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Selective coating of cylindrical matrices with a central hole. I. An interpretation of the swelling process

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Summary

Cylindrical matrices were prepared by compression either of polyvinyl alcohol 100 000 or mixtures of the excipient and a drug (sodium salicylate or theophylline). To modify the cylindrical shape, a hole was bored in the centre of the flat surface through both sides of the matrices. Different swellable systems were obtained applying an impermeable coating to one, two or three surfaces of the perforated matrices. The swelling of the perforated matrices was modified according to the number and the position of the coated surfaces (selective coating) and the loaded drug. Pseudo-zero order kinetics were obtained when the interior hole was the only uncoated surface.

Introduction

The shape of a matrix is a factor affecting drug release (Rippie and Johnson, 1969; Cobby et al., 1974; Hsieh et al., 1983). In the pharmaceutical field a cylindrical shape is often chosen in the preparation of solid oral dosage forms. This shape involves a decrease in the releasing area of the drug core as the diffusion path length increases. A perforated matrix (Cleave, 1965) and the coating of appropriate surfaces (Colombo et al., 1990) were proposed to compensate for the influence of the cylindrical shape.

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To combine the advantages of both approaches, we suggested the modification of a perforated non-swellable matrix by coating different surfaces (Forni et al., 1990). The diffusion-type kinetics of the release shifted towards zero-order kinetics according to the number and the position of the coated surfaces (selective coating). Thus, the conclusion was drawn that the drug release kinetics could be affected by the selective coating of a perforated non-swellable matrix.

As the drug release from a swellable matrix is also affected by matrix swelling, the influence of both the central hole and the selective coating on the swelling process appeared an interesting subject to investigate.

Therefore, this work aimed at the evaluation of the effect of the selective coating on the swelling process of perforated swellable matrices.

To clarify the influence of the drug solubility, either sodium salicylate or theophylline were used to load the matrices.

Experimental

Materials

Sodium salicylate (NaS) (USP, Carlo Erba, Milan, Italy; Mol. Wt 160.1; water solubility 1 g · ml^{-1}) and theophylline (Theo) (USP, Carlo Erba; Mol. Wt 198.2; water solubility 8.3×10^{-3} g ml^{-1}) were used. Polyvinyl alcohol (PVA) (polyvinyl alcohol 100000, Fluka, Buchs, Switzerland) (viscosity of a 4% water solution at 20°C, 35–45 mPa · s; degree of polymerisation, 2000; degree of hydrolysis, 86–89 mol%) was the excipient. The drugs and the excipient were separately ground (Pulverisette 0, Fritsch, Idar-Oberstein, Germany) and sieved (Harver and Boecker, Oelde, Germany) before matrix preparation. The granulometric fraction between 90 and 125 μm was used. Cellulose acetate phthalate (Fluka) and diethyl phthalate (Fluka) were used to coat the matrices as received from the manufacturer. All the solvents were of pure grade (Carlo Erba).

Methods

Preparation of the uncoated matrices

To prepare the cylindrical matrices (matrices A1) (Fig. 1), PVA or a homogeneous mixture of drug (NaS or Theo) and the excipient (1 : 9, w/w) were directly compressed using a hydraulic press (model N, Carver, Menomonee Falls, WI, U.S.A.) (1 min; 300 kg · cm^{-2}). The mean values of the weight, diameter (d_e), and thickness (h) of the matrices were 420 ± 5 mg, 13 ± 0.2 mm, and 2.9 ± 0.1 mm, respectively.

To prepare the perforated uncoated matrices (matrices A2: mean values of weight 420 ± 5 mg, d_e 13 ± 0.1 mm and h 3.8 ± 0.1), a hole (diameter (d_i): 5 ± 0.1 mm) was bored in the centre of the flat surface through both sides of cylindrical matrices weighing 450 ± 5 mg, previously prepared as described for the A1 matrices (Fig. 1). The annulus, i.e., the area enclosed by two concentric circles (matrix and hole), had a width (($d_e - d_i$)/2) of 4 mm.

