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COMMUNICATION

Effects of Excipients on Swelling and Drug Release from Compressed Matrices

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ABSTRACT

Polymers, and particularly hydrogels, are becoming very popular in formulating controlled-release tablets because they are excellent drug carriers. The effects of hydrophilic and hydrophobic polymers, incorporated in matrices containing soluble (propranolol HCl) or less soluble (flurbiprofen) drugs, on swelling and release kinetics were investigated. The results indicate that swelling and release profiles were affected by the amount of ingredients, the characteristics of the polymer, and the drug substances incorporated in the matrices. Swelling may influence the release rate of the drugs from the matrices. The data obtained from the in vitro dissolution study were evaluated on the basis of a theoretical dissolution equation, by linear transformation of the dissolution curve, and by the Peppas equation. The release mechanisms appeared complex and are affected by the composition of the matrix.

INTRODUCTION

Matrix systems composed of polymers and other excipients as vehicles for drug delivery have been extremely popular in controlling the release rate. Several studies have shown the relationship between drug release rate, excipients incorporated in the matrix, and swelling (1-3).

Swellable systems consisting of hydrophilic polymers, in the presence of water, absorb a significant amount of water dissolution medium to form gel. As the dissolution medium penetrates the matrix, polymer material swelling starts and drug molecules begin to move out of the system by diffusion. Swelling therefore modifies the drug release; and compared with a porous, inert, nonswellable matrix, the porosity and tortuosity of a swellable matrix are primarily attributed to the polymer swellability. In swellable systems, the drug release occurs by water absorption, matrix swelling, and subsequent drug diffusion through the gel layer.

In nonswellable systems, the drug is released by leaching out of the drug by the fluid, which is able to

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enter the matrix through pores and cracks. The drug is presumed to be dissolved into the permeating fluid phase and to diffuse from the system along the cracks and channels filled with the dissolution medium.

The aim of the present study was to investigate the role and influence of the ingredients on swelling, the effects of swelling on drug release, and also to describe the release kinetics. The drug release results were evaluated on the basis of dissolution equations and by linear transformation of dissolution curves. Thus, an attempt was made to determine whether the rates of release of the drug from the different formulations followed zero-order, first-order (as log of undissolved percent of drug vs. time), the Higuchi model (4), or the Peppas equation (5).

MATERIALS AND METHODS

Materials

For preparation of the tablets, the following materials were used:

Flurbiprofen (kindly provided by Boots)
Propranolol HCl (kindly donated by ICI)
Acrylic resin was Eudragit RS100 (kindly given by Rohm Pharma)
Polyethylene oxide was Polyox NF coagulent (kindly offered by Union Carbide)
Hydroxypropylmethycellulose was Methocel K 100MCR (kindly provided by Dow Co.)
Lactose (Mendel)
Dextrose (Megglie)
Sodium carboxymethycellulose (NaCMC) (Aqualon)
Magnesium stearate (BDH)
Sodium taurocholate (Fluka)
Sodium laurylsulfate (BDH)

Methods

The mixture—i.e., the drug excipients (the acrylic resin was first powdered in a ball mill and sieved through a 300-mm sieve) and the magnesium stearate—was thoroughly mixed in a blender for 10 min. The tablets (500 mg) were compressed using the direct compression technique on an instrumented single-punch tablet machine (Korsch-Erweka). The formulations prepared are listed in Table 1.

The ratio between the diameter and thickness of cylindrical tablets was within the range of 0.7–0.9. The tablets were compressed to a hardness level between 9 and 10 kg (measured in the Erweka hardness tester). The dissolution study was carried out using the USP dissolution apparatus (paddle method) in 900 ml of intestinal fluid (pH = 7.4) maintained at 37 ± 0.2°C and rotated at 50 rpm. Flurbiprofen and propranolol HCl were assayed spectrophotometrically at 248 and 289 nm, respectively, using a Perkin-Elmer Lambda 6 spectrophotometer. Each data point represents the mean of measurements from three tablets.

