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Effect of water-soluble additives on drug release from silicone rubber matrices. III. A study of release mechanism by differential scanning calorimetry

V. Carelli, G. Di Colo and E. Nannipieri

Pharmaceutical Technology Laboratory, Institute of Pharmaceutical Chemistry, University of Pisa, 56100 Pisa (Italy)

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Summary

The mechanism of prednisolone release from non-swelling additive-activated silicone rubber matrices is investigated using differential scanning calorimetry (DSC). The formation of pores of such a size as to allow rapid replacement of additive by the elution medium is demonstrated. The release process is shown to be controlled by a composite dissolution–diffusion mechanism. In a first stage the whole matrix volume is cleared of drug particles with a high dissolution rate due to having most of the surface in direct contact with the pore fluid. In the second stage particles are dissolved that are either partly or totally surrounded by polymer. The behavioral differences between the various additives and the effects of formulation variables and matrix thickness on drug release that were illustrated in Part II are discussed in mechanistic terms.

Introduction

In the latest report of this series on facilitated drug delivery from polydimethylsiloxane (PDS) the release of 20% loading doses of micronized prednisolone was shown to be activated by liquid hydrophilic additives, such as glycerol, ethylene glycol and polyethylene glycol (PEG) 200 (Di Colo et al., 1985). No definite proof of the mode of action of the additives was presented, except that it did not involve matrix swelling. Nevertheless, the hypothesis was advanced in that report that interconnected pores allowing convective liquid flow might have formed through the combined action of the water carriers and the dispersed drug particles.

This work was aimed at substantiating such a hypothesis and elucidating the important mechanistic features of those release systems, in order for their practical advantages to be best evaluated and useful information concerning the general subject of drug delivery from porous monolithic matrices to be contributed. Differential scanning calorimetry (DSC) was the technique used to pursue the above goals.

Materials and Methods

The formulae of the matrices used in this study are specified in Table 1. They were prepared as

Correspondence: G. Di Colo, Istituto di Chimica Farmaceutica, Università di Pisa, Via Bonanno 6, 56100 Pisa, Italy.

TABLE 1
FORMULAE OF MATRICES

Matrix	Water carrier	Drug load (%)	Water carrier/ PDS ratio $\times 10^2$ (w/w)
G 20/14	Glycerol	20	14
G 20/25	Glycerol	20	25
G 10/14	Glycerol	10	14
EG 20/14	Ethylene glycol	20	14
P 20/14	PEG 200	20	14
Control	None	20	0

disks of 1 cm diameter and 0.1 cm thickness using the same materials and procedure as those reported previously (Di Colo et al., 1985). The commercial prednisolone powder was always used. The volume of entrapped air per unit polymer weight of the prepared matrices was calculated from knowledge of matrix volume, as determined with the aid of a micrometer, matrix weight and composition, and densities of components. Matrices with an air content ranging from less than 0.01 up to 0.085 cm^3/g were obtained by the procedure adopted. Only specimens with an air content less than 0.02 cm^3/g were used for study. These were eluted in 0.13 N pH 7.4 phosphate buffer under exactly the same conditions as those of the previous drug release determinations (Di Colo et al., 1985). After a measured elution period they were tested for swelling by weighing in the usual fashion (Di Colo et al., 1982), then used for analysis by DSC. No swelling was generally observed, except for a slight weight increase ($\sim$ 10%) of the P 20/14 type after 1 day elution disappearing in a few days.

Determination of prednisolone density

The density of prednisolone macrocrystals obtained through recrystallization of the commercial product from quiescent ethanol was determined pycnometrically using petroleum ether (b.p. 100–140°C) as the pycnometer liquid. The suspension in the pycnometer was de-aerated under reduced pressure. The determined value of prednisolone density was 1.275 g/cm^3.

Differential scanning calorimetric studies

The Mettler TA 3000 Thermal Analysis System consisting of the TC 10 TA Processor, the DSC 20 measuring cell and printer/plotter was used for these studies. Aluminum pans and lids were always used.

