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Drug release modulation by physical restrictions of matrix swelling

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Summary

Swellable matrix systems with anomalous release kinetics are suitable solutions for drug release control for oral administration. Generally, the release rate modulation is achieved through the use of different types of polymer or the employment of soluble or insoluble fillers. The resulting release mechanism depends on the relative importance of tablet relaxation and drug diffusion rates. By adjusting these two rates, it is possible simultaneously to control the release mechanism and the release rate. In this work, we present the results obtained by changing the relaxation rate of the matrix by means of the application of impermeable coatings that partially cover the matrix. The applied impermeable coating modifies the relaxation rate of the matrix by affecting the dimension of the swelling of the plain matrix while leaving the diffusion characteristics of the drug practically intact. The overall result is that the original kinetics of the uncoated matrix is shifted towards constant release, dependent on the extension and position of the impermeable coating.

Introduction

Swellable matrices, as drug delivery systems, exhibit anomalous release kinetics (Ritger and Peppas, 1987), and are suitable forms for release control in oral drug administration. Generally, their release rate modulation is achieved using different types of polymers (Baveja et al., 1987) or soluble or insoluble fillers (Catellani et al., 1988). The resulting release mechanism depends on the relative importance of tablet relaxation and drug diffusion rates (Lee, 1985).

In order to improve the control of drug release kinetics many attempts to manipulate the relative influence of the two described rates have been made. Surface cross-linking of the matrix (Colombo et al., 1985), initially non-uniform drug distribution (Lee, 1984) and use of ionic-exchange resin in the matrix (Feely and Davis, 1988) are examples of the changing of drug diffusion or relaxation rates for the design of drug release from these systems.

The aim of this work was to provide a new method for easy and predictable control of drug release from a swellable matrix. The idea was to

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change the relaxation rate of a cylindrical matrix by the application of impermeable coatings that cover one or two bases of the matrix itself. The applied impermeable coating could affect the relaxation of the matrix by changing the dimensionality of the swelling of the plain matrix, leaving the diffusion characteristics of the drug practically intact. The overall results could be a modulation of drug release rate and a shift of the original kinetics of the uncoated matrix towards constant drug release.

Materials and Methods

Matrix preparation

A mixture of 35 parts hydroxypropylmethylcellulose (Methocel® K100 M, Colorcon, Orpington, U.K.), 14 parts mannitol (USP XXI), and 45 parts diltiazem HCl (Profarmaco, Milan, Italy) was kneaded with 5 parts ethylcellulose (Ethocel, BDH Chemicals, Poole, U.K.), dissolved in acetone-alcohol (concentration 10% w/w) and granulated with an oscillating granulator (Erweka, type FGS, Frankfurt am Main, F.R.G; screen ASTM no. 25, 710 μm).

The dried granules were lubricated with 1 part magnesium stearate (USP XXI) and compressed using a reciprocating tabletting machine (Korsch EKO, Berlin, Germany) equipped with concave punches of 0.700 cm diameter. The obtained matrices were 0.704 cm in diameter and 0.265 cm in thickness (aspect ratio 2.6).

One or two of the bases of the obtained matrices were coated with acetonic solution of 12% w/v cellulose acetate propionate (CAP 482-20, Eastman Kodak, Rochester, NY, U.S.A.): 0.1–0.2 ml of the CAP solution was dropped on the cylindrical matrix base. The dropped solution, after spreading to coat the entire base, was dried in an air circulating oven at a temperature not exceeding 35°C. This operation produces matrices having only one base coated, leaving free for dissolution the second base plus the lateral surface. When the coating operation was repeated on the second base, matrices having two bases coated were obtained, leaving only the lateral surface free for dissolution.

Three types of systems were prepared: plain matrix, matrix coated on one face and matrix coated on two faces.

Swelling and release experiments

All matrices were swollen in deionized water at 37°C in the cell of a flow-through dissolution apparatus (Sotax AG, Basel, Switzerland). Drug release measurements were obtained in the same apparatus, concomitantly with the matrix swelling observation. The drug concentration was measured spectrophotometrically at 236 nm. During the release experiment, pictures were taken in order to measure the height and diameter of the systems undergoing swelling.