Swelling was evaluated by weight. The matrices were placed in 900 ml phosphate buffer pH = 7.4 at 37°C. At hourly intervals, the previously weighed tablets were removed, gently wiped with a tissue to remove surface water, and reweighed. The degree of swelling was calculated using the following equation:

$$\text{Degree of swelling } \% = \frac{W_s - W_d}{W_d} \times 100$$

Table 1

Formulations Used in the Study

Ingredient	Percentage in Each Formulation										
	F1	F2	F3	F4	F5	P1	P2	P3	P4	P5	P6
Flurbiprofen	49	49	49	49	49	—	—	—	—	—	—
Propranolol HCl	—	—	—	—	—	49	49	32	32	32	32
Eudragit RS 100	25	25	25	—	—	—	—	—	17	33.5	67
Methocel K100MCR	—	—	—	—	13	—	13	—	—	—	—
Sodium carboxymethylcellulose	—	—	—	—	—	—	—	67	50	33.5	—
Polyox	—	—	—	13	—	13	—	—	—	—	—
Lactose	—	—	—	37	37	37	37	—	—	—	—
Dextrose	25	25	25	—	—	—	—	—	—	—	—
Sodium laurylsulfate	—	1	—	—	—	—	—	—	—	—	—
Sodium taurocholate	—	—	1	—	—	—	—	—	—	—	—
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1

where W_d is the final dry weight of matrix and W_s is the swollen weight of the same matrix at immersion time (t) in the buffer. The swelling degree was the mean of at least three determinations.

RESULTS AND DISCUSSION

When the matrices were prepared of nonsoluble, hydrophobic, insoluble in pH acrylic resins, and flurbiprofen as a model drug (only slightly soluble in water)—i.e., formulations F1–F3—the swelling of the matrix was low and the release rate of the drug was limited. Within 8 hr, only about 30% of the incorporated drug was released (Fig. 1). Incorporation of the surface-active agents sodium laurylsulfate and sodium taurochlolate resulted in a minor increase in swelling of the matrices (Fig. 1), followed by a low increase of release of the drug. Apparently, the incorporation of surfactants has as a result the increase of drug release which mainly comes from the release of the drug from the outer zone of the matrix and may be attributed to the increase of wetting and the lowering of surface tension of the medium resulting in increased porosity. Furthermore, a small amount of drug may be released from the interior, due mainly to increased swelling and diffusion process. The faster release of the drug from matrices containing sodium taurocholate (ST) may be attributed to the higher swelling of ST matrices and the higher solubility of this surfactant in water. ST has a solubility of 2 in 1 in water, while sodium laurylsulfate (SLS) has a solubility 1 in 20 in water (6).

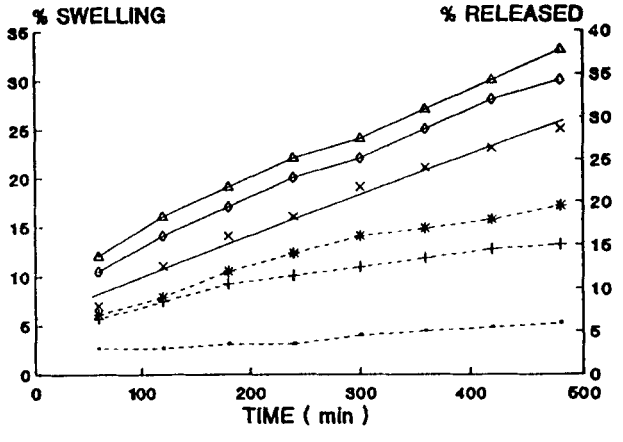

Figure 1. Double -y plots showing dissolution profiles of flurbiprofen release (F1 --X--; F2 --◇--; F3 --Δ--) and swelling (F1 --■--; F2 --+--; F3 --*--) from matrices containing Eudragit RS 100.

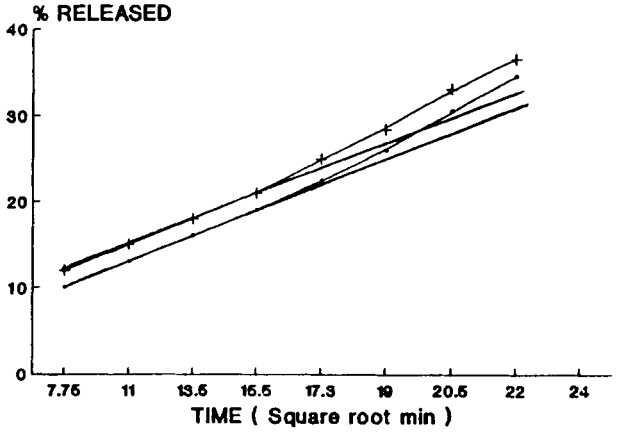

Figure 2. Flurbiprofen release vs. square root of time (F2 --+--; F3 --■--).

Higuchi plots of mean percent release versus square root of time (Fig. 2) show that the cumulative amount of flurbiprofen released at time t was linearly proportional to the square root of time, up to the fourth hour. As shown, drug is released by a diffusion process which is accelerated after the fourth hour due to attrition of tablet surface (7).