Temperature calibrations were made using indium (156.6°C), lead (327.4°C) and zinc (419.5°C). The heat of fusion of an exactly known quantity of indium was used for heat flow calibration. The matrices were analyzed for their aqueous phases by the purity analysis method, automatically executed by the instrument, over a temperature range of -20 to $+10$°C, at a heating rate of 2°C/min (the measuring cell worked in a freezer at -40°C). The temperature limits for integration of the fusion peak were automatically selected by the instrument. Type 8 was chosen as the integral baseline. This is a curve joining the measured points at the start and end of integration, allowing determination of the pure energy of transition in cases where a change in the specific heat for the sample is associated with the transition (Mettler, 1983). The samples were small disks (0.5 cm diameter, around 20 mg weight) cut out of the centres of matrices immediately following the swelling test. They were analyzed in hermetically sealed pans. The corrected heat of fusion and the interval of fusion (ΔT_m, difference between the melting point of the last crystals and the temperature corresponding to a 10% degree of melting) supplied by the purity analysis method were the data used for the present investigation. Data for the matrix samples were compared with those for standards such as double-distilled water, the phosphate buffer used as the elution medium, and aqueous solutions of known additive concentration. Following thermal analysis, the prednisolone content in each of the matrix samples was determined through extraction with ethanol and spectrophotometric analysis of the extracts at 242 nm.

Qualitative thermal analysis of prednisolone in the outer or inner regions of matrix was carried out as follows. Each of two 0.5-cm diameter disks cut out of the centres of two equal matrices was severed into three sections, the outer ones $\sim$ 0.2 mm and the inner one $\sim$ 0.5 mm thick. The resulting four outer and two inner disks, respectively, brought together, were desiccated over P_2O_5 at

room temperature and reduced pressure for 1.5 h, then scanned in sealed pans over a 50–300°C range, at a heating rate of 8°C/min. Matrices of the G20/14 and G20/25 types eluted 4 or 7 days were analyzed by this procedure, and the resulting thermograms compared with those for control matrix, commercial prednisolone and hydrous crystal form of prednisolone, the last obtained as described by Wurster and Taylor (1965).

Results and Discussion

Porous nature of matrices

The presence of bulk water in all of the matrices compounded with the additives appeared ever since the first day of elution from a sharp melting endotherm around 0°C in the DSC trace. This is typified in Fig. 1 by the thermogram for a G20/14 specimen (trace D). The thermogram for the control matrix eluted 90 days (trace A) displayed no appreciable transition peak indicating that in the absence of a water carrier the released drug was not replaced in matrix by the external solution. Otherwise, the sample analyzed by DSC should have contained 0.68 mg of water (readily calculated from sample weight, drug density and fraction drug released) melting of which should have absorbed ~ 230 mJ, i.e. an energy amount clearly detectable by the instrument.

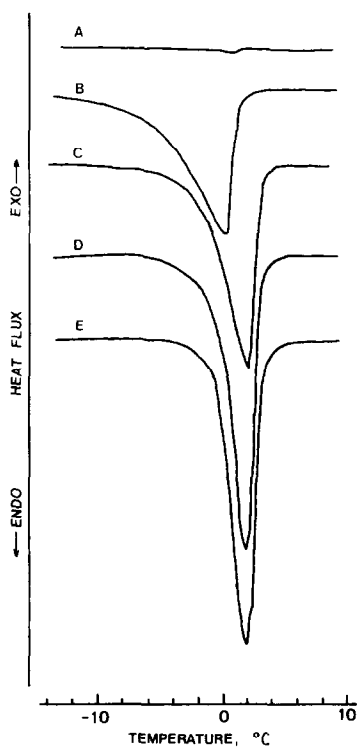

Fig. 1. Thermograms for the DSC purity analysis of representative matrices and reference solutions. (A) control matrix (eluted 90 days); (B) 10% (w/w) glycerol; (C) 2.6% (w/w) glycerol (iso-osmotic); (D) matrix G 20/14 (eluted 1 day); (E) 0.13 N pH 7.4 phosphate buffer (iso-osmotic).

Water carrier content in matrix fluid

Information on the water carrier content in matrix fluid was sought in comparing the interval of fusion of this fluid with those of standard solutions. The ΔT_m values for matrices eluted different periods and the references are found in the Tables 2 and 3, respectively. For each item in the Tables, the Sondack linearization corrections (Sondack, 1972) for the single measurements are reported as percent of corrected heat of fusion (K%). For validity of determinations to be granted such corrections should not exceed 15% (Mettler, 1983). Therefore, the data in Table 3 for the 10% glycerol and 10% ethylene glycol solutions should be taken as merely indicative. Comparison of data clearly indicates additive concentrations in the aqueous phases of the matrices G 20/14, G 10/14 and EG 20/14 not exceeding the respective iso-osmotic values ever since the first day of elu-