Results and Discussion

Morphology of systems during release

For the sake of simplicity the systems prepared are coded: Case 0, the plain matrix; Case 1, the one coated on one face; Case 2, the one coated on two faces.

The morphological changes in the three types of system were observed by photography. In spite of the cylindrical form of the systems, their aspect ratio determines a slab like behavior, in which, initially, the swelling is axial to the large surface of slab and, successively, is in a radial direction. This is caused by the restriction to the swelling due to the central glassy core of the slab (Urdhal and Peppas, 1987).

In fact, at the beginning of the release experiment, the swelling of the uncoated system (Case 0) is predominantly axial, showing an evident restriction to swelling due to a glassy core that limits the radial swelling of the matrix. Very quickly (after 15 min) the swelling of the matrix moves both in axial and radial directions.

After coating on one face (Case 1), the dimensionality of the matrix relaxation behavior changes. In the early stages (less than 60 min) the swelling direction close to the coated face is radial and close to the uncoated face it is axial. The swelling of the system coated on two bases (Case 2) becomes predominantly radial. The form of the three

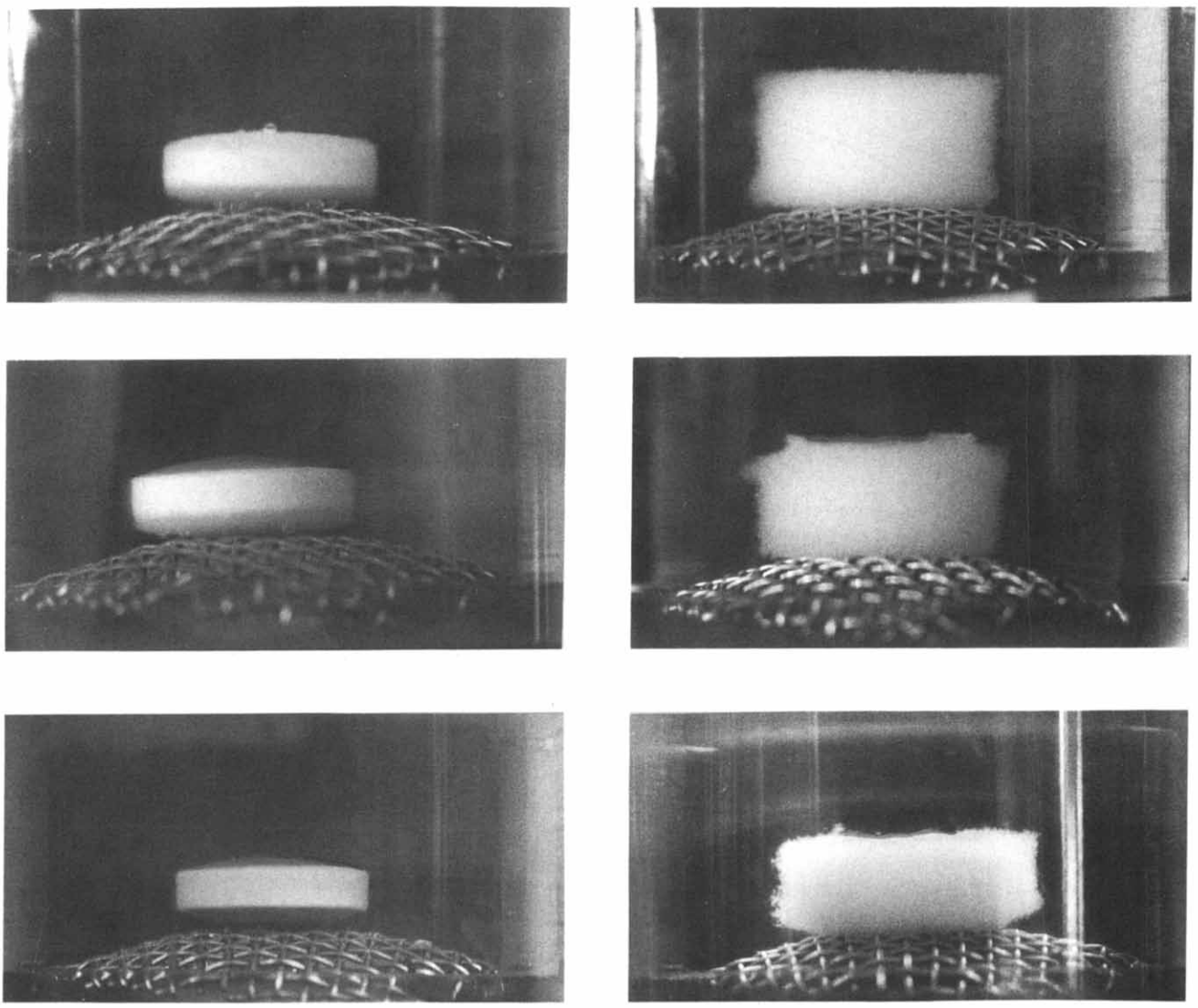

Fig. 1. Photographs of the progressive swelling of the matrices in Case 0 (top), Case 1 (middle) and Case 2 (bottom) for $t = 5$ s (left column) or $t = 120$ min (right column).