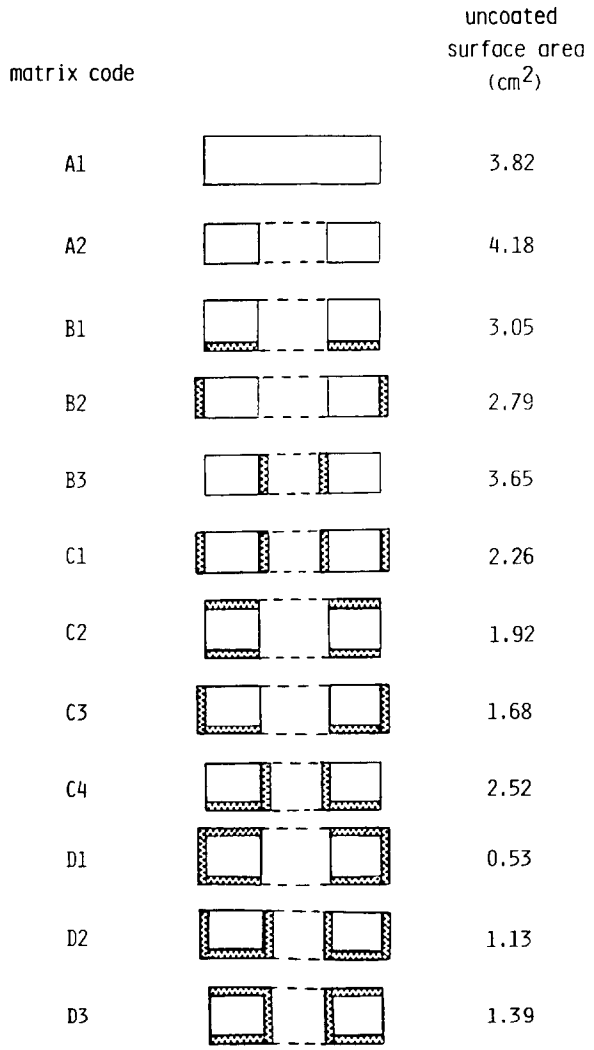

Fig. 1. Matrix geometry, code and uncoated surface area of the different matrices.

The dimensions of the matrices A1 and A2 were not markedly affected by the different drug.

Coating of the perforated matrix

One (matrices B), two (matrices C), or three (matrices D) surfaces of the perforated loaded matrix were coated by hand (Fig. 1). To prepare the coating, a solution of cellulose acetate phthalate in acetone (1 : 4, w/v) was mixed with diethyl

phthalate in CH_2Cl_2 (1:20, v/v) in a 1:1 (v/v) ratio. The coating was applied five times, each time allowing the matrices to dry at 30°C for 30 min and then finally overnight at room temperature. The coating was proved to be water-impermeable under the experimental swelling conditions.

Dynamic swelling of the matrices

Dynamic swelling was carried out using a column-type apparatus (Dissotest CE-1, Sotax, Basel, Switzerland), allowing the dry matrices to swell in 1000 ml of deionized water. All experiments were performed at a flow rate of 25 ml · min^{-1} and a temperature of 37 ± 0.2°C. The matrices were withdrawn at fixed time intervals and the dimensions (d_e, d_i, and h) were measured with a gauge before returning the matrices to swell in water. The measured values of the dimensions were normalised to the initial ones of the dry matrix. The surface (S) and the volume (V) values of the matrices were calculated using the dimension values. All the data averaged at least three determinations.

Analysis of dynamic swelling

Analysis of the swelling process of the matrices was conducted using the power-law expression (Ritger and Peppas, 1987):

$$(V_t - V_0)/V_0 = kt^n \quad (1)$$

where V_t is the volume of the swollen matrix at the experimental time t, V_0 denotes the volume of the dry matrix at the beginning of the experiment ($t = 0$), k is the kinetic constant of the process and n represents the kinetic exponent characterising the swelling mechanism.

According to the above equation, the instantaneous swelling rate (IRS) is defined as:

$$d[(V_t - V_0)/V_0]/dt = nkt^{n-1} \quad (2)$$

Results and Discussion

When water penetrates into the matrices, the polymer particles swell modifying the matrix dimensions according to the loaded drug, and the number and position of the coated surfaces (selective coating).