TABLE 2
DATA FROM DSC PURITY ANALYSIS OF MATRICES

Matrix	Elution period (days)	$\Delta T_m \pm s$ [a] (°C)	K% (endothermal)
G 20/14	1	1.8 ± 0.5	5.06; 8.49, 9.98
	60	2.2 ± 0.2	6.61; 8.95; 9.58
G 10/14	1	2.2 ± 0.2	9.02; 9.55, 9.83
	60	2.1 ± 0.1	5.93, 8.91; 10.12
EG 20/14	1	1.4 ± 0.7	3.25; 9.21; 10.72
	60	0.8 ± 0.1	3.56; 3.79; 4.08
P 20/14	1	3.5 ± 0.5	9.54; 9.73; 10.01
	5	1.3 ± 0.2	5.24; 5.31; 6.68
	30	1.0 ± 0.1	5.33; 6.04; 7.08

[a] Mean of three samples from distinct batches ± standard deviation.

TABLE 3
DATA FROM DSC PURITY ANALYSIS OF STANDARD AQUEOUS SOLUTIONS

Solution	ΔT_m[a] (°C)	U% ± s[b]	K% (endothermal)
Phosphate buffer 0.13 N pH 7.4 (iso-osmotic) [c]	0.4	4 ± 2	0.67; 0.80; 1.44
Glycerol 2.6%, w/w (iso-osmotic) [c]	2.2	7 ± 2	6.69; 6.96; 7.64
Glycerol 10%, w/w	4.9	20 ± 2	13.93; 14.78; 15.15
Ethylene glycol 1.7%, w/w (iso-osmotic) [c]	2.2	7 ± 2	6 73; 6.84; 7.80
Ethylene glycol 10%, w/w	5.3	22 ± 2	16.18; 16.67; 17.01
PEG 200 4%, w/w (iso-osmotic) [c]	2.0	11 ± 0	6.21; 6.52; 6.78
PEG 200 10%, w/w	3.9	19 ± 2	10.84; 11.23; 11.78
Pure water	0.0	–	0.02, 0.03; 0.23

[a] Mean of three samples. The standard deviation was always $< 10^{-1}$.
[b] Mean of three samples ± standard deviation.
[c] According to melting point depression as determined by DSC.

tion. This finding and the absence of any detectable matrix swelling support the previous hypothesis of pores having formed to be large enough to allow a rapid fluid flow. For the matrix P 20/14, on the other hand, the analysis indicates a carrier level in the pore fluid approaching 10% at 1 day elution, and then dropping to less than 4% (approximate iso-osmotic value) within 5 days. Explanation of such a delayed clearance of PEG 200 required further analysis to be discussed later in this report. The matrices of the G 20/25 type could not be analyzed by the DSC purity method because the filter paper used to clear the sample surface of clinging solvent also extracted liquid from the inside, evidently due to a larger pore size of this matrix type.

Water content in matrix

The water content in each matrix sample was calculated as the ratio of the heat of fusion of sample to that of unit mass of double-distilled water. Inherent of this determination was an underestimation due to the presence of solutes in the pore water. The size of this error was evaluated for each of the reference solutions and is reported in Table 3 as percent of true value (U%). Since the ΔT_m values for the glycerol and ethylene glycol matrices are between the limits of the respective iso-osmotic reference solutions and the buffer (see Tables 2 and 3), then the U% values for these matrices should be between 7 and 4%. Along this line we can expect the U% value for the PEG matrices to be between 11 and 4% ever since the fifth day of elution, and short of 20% after just one day.

The water content in matrix was expressed as volume per unit polymer weight (V_w), taking the