When propranolol HCl (a very soluble compound in water) was used as a model drug, the matrices were disintegrated and the drug was released in less than 2 hr, due basically to its high solubility in water.

Flurbiprofen matrices prepared of hydrophilic materials—i.e., polyox F4 and methocel F5—show a significant swelling. Polyox matrices containing flurbiprofen show a fast increase of swelling with maxima observed at the fourth hour and at the time period when about 40% of the drug load was released, although from the first hour maximal swelling was approached (Fig. 3). Further, a continuous, initially sharp, decrease of swelling is observed between the fourth and fifth hours due, presumably, to release of the drug, disintegration (cracks developed on matrix surface after the fourth hour), and dissolution of part of the polymer. Methocel matrices also exhibit a fast swelling with a maximal swelling between the third and the fourth hours, when about 30% of the drug was released. Swelling decreases more smoothly and no cracks were observed on matrix surfaces.

When propranolol HCl was incorporated the swelling of polyox P1 and methocel P2 matrices exhibited a different behavior, as shown in Fig. 4. Both matrices show a continuous increase of swelling with maxima at the sixth hour for polyox and the seventh for methocel

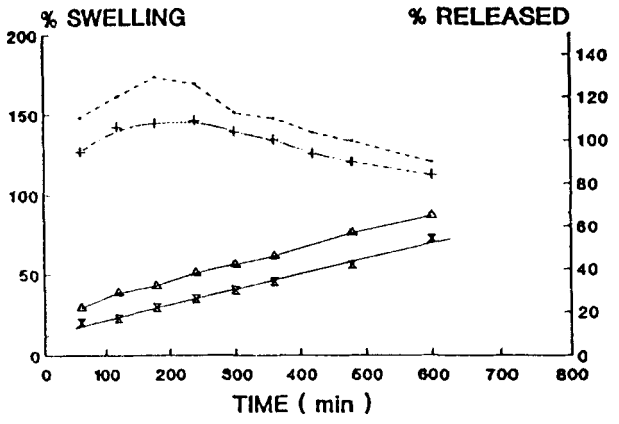

Figure 3. Double -y plots showing dissolution profiles of flurbiprofen release (F4 --Δ--; F5 --⧖--) and swelling (F4 --■--; F5 --+--) from matrices containing methocel K100MCR and polyox.

matrices, when the 95% and 50% of the drug has been released, respectively. Thus for the P1 matrices it is reasonable to assume that, since drug release and matrix swelling are comparable, the release kinetics are influenced by polymer hydration and swelling, while this phenomenon is less profound for P2. For F4 and F5 matrices it appears that the release kinetics are not influenced significantly by the swelling kinetics. In this respect the solubility of propranolol HCl may explain this behavior. Release data (Fig. 3 and Fig. 4) show that polyox matrices always exhibit a faster release of drugs, presumably due to faster hydration and highest swelling of polyox compared with methocel (8).

Matrices containing a mixture of hydrophobic moiety, i.e., acrylic resins, hydrophilic polymeric materials NaCMC, and propranolol HCl as a model drug reveal a significant swelling depending on the content of the hydrophilic polymer (Fig. 5). Matrices containing only acrylic resins P6 showed a minor increase in swelling, while in matrices (P3–P5) containing high amount of NaCMC, significant swelling was observed, with a maximal between the third and fourth hours. Dissolution curves (Fig. 5) show that release of the drug is dependent upon the content of NaCMC, and consequently swelling in these matrices increased as the content of NaCMC was increased while release rates were decreased. In matrices containing only acrylic resin, swelling is very low and release is very high, a fact which is attributed to the attrition and disintegration of the matrix. The least square equation for the data indicates that a linear relationship exists between t_{50} value and the percentage of NaCMC content in the matrices: $y = 2.77x + 69.33$, $r = 0.997$.