systems after swelling reflects the influence of partial coating on systems relaxation (Fig. 1).

In order to compare quantitatively the morphological behavior of the three systems, thickness and diameter increases during relaxation were measured.

Figs 2 and 3 show the measured values of thickness and diameter, normalized to the initial values, plotted vs time. The fastest thickness increase is exhibited by the plain matrix. After application of coating this rate decreases noticeably for the Case 2 system, while the Case 1 system shows an intermediate variation. On the other hand, the diameter increases more quickly for the Case 2 system, whereas the Case 1 and Case 0 curves are practically superimposed.

These measurements clearly demonstrate that the coating application on the bases changes the relaxation of the plain matrix from axial to radial direction.

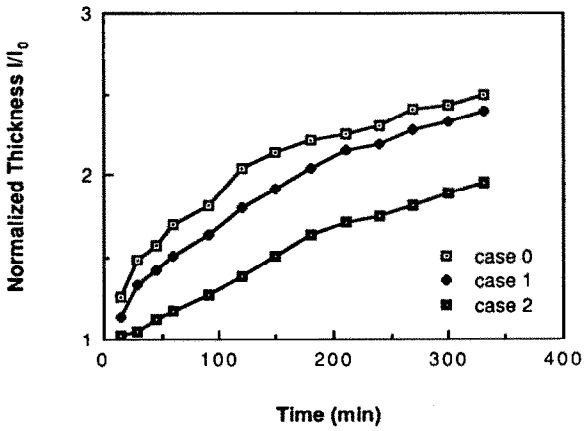

Fig. 2. Increase of normalized thickness of the systems during drug release experiments.

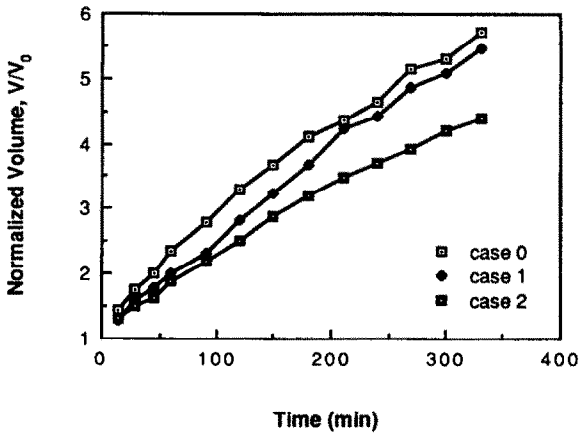

Fig. 4. Increase of normalized volume of the systems during drug release experiments.

In order to evaluate globally the relaxation of the three different systems, the equilibrium degree of swelling (fraction of volume increase), Q, was calculated from the radial and axial swelling ratio as:

$$Q = V_t/V_0 = (R_t/R_0)^2 \cdot (l_t/l_0) \qquad (1)$$

where V_t and V_0 are volumes, R_t and R_0 radii, and l_t and l_0 thicknesses at time t and time zero. The results are presented in Fig. 4.