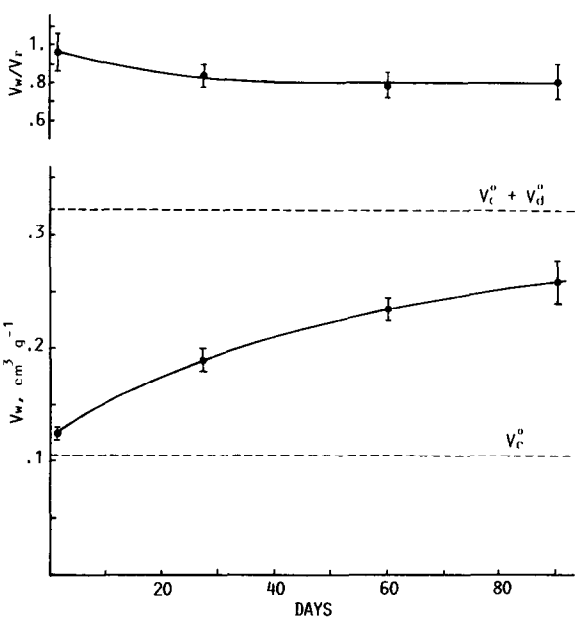

Fig. 2. Water content and replacement ratio for matrix G 20/14 as functions of time. Vw = volume of absorbed water per unit polymer weight; Vr = total volume of drug and water carrier released per unit polymer weight; V_c° = volume of water carrier formulated within matrix per unit polymer weight; V_d° = volume of drug formulated within matrix per unit polymer weight. Each point represents the mean of 3 samples from distinct batches. Vertical bars represent the standard deviation.

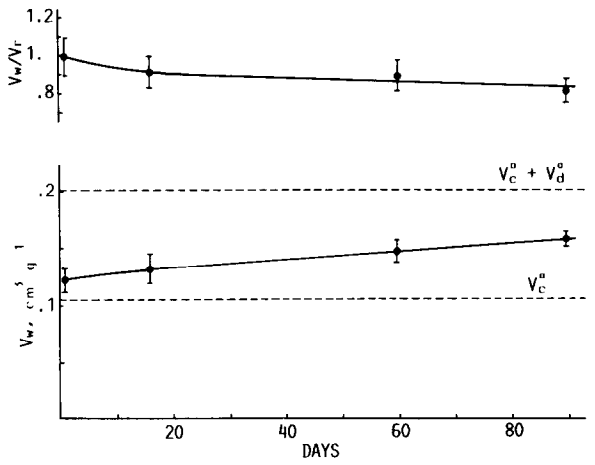

Fig 3. Water content and replacement ratio for matrix G 10/14 as functions of time. Each point represents the mean of 3 samples from distinct batches. Vertical bars represent the standard deviation. Symbols as in Fig. 2.

density of matrix fluid as equal to 1 g/cm^3. This volume is reported as a function of time for the different matrix types in the Figs. 2–5. Also plotted against time in the same figures is the ratio of V_w

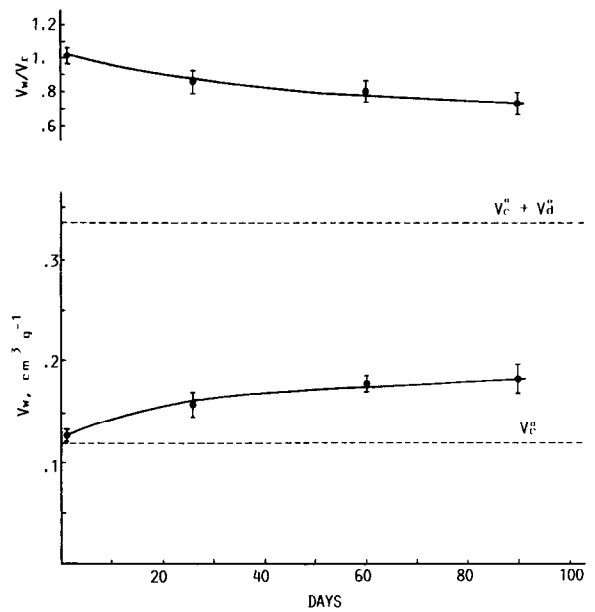

Fig. 4. Water content and replacement ratio for matrix EG 20/14 as functions of time. Each point represents the mean of 3 samples from distinct batches. Vertical bars represent the standard deviation. Symbols as in Fig. 2.