In order to elucidate the release mechanism, the data were fitted to models representing zero-order, first-order, Higuchi, and Peppas equations indicative of release mechanisms related to time (9,10). In Table 2 the estimated values of slope, intercept correlation coefficient following regression of release data, and the diffusional exponent n are listed. Although the release curves of swelling controlled systems do not fit often, we attempted to fit our results (only for $M_t/M < 0.7$) in equation

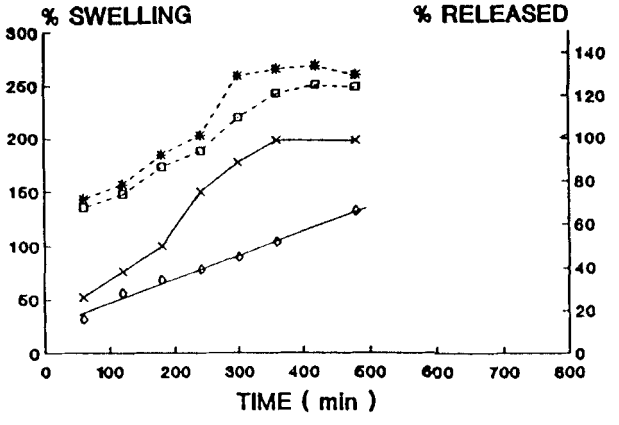

Figure 4. Double -y plots showing dissolution profiles of propranolol HCl release (P1 --×--; P2 --◇--) and swelling (P1 --*--; P2 --□--) from matrices containing methocel K100MCR and polyox.

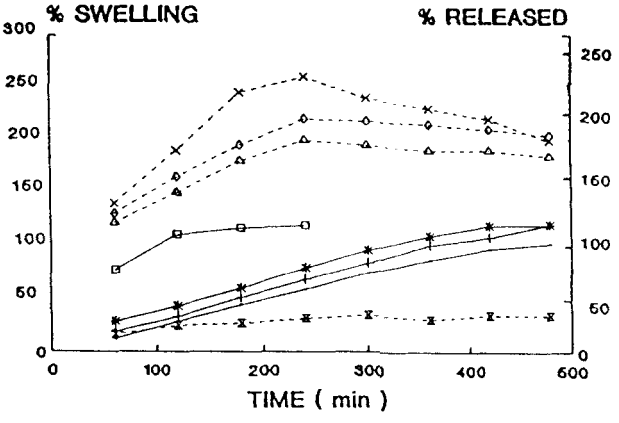

Figure 5. Double -y plots showing dissolution profiles of propranolol HCl release (P3 --■--; P4 --+--; P5 --*--; P6 --□--) and swelling (P3 --×--; P4 --◇--; P5 --Δ--; P6 --⧖--) from matrices containing Eudragit RS 100 and NaCMC.

Table 2

Kinetic Assessment of Release Data

Formulation	Zero-Order			First-Order			Higuchi Equation			Diffusional Exponent
	Slope	Intercept	r^2	Slope	Intercept	r^2	Slope	Intercept	r^2	(n)
F1	0.055	3.08	0.985	-0.003	1.98	0.992	1.291	-1.99	0.989	0.65
F2	0.053	5.64	0.960	-0.003	1.97	0.972	1.300	-0.08	0.997	0.47
F3	0.061	5.73	0.967	-0.003	1.97	0.979	1.482	-0.50	0.998	0.51
F4	0.094	12.30	0.960	-0.007	1.96	0.988	2.551	-0.11	0.995	0.48
F5	0.062	10.01	0.996	-0.004	1.97	0.987	2.04	-3.64	0.992	0.70
P1	0.271	4.22	0.978	-0.016	1.98	0.988	5.151	-9.80	0.995	0.58
P2	0.011	13.19	0.997	-0.009	1.98	0.989	2.903	-3.15	0.992	0.68
P3	0.181	2.04	0.995	-0.002	2.07	0.987	3.892	-10.41	0.950	1.01
P4	0.200	5.60	0.995	-0.003	2.25	0.941	3.543	-4.92	0.960	0.95
P5	0.232	6.58	0.994	-0.003	2.08	0.960	3.600	-1.42	0.988	0.85
P6	0.385	24.21	0.873	-0.009	2.00	0.997	[a]	[a]	[a]	[a]

[a]Insufficient data.

3 of Ref. 11. The results indicate that the mechanism of release is influenced greatly by the excipients of the formulation as can be seen from the r^2 values and n was generally in accordance with these indications.

