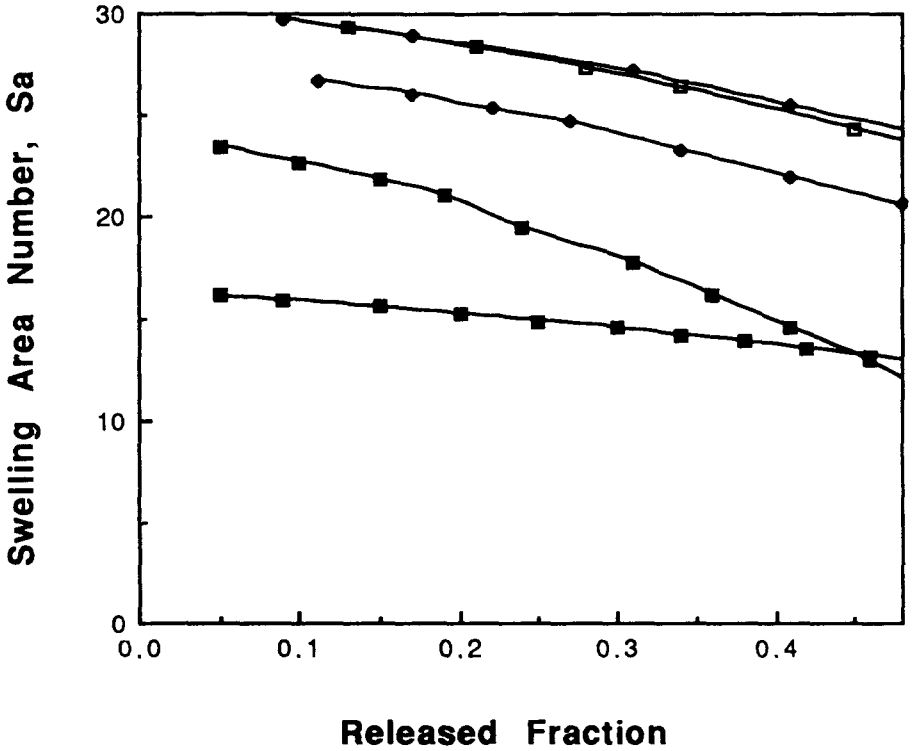

Fig. 9 Calculated swelling area number vs fractional diltiazem release from the five systems prepared Case 0 (⊡), case 1 (♦), case 2 (■), case 3 (◆), case 4 (■).

to Eqn A1, this number is analogous to a Peclet number in that it compares a pseudo-convective process to a diffusional process. However, whereas the Peclet number defines these processes for the same diffusant, the swelling interface number relates transport phenomena of a penetrant and a solute (drug):

$$\mathrm{Sw} = \frac{v \cdot \delta(t)}{D} \tag{A1}$$

where, v is the penetrant front velocity, $\delta(t)$ denotes the swollen layer thickness and D is the drug diffusivity.

As the term $v\delta(t)$ has units of area, it is evident that a similar dimensionless number may be defined to describe the significant expansion of three-dimensional systems due to swelling and its associated influence on drug release. This is important since Sw is inherently related to one-dimensional transport (transport into and release from thin discs or films), whereas the improved dimensionless number can be used to describe the behavior of truly three-dimensional systems (e.g., tablets).

The swelling area number, Sa, is defined as:

$$\mathrm{Sa} = \frac{1}{D} \cdot \frac{\mathrm{d}A}{\mathrm{d}t} \tag{A2}$$

where $\mathrm{d}A/\mathrm{d}t$ is the expansion rate of the surface area of the swelling system.

The swelling area number may describe the swelling behavior under both non-isotropic and isotropic conditions. The first case is that of slow change from glassy to rubbery front, whereas the second is that of a system that continues swelling past the glassy/rubbery transition.

It is evident that for isotropic swelling, Sa can be written in terms of the changing front velocity in one direction, $\mathrm{d}l/\mathrm{d}t = v$, as follows:

$$\mathrm{Sa} = \frac{1}{D} \cdot \frac{\mathrm{d}A}{\mathrm{d}t} = \frac{1}{D} \cdot \frac{\mathrm{d}t \cdot \delta(t)}{\mathrm{d}l} = \frac{v \cdot \delta(t)}{D} = \mathrm{Sw} \tag{A3}$$

The advantage of the new analysis is that one may obtain data of the expanding area of a system as a function of time. Such data may be usually fitted to a second-order polynomial expression of the type:

$$A = \alpha' + \beta' t + \gamma' t^2 \tag{A4}$$

Then, the expansion area change can be calculated as:

$$\mathrm{d}A/\mathrm{d}t = \beta' + 2\gamma' t \tag{A5}$$

and evaluated either at the beginning of the swelling process or at various intervals past the point when the glassy/rubbery fronts have reached the center of the system.

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