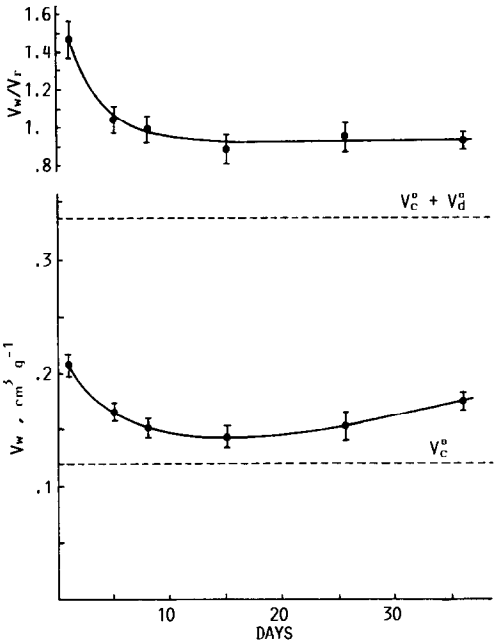

Fig. 5. Water content and replacement ratio for matrix P 20/14 as functions of time. Each point represents the mean of 3 samples from distinct batches. Vertical bars represent the standard deviation. Symbols as in Fig. 2.

to total volume of drug and water carrier released per unit polymer weight (V_r). This ratio gives the degree of replacement of the ingredients released from matrix by the eluting medium. For computation of V_r the volume of water carrier released was taken as equal to the carrier volume formulated within matrix (V_c°). In the Figs. 2–4 the V_w value for the glycerol and ethylene glycol matrices at 1 day elution is greater than the V_c° value, while the V_w/V_r value is around 1, in accord with a practically complete replacement of water carrier by the elution medium. As drug delivery proceeded, solvent absorption into matrix proceeded all along while the replacement ratio became less than 1 and tended to decrease. Since void spaces in matrix, solvent interactions with polymer and osmotic effects were either absent or negligible, such a solvent uptake could only occur through direct replacement of drug as it was dissolved. Therefore a fractional replacement points to the occurrence in the matrices of particles wetted by pore fluid, either totally or partially, along with particles

pletely surrounded by polymer. When dissolved, the former type was replaced by fluid whereas the latter was not replaceable. Both types should be contributing to the release rate, the contribution of the former being predominant at the early stages of the process. Dissolution of the latter type into pore fluid, being mediated by polymer, is indeed supposed to be slower. The fractional contribution from wetted particles to the amount of drug released at time t was calculated from data in Figs. 2–4 as $(V_w - V_c^\circ)/(Vr - V_c^\circ)$. At t = 90 days, when the matrix G20/14 was virtually depleted of drug, the values for the matrices G 20/14, G 10/14 and EG 20/14, accounted for the stated 4–7% underestimate of V_w, were 0.78–0.82 (±0.15), 0.68–0.74 (±0.12) and 0.53–0.57 (±0.11), respectively. Due to the high standard deviations of values, a clear difference between the matrices G 20/14 and G 10/14 cannot be stated, whereas the value for G 20/14 unquestionably appears to be higher than that for EG 20/14. Although the initial porosity and drug load of these two matrices were practically identical, the one formulated with glycerol then seems to have contained a higher fraction of wetted particles. This would explain the higher release rate for this matrix. For the matrix P 20/14 Fig. 5 shows a V_w/V_r value at 1 day elution largely greater than 1. Such an excess of solvent took about a week to disappear, then either V_w or V_w/V_r exhibited much the same trend as that seen with the other water carriers. These findings, and the delayed PEG 200 escape from matrix pointed out before, can be explained with more difficulty for polymer to break into macro-pores, due to either a weaker osmotic power or a more effective polymer plasticizing effect of this additive compared to the other ones (Di Colo et al., 1982, 1984). These properties of PEG 200 are felt to be responsible for its reported less effectiveness as a release promoter (Di Colo et al., 1985).

Rate-controlling factors

Once unstressed pores had been established, drug flux to the exterior of matrix should mainly be carried by diffusion within the pores. The PDS polymer, indeed, has proved too little permeable to prednisolone to contribute an effective parallel route of escape. The release process might be limited by sole diffusion, according to a well-known model (Higuchi, 1963), or alternatively, drug dissolution into pore fluid might contribute a further rate-limiting resistance. Occurrence of the former mechanism would imply an aqueous phase in the inner regions of matrix saturated with drug (semi-infinite assumption), whereas this is not a necessity for the latter instance. Since prednisolone re-crystallizes as the hydrous crystal form from an aqueous solution saturated with anhydrous crystals (Wurster and Taylor, 1965) the validity of the semi-infinite assumption for the present release systems could be put to the test by monitoring the hydrous form in time in different matrix zones. This could be done by DSC, by virtue of a highly energetic endothermal peak associated with water release from crystals (see Fig. 6, trace B). The results obtained with the matrix G 20/14 are presented in Fig. 6. The trace C, relative to a ~ 0.05-cm thick inner section of a matrix