In preparations consisting of nonswellable materials (F1), the release mechanism is explained better by first-order kinetics; however, with the value of diffusional exponent $n = 0.67$ it seems to follow anomalous kinetics (12). Incorporation of the surfactants sodium lauryl sulfate F2 and sodium taurocholate F3 results in an increase of swelling (Fig. 1) and a change in release mechanism, since the data appear to fit better the Higuchi model. The release is mainly determined by Fickian diffusion which is also confirmed from the n values. Formulation F2 has $n = 0.47$ and F3 has $n = 0.51$, values which are very close to $n = 0.5$ indicating that the release mechanism is very close to Fickian transport; i.e., belong to the Higuchi model (Table 2). Formulations F4 and P1 containing the swellable hydrophilic material polyox, lactose as diluent, and flurbiprofen and propranolol HCl, respectively, both show a significant fit to the Higuchi model, with n values for F4, $n = 0.48$; and P1, $n = 0.58$, indicate a mechanism close to Fickian. Formulations F5 and P2 contain the other swellable hydrophilic material methocel, lactose, flurbiprofen, and propranolol HCl, respectively. In these formulations the determination of mechanism is rather difficult since no significant differences were observed, between zero-order release and Higuchi model indicating that a complex mechanism influences the release of the drug. Values of the diffusional exponent in this range F5, $n = 0.70$; and P2, $n = 0.68$, are indicative of a coupling of diffusional and macromolecular relaxation release mechanisms (13). Eventually propranolol HCl formulations P4 and P5 contain a mixture of hydrophilic NaCMC and hydrophobic Eudragit RS100, P3 contains only NaCMC, and P6 only Eudragit RS100. As can be seen from the Table 2, all formulations containing NaCMC appear to follow zero-order kinetics; n values confirm this since they have P3, $n = 1.01$; P4, $n = 0.95$; and P5, $n = 0.85$. A close look at these values also shows that increase of NaCMC content has as a result increase of n value and the release mechanism is approaching zero-order; similar results were observed by Ranga et al. (14) in their studies. In contradiction, formulation P6 shows a first-order release mechanism.

In this investigation it has been demonstrated that when water penetrates into swellable matrices, the particles of polymer swell, modifying the matrix volume and behavior according to the solubility of the loaded drug and the characteristics of incorporated excipients. The differences can be due to variation in water penetration. Soluble material can produce greater increases in the matrix swelling than the less soluble and exhibit faster release rates. The water penetration increases and the drug diffusion decreases the matrix volume. The swelling and release kinetics are affected by the drug and excipient characteristics.

Polyox matrices exhibit greater swelling and faster release of drug among the polymers used; furthermore in these matrices the time scale of drug release and

matrix swelling are comparable, and therefore the release kinetics are influenced by polymer hydration and swelling. The phenomenon is more profound with the soluble material propranolol HCl.

In the nonswelling hydrophobic matrices of acrylic resins, the release of drug is slow when a hydrophobic drug has been incorporated. The addition of surfactants does increase the release rate to a great extent. In the case of incorporation of a highly water-soluble drug like propranolol HCl, it is obvious that drug dissolution controls the release.

The release mechanism could be complex and is affected by the composition of the matrix. The diffusional exponent n generally agreed with the release kinetic models employed and increased with polymer concentration in the NaCMC formulations.

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REFERENCES

1. L. T. Fan and S. K. Sing, *Controlled Release*, Springer-Verlag, New York, 1989, p. 111.
2. K. V. Ranga Rao and K. Padmalatha Devi, Int. J. Pharm., 48, 1 (1988).
3. E. Doelker, in *Hydrogels in Medicine and Pharmacy*, Vol. 2 (N. A. Peppas, ed.), CRC Press, Boca Raton, FL, 1987, p. 115.
4. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
5. R. W. Korsmeyer, R. Gurny, E. Buri, and N. Peppas, Int. J. Pharm., 15, 23 (1983).
6. M. Efentakis, H. AlHmoud, G. Buckton, and Z. Rajan, Int. J. Pharm., 70, 153 (1991).
7. H. Lapidus and N. G. Lords, J. Pharm. Sci., 57, 1292 (1968).
8. M. Efentakis and M. Vlachou, unpublished data.
9. M. Bamba, F. Pursieux, J. P. Marty, and J. T. Carstensen, Int. J. Pharm., 2, 307 (1979).
10. P. Albin, A. Markus, Z. Ben-Zvi, and Z. Pelah, J. Contr. Rel., 23, 1 (1993).
11. N. A. Peppas and R. W. Korsmeyer, in *Hydrogels in Medicine and Pharmacy* Vol. 3 (N. A. Peppas, ed.), CRC Press, Boca Raton, FL, 1987, p. 124.
12. N. A. Peppas, Pharm. Acta Helv., 60, 110 (1985).
13. J. W. Skoug, M. T. Fleishaker, and A. M. Cooper, Pharm. Res., 8, 1482 (1991).
14. K. V. Ranga Rao, K. Padmaletha Devi, and P. Buri, Drug Dev. Ind. Pharm., 14, 2299 (1988).