The swelling of the polymer particles arranged along a circumference involves an increase in the length of the circumference. Therefore, d_i and d_e should increase during the process. The dimensional changes in d_i and d_e were consistent with

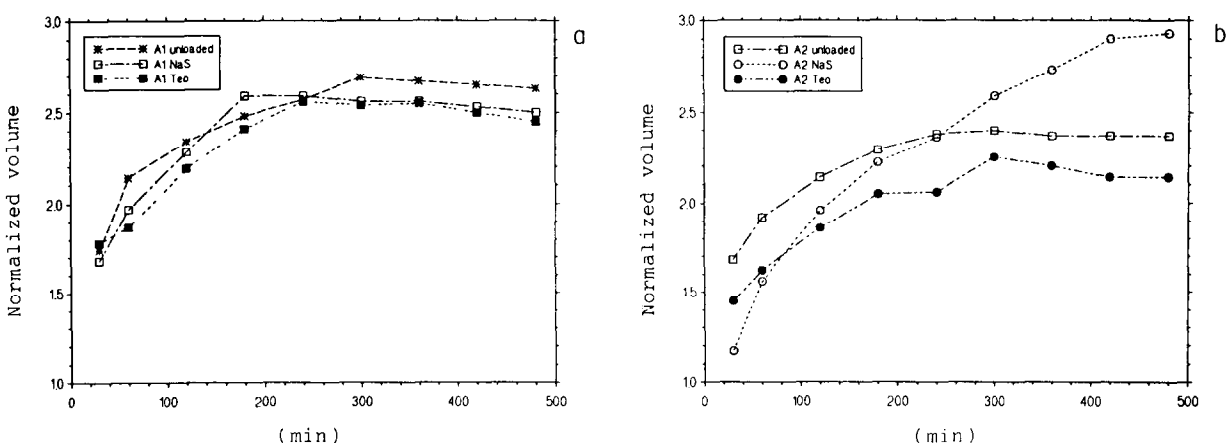

Fig. 2. Swelling profiles of uncoated cylindrical (a) and perforated (b) matrices. NaS, sodium salicylate; Theo, theophylline. Codes are defined in Fig. 1.

this rationale, except for the B2 matrix whose hole became narrower after a period where no marked changes were emphasised.

The changes in d_e and in the annulus width $(d_e - d_i)$ allowed analysis of the radial directions of swelling for both the cylindrical and perforated matrices, respectively. The axial direction of swelling was investigated based on the changes in matrix thickness (h).

Since h usually showed greater increases than d_c or $(d_e - d_i)$, it may be concluded that swelling predominates in the axial directions. At the end of the experiment, the decrease in the h values induced a reduction of the axial predominance of the A1 matrices. Throughout the process, the swelling of the A2 matrices showed an axial predominance, which was reduced by the selective coating of the matrices loaded with NaS. This behaviour was more evident for the D1 and D2 matrices, showing comparable swelling in the axial and radial directions.

At the end of the experimental period, a wet unswollen core remained in the centre of the cylindrical A1 matrices. The unswollen core was larger in the unloaded A1 matrix than in the loaded ones of which the matrix loaded with Theo showed the greatest core. The differences in the core dimensions can be due to the different susceptibility of the polymer and of the drugs to water penetration. Thus, loaded matrices