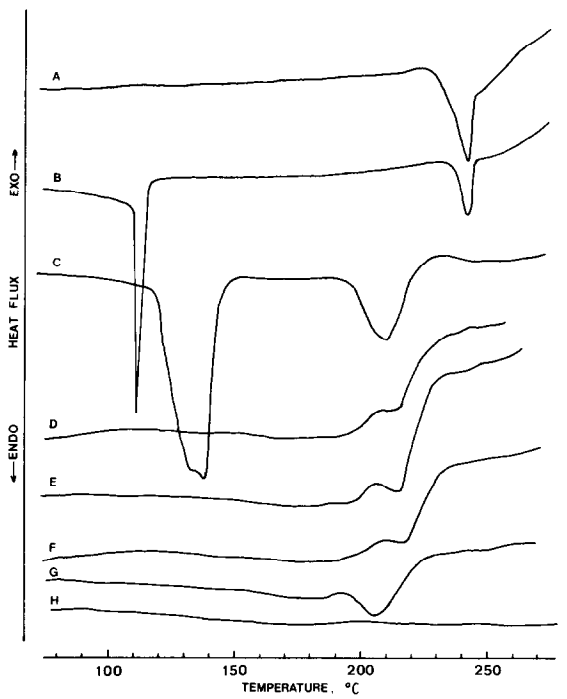

Fig. 6. DSC thermograms of (A) commercial prednisolone, (B) prednisolone hydrous crystal form, (C) inner section of matrix G 20/14 eluted 4 days, (D) outer section of matrix G 20/14 eluted 4 days, (E) inner section of matrix G 20/14 eluted 7 days, (F) outer section of matrix G 20/14 eluted 7 days, (G) control matrix, and (H) vulcanized PDS

eluted 4 days displays the characteristic features of the hydrous crystal form, in spite of a shift of the onset of the water release peak from 112°C to 120°C and a move of the fusion–decomposition peak toward lower temperatures, the latter also noticeable in the thermogram for the control matrix (trace G). The thermogram for a ~ 0.02-cm thick outer layer of the same matrix (trace D), and those for the inner and outer sections of a similar matrix eluted 7 days (traces E and F, respectively) all show absence of hydrous form. Similar results as the above were obtained with the matrix G 20/25. The analysis indicates that the semi-infinite conditions held for less than one week, then the dissolved drug concentration in the inner section of matrix dropped below solubility. Then the purely diffusion-controlled model should be rejected and control of release process ascribed to a composite dissolution–diffusion mechanism. Disappearance in a short initial period of hydrous crystals from the whole matrix volume is indicative of a comparatively high dissolution rate of these particles, due to having most of their surfaces at direct contact with fluid. In the subsequent period, on the other hand, particles were dissolved that were either partly or totally surrounded by polymer.

That release should essentially be two-stage was argued in the preceding report on the basis of release data (Di Colo et al., 1985). Consistency of such data with the mechanism proposed here is verified as follows. The release "rate" (slope of $\sqrt{t}$ plot of release data) in the first stage was little sensitive to matrix thickness, in accord with the semi-infinite conditions which have been proved to hold in this stage. This was not the case of the second stage when particles in the whole matrix volume should be at all times contributing to the "rate". A thickness dependence of this "rate" was more evident for the matrix G 20/25, probably because its higher porosity made the rate control by dissolution more effective, by facilitating diffusion. Although an increased porosity is expected to favour both stages of release , if pores rather larger in size than greater in number resulted from such an increase, the second stage should be less favoured with respect to the first one; this effect was indeed evident when the glycerol level in a 0.05-cm thick matrix of formula G 20/14 was raised according to formula G 20/25.

Conclusions

The present release systems have been shown to be far more complex than the Higuchi's theoretical model of a planar porous matrix, even if the apparent release kinetics was in most cases of the $\sqrt{t}$ type. Nor did such systems comply with all of the assumptions of a more recent dissolution-controlled model for porous hydrophobic polymers implying zero-order release kinetics (Gurny et al., 1982). In our opinion similar deviations from the above theoretical models as those evidenced in this work should not be unusual with porous polymeric matrices. We therefore want to stress the need for experimental evidence other than the mere release data whenever a release mechanism has to be established. Differential scanning calorimetry has proved a tool for the purpose.

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