The fastest increase in volume is exhibited by the Case 0 system, the slowest by Case 2 while Case 1 shows a behavior parallel to Case 2 at the beginning and to Case 0 at the end of the swelling history. This result is not totally unexpected, if one considers that impermeable coatings reduce the matrix area available for interaction. It is, however, interesting to note the intermediate behavior of the Case 1 system.

Drug release from the three systems

The release behaviors of the three systems studied were significantly different. The release rate of diltiazem HCl was markedly reduced because of the coating of the matrix bases (Fig. 5). For example, the release half-times obtained with flow-through apparatus for three identical matrices

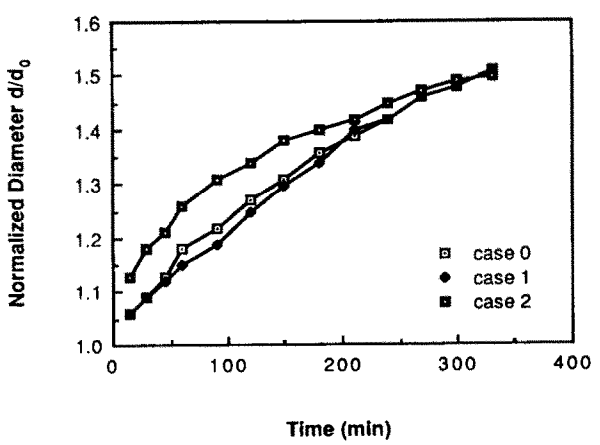

Fig. 3. Increase of normalized diameter of the systems during drug release experiments.

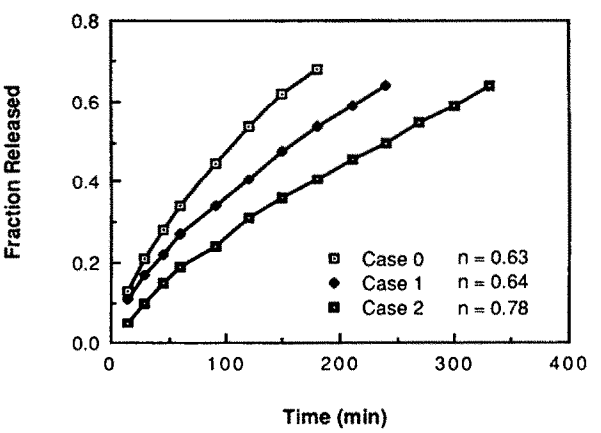

Fig. 5. Drug release profiles of the systems. Calculated values of exponent n of Eqn 2 are also shown.

coated in order to prepare Case 0, 1 and 2 systems, were 108, 160 and 234 min, respectively.

The kinetics of drug release was evaluated by using the well-known exponential release equation (Ritger and Peppas, 1987):

$$\text{fraction released} = kt^n \qquad (2)$$

(t = time, k and n = constant), in which the exponent n indicates the kinetics of the release (it ranges from Fickian ($n = 0.5$) to zero order ($n = 1$), being anomalous for the intermediate values).

The n values obtained show that the kinetics of the plain matrix is anomalous, as expected for a swellable system, and tends to approach constant release, as a function of the number or extension of coatings applied.

The differences in release of the systems are more clearly represented in Fig. 6, where the instantaneous release rates of the three systems vs time are shown. The change in the release rate of the Case 0 system is more evident than that of Case 2, which presents a smaller range of rate variation. Since this comparison does not take into account the fact that the three systems expose differing releasing areas, from the pictures taken the instantaneous releasing areas of the systems were measured. The results are presented in Fig. 7.

Starting from different initial areas, the releasing area of the Case 0 system increases with a kinetics evidently different from the Case 2 system. The behavior of Case 1 is confirmed as being between the previous two.