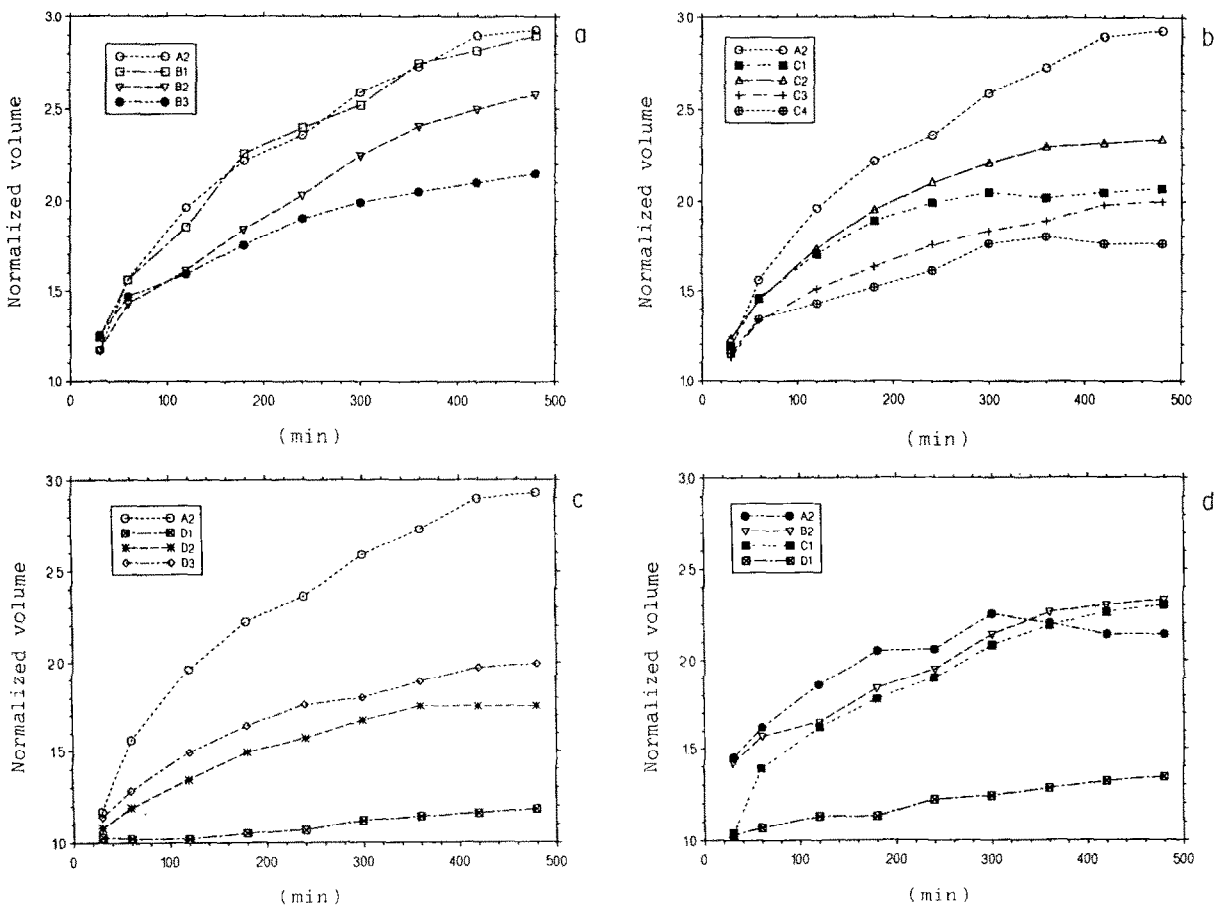

Fig. 3. Swelling profiles of coated perforated matrices loaded with sodium salicylate (NaS) ((a) matrices B; (b) matrices C; (c) matrices D) or (d) theophylline (Theo). Codes are defined in Fig. 1.

should undergo greater swelling than unloaded ones and NaS should have produced greater increases in the matrix volume than Theo. However, the unloaded and loaded A1 matrices showed the same swelling profiles (Fig. 2a).

In contrast, the drug affected the swelling profiles of the perforated A2 matrices (Fig. 2b) where no unswollen core was evident at the end of the experimental period. The volume of the A2 matrix loaded with NaS was smallest during the early stages and greatest towards the end of the experimental period. Throughout the experiments, the matrix loaded with Theo showed a lower swelling profile with respect to the unloaded one.

To explain the swelling behaviour of both the A1 and A2 matrices, it should be borne in mind that the swelling of an unloaded matrix is due to water penetration, whereas the combination of water penetration and drug diffusion produces the changes of a loaded matrix. Obviously, water penetration increases and drug diffusion decreases the matrix volume (Lee, 1985).

Thus, the unloaded and loaded A1 matrices showed the same swelling profile as the volume of water penetrating into the unloaded matrices is equal to the difference between the volume of water penetrating and drug (NaS or Theo) diffusing into the loaded matrices. If such a difference were lower or greater than the volume of water penetrating into the unloaded matrices, the swelling profiles of the loaded ones should be greater or smaller as shown by the loaded A2 matrices. According to this rationale, the different swelling behaviour of the A2 matrices loaded with NaS or Theo can be justified by the different susceptibility of the drugs to water penetration and by the different drug diffusion.

The unloaded A2 matrix and that loaded with Theo showed the same swelling behaviour as the A1 matrices, i.e., the matrix swelled at the beginning of the process and then the volume did not change (Fig. 2). The volume of the A2 matrix loaded with NaS increased throughout the experiment (Fig. 2b).

In the perforated coated matrices, the restriction due to the selective coating forces the polymer particles to swell, thereby modifying the original perforated geometry. As the volume of the modified geometry is difficult to calculate, the matrix volume was approximated to the volume of a perforated cylinder having the mean dimensions (annulus and height) of the swollen matrix.

The volume of the B1 matrix loaded with NaS exhibited the same swelling behaviour as the uncoated one (Fig. 3a) although the matrix swelling usually slowed down owing to the selective coating. Only the swelling profiles of the D matrices were related to the uncoated surface area of the dry matrix (Fig. 3). The contribution to the swelling of any uncoated surface can be evident in the D matrices. Thus, the swelling process of the B and C matrices might be calculated by adding the contribution of each D matrix. In contrast, the swelling of the B3, C1 and C4 matrices (Fig. 3) was not the mere addition of the contribution of any uncoated surface. As these latter matrices are the only ones whose interior hole had a surface coat, it can be hypothesised that the coating of the interior surface acts as a dry core producing a restriction of the matrix swelling (core restriction). The effect of the core restriction might be reduced when water penetration occurs only from the axial directions (matrices C1).

Kinetics of the swelling process

The swelling kinetics of the cylindrical matrices (matrices A1) were not affected by the drug loaded (Table 1). The A2 matrix loaded with NaS swelled according to anomalous kinetics, whereas the unloaded matrix and that loaded with Theo showed diffusion-type kinetics (Table 1).

By coating one matrix surface of the perforated matrix (matrices B), the kinetic exponents of the swelling process were not modified (Table 1). Thus, the drug can have a greater effect on the swelling mechanism than the coating of one surface.

When an impermeable coating was applied to two (matrices C) or three surfaces (matrices D) (Table 1), the shift of the swelling kinetics towards a time-independent process was clearly evident only when Theo was the loaded drug. The swelling process of the D1 matrices followed pseudo-zero order kinetics regardless of the drug

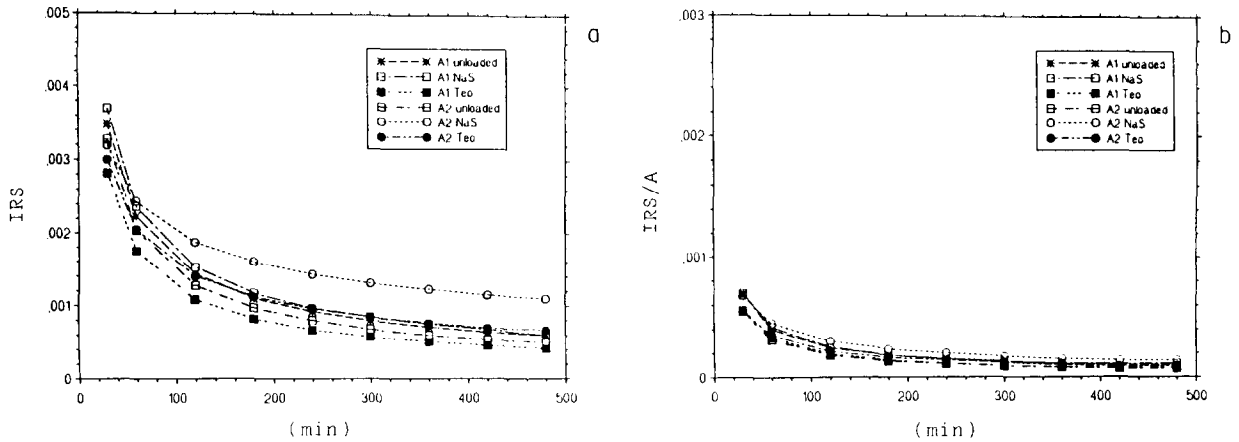

Fig. 4. Instantaneous rate of swelling (IRS) and instantaneous rate of swelling per unit swelling area (IRS/A) of the uncoated cylindrical and perforated matrices. NaS, sodium salicylate; Theo, theophylline. Codes are defined in Fig. 1.