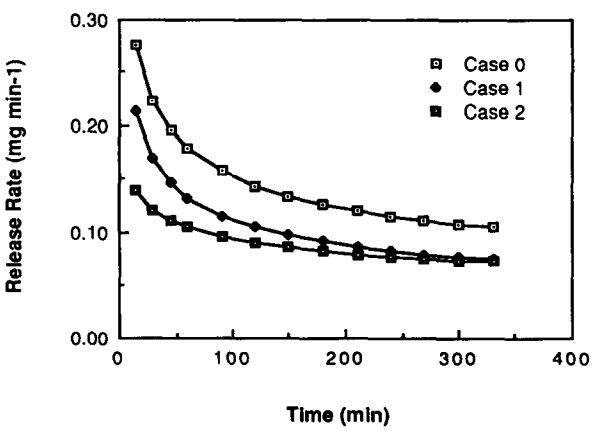

Fig. 6. Instantaneous release rates of the three systems measured from the flow-through drug release profiles.

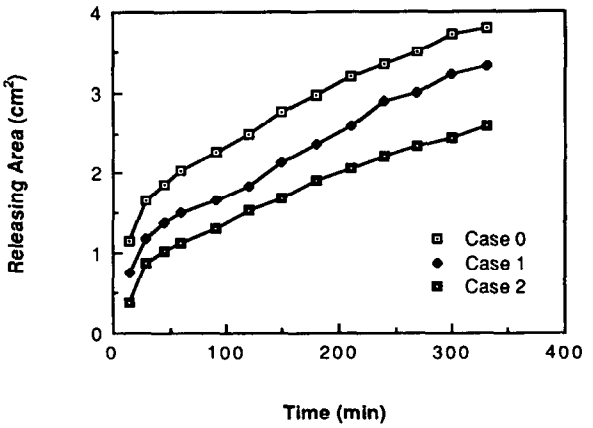

Fig. 7. Releasing area increase of the three systems measured during the flow-through release experiments.

Thus it is possible to explain the different release rates and kinetics observed: the kinetics of the releasing area modification of the system is responsible for the drug release kinetics, whereas the amount of area determines the amount of drug released.

This is fully demonstrated by the fact that when the instantaneous release rates are normalized by the corresponding values of the releasing area, the release rates per unitary area are practically identical for all the systems examined (Fig. 8).

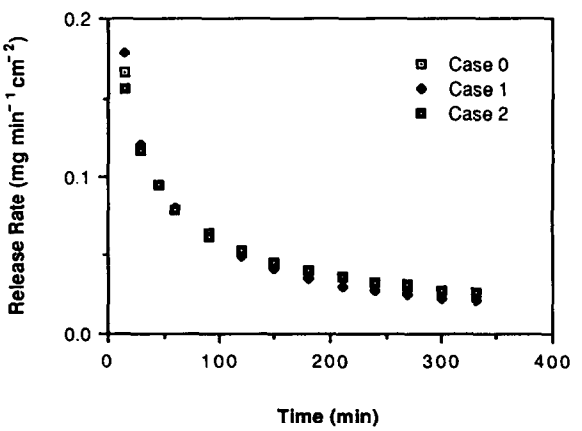

Fig. 8. Release rate per unitary releasing area of the three systems measured from the flow-through drug release experiments.

The application of an impermeable partial coating to a swellable matrix reduces the amount of drug released by reducing the available releasing area of the system. The extension of releasing surface during swelling increases more slowly as the area of the coating applied increases. Because the coating changes the dimensionality of the matrix swelling, the kinetics of matrix relaxation is changed, as compared to the kinetics of the uncoated matrix.

The drug release kinetics follows the kinetics of matrix relaxation, expressed by the external releasing surface increase of the matrix.

The fact that the kinetics of the drug release shifts towards constant release is probably due to the change in the relative importance of the matrix relaxation and drug diffusion rates.

Conclusions

In the systems prepared, the matrix release rate decreases with the extension of the coating, but the release rate per exposed area remains unchanged.

The release kinetics of the drug from the matrix depends on the kinetics of swelling, expressed as releasing area produced. The different release mechanisms connected with the different coating positions are the result of the change in the relative magnitude of the rate of polymer relaxation compared to the rate of drug diffusion.

Finally, these systems release the drug at the same rate per area but with different kinetics.

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