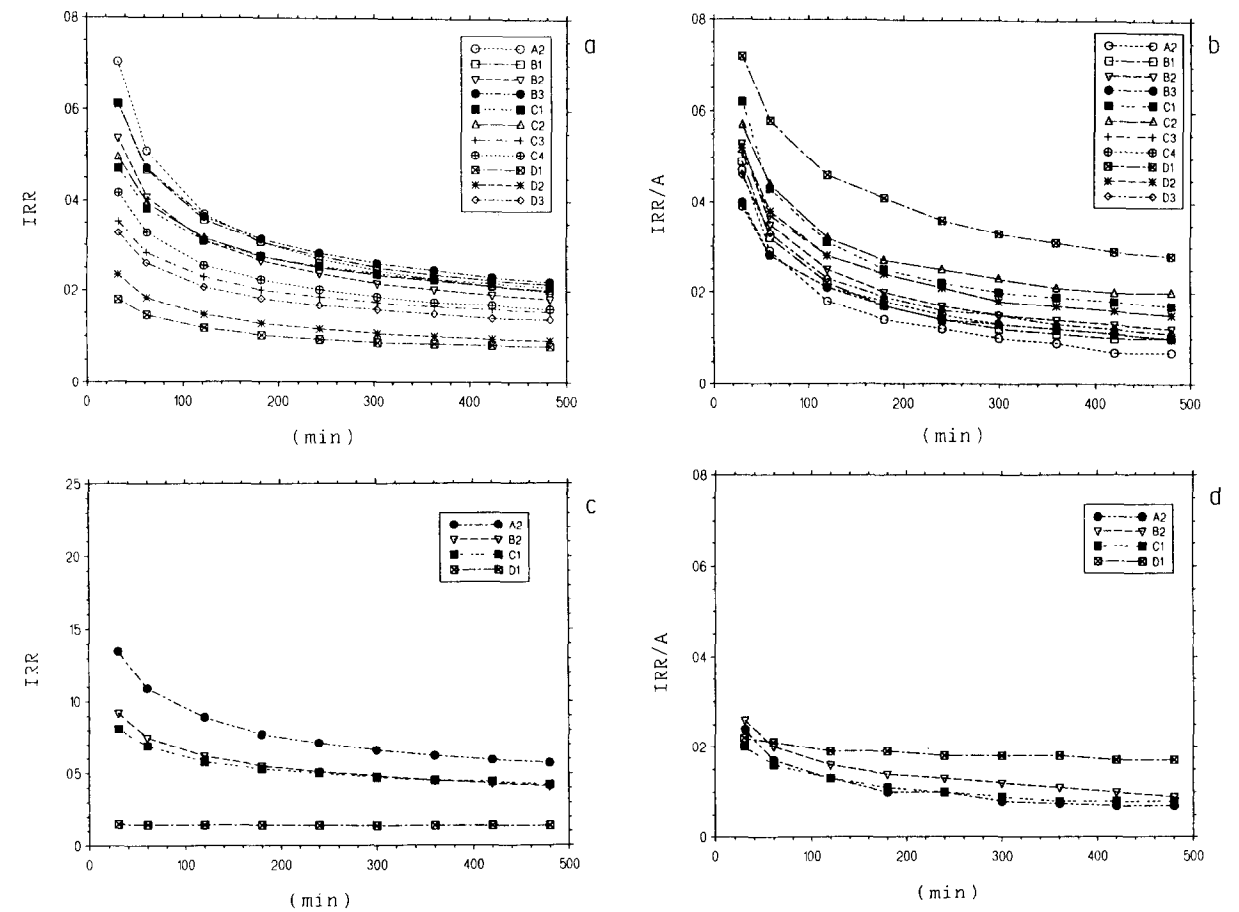

Fig. 5. Instantaneous rate of swelling (IRS) and instantaneous rate of swelling per unit swelling area (IRS/A) of the coated perforated matrices loaded with sodium salicylate (NaS) (a,b) or theophylline (Theo) (c,d). Codes are defined in Fig. 1.

TABLE 1

Swelling parameters of the PVA cylindrical and perforated matrices calculated according to the power-law expression (Eqn 1)

Matrix code	k ($\times 10^2$)	n	r
Unloaded matrices			
A1	22.4 (0.4)	0.36 (0.04)	0.9918
A2	23.8 (0.3)	0.32 (0.02)	0.9918
Matrices loaded with sodium salicylate			
A1	23.0 (0.2)	0.36 (0.04)	0.9918
A2	4.8 (0.7)	0.62 (0.03)	0.9953
B1	4.6 (0.1)	0.62 (0.05)	0.9920
B2	2.6 (0.5)	0.67 (0.02)	0.9962
B3	3.7 (0.4)	0.57 (0.02)	0.9964
C1	2.5 (0.6)	0.69 (0.03)	0.9911
C2	5.5 (0.9)	0.53 (0.03)	0.9923
C3	3.5 (0.2)	0.55 (0.01)	0.9982
C4	5.9 (0.7)	0.42 (0.01)	0.9967
D1	0.1 (0.01)	0.90 (0.01)	0.9934
D2	0.8 (0.07)	0.77 (0.01)	0.9970
D3	2.3 (0.2)	0.62 (0.02)	0.9908
Matrices loaded with theophylline			
A1	24.4 (0.3)	0.31 (0.02)	0.9975
A2	1.0 (0.1)	0.45 (0.02)	0.9958
B2	1.0 (0.1)	0.43 (0.02)	0.9949
C1	3.3 (0.2)	0.61 (0.01)	0.9986
D1	0.2 (0.01)	0.87 (0.01)	0.9933

Standard deviation in parentheses. Codes are defined in Fig. 1.

loaded. Thus, the expected effect of the drug on matrix swelling can be avoided by using a geometrical shape where the water is able to penetrate only through the interior surface of the hole (matrix D1).

The uncoated matrices showed approximately equal values of the instantaneous rate of swelling (IRS), except for the A2 matrix loaded with NaS (Fig. 4a). Throughout the experimental period, the IRS decreased, remaining constant irrespective of the drug only for the D1 matrix (Figs 4a and 5a and c).

It is clearly evident that matrix swelling produces the increase in the matrix area along with the volume. Thus, the IRS was normalised by the corresponding values of the swelling area.

The instantaneous rate of swelling per unit swelling area (IRS/A) was equal for all the uncoated matrices (Fig. 4b). Thus, the swelling rate is closely related to the surface area from which water can penetrate and drug can diffuse. The IRS/A ratio of the coated matrices (Fig. 5b and d) was generally about the same, regardless of the drug and the position of the coating, even when a few matrices showed different IRS/A profiles. Hence, the swelling rate of the coated matrices cannot entirely be related to the surface area.

When water penetration occurred from the flat surface of one basis (matrix D2), the IRS/A was greater than that of the matrices in which water penetration also took place from the interior or exterior surface (Fig. 5b). Thus, it is reasonable to relate the highest IRS/A ratio to the axial penetration of water. This hypothesis can also explain the behaviour of the C1 matrix whose IRS/A value was affected by the drug solubility (Fig. 5b and d).

The effect of drug solubility was clearly evident for the D1 matrices, whose IRS/A ratio was greatest when Theo was the loaded drug. As the IRS of the D1 matrices was about equal regardless of the loaded drug, this findings could provide evidence of the effect of drug diffusion on the surface area.

Conclusions

A selective coating can modify the relative importance of the radial and axial components of water penetration allowing the water to penetrate from appropriate surfaces. On the other hand, the selective coating can act as a mechanical hindrance to polymer swelling, forcing the particles to swell towards preferential directions. In our opinion, the coating of the surface of the interior hole acts as a dry core producing a restriction of swelling. However, water penetration from the axial directions might reduce the coating restriction, as demonstrated by the C1 matrices.

The effect of the selective coating is clearly evident for appropriate geometry, i.e., when the surface of the interior hole (matrices D1) is the only one uncoated. The selective coating allows this matrix to swell following pseudo-zero order kinetics, irrespective of the drug loaded (NaS or Theo).

The swelling rate of the matrix was generally related to the swelling surface area from which water could penetrate and drug could diffuse, although a few matrices showed instantaneous swelling rates per unit swelling area that were affected by drug solubility.

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