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Effect of ageing on the release of indomethacin from solid dispersions with Eudragits

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Abstract

The effect of ageing on the release of indomethacin from coprecipitates with Eudragit RS, Eudragit E and blends of these polymers was studied. DSC thermograms were carried out to control the glass transition temperature (T_g) of polymers and the physical state of indomethacin after 2 and 3 years of storage in closed containers at room temperature. The rotating disk method was used on compressed powders in order to test drug release under controlled conditions. Data treatments were carried out in order to verify modifications in the diffusion coefficient and mechanism of drug release. Results indicated that, for all the systems investigated, randomness was reduced within the polymeric network during storage, and this observation was confirmed by the appearance of a peak at the polymeric T_g. The drug diffusion coefficient from Eudragit RS was not influenced by storage, while, in the case of Eudragit E and a blend of polymers, a significant reduction of the diffusion coefficient was noticed after 3 years, probably due to an interaction between the drug and Eudragit E.

Keywords: Indomethacin; Solid dispersion; Storage stability

1. Introduction

During the last decade, the solid dispersion technique has been largely utilised to obtain the controlled release of the pharmaceutical forms of both water soluble and very sparingly soluble drugs using hydrophobic or hydrophilic polymers, respectively (Ford, 1986; Bloch and Speiser, 1987). Limitations in the development of solid dispersions was mainly due to the physical instability of these systems. During this time, phase separation of the components can occur. Furthermore, polymeric materials are not in thermodynamic equilibrium below their glass transition temperatures (T_g), so the solid polymer approaches its more stable state (lower energy). If these macromolecular rearrangements occur during the experiments, a variation of the mechanical and permeation properties of the materials can be observed (Sinko et al., 1990). This process is known as physical ageing (Guo et al., 1991).

In this work, we have studied the release of an acidic drug (indomethacin) from solid dispersions with two types of Eudragit stored in closed containers at room temperature for 3 years, to assess

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the stability of the systems with respect to phase separation and/or physical ageing. Accelerated tests are often utilised to verify the stability of a pharmaceutical form, but sometimes they can be considered dubious (Van Krevelen, 1990).

Indomethacin is a well known drug showing several polymorphic modifications and a pH-dependent dissolution behaviour (Gueurten and Dubois, 1980). Solid dispersion with Eudragits has shown that up to 30% (w/w) of this drug can be incorporated amorphously in Eudragit RS (Oth and Moës, 1989), while up to 50% (w/w) can be dispersed amorphously in Eudragit E (De Filippis et al., 1991).

Eudragit RS and Eudragit E are glassy methacrylic polymers. In the RS type an ammonium quaternary group (with a positive charge) is present, while in the E type a basic amine function can be observed.

In our work, the physical state of the systems was characterized using DSC analysis, and drug release was carried out on compressed coprecipitate powders using the rotating disk method. This method was selected on the basis of the number of variables that can be held constant during the drug release process, and appropriate equations were selected for experimental data analysis. Although pores were present in the compressed powder systems, it has been demonstrated (Carli et al., 1984) that drug release in non-wetting liquids was not influenced by porosity, and that drug release was controlled by intraparticle diffusion. Furthermore, we have used this method, with the drug loaded above its solubility limit in the polymer, in order to analyse the drug diffusion coefficient, assuming that differences noticed in the mechanism of drug release can be related to modifications of the polymeric network during storage.

2. Materials and methods

2.1. Materials

Indomethacin was purchased from Sigma Chemical Co. (St Louis, MO, USA) and Eudragit RS 100 and Eudragit E 100 were kindly supplied by Röhm Pharma (Darmstadt, Germany). These materials were used as received.

All other chemicals utilised were of analytical grade. Demineralized distilled water was used to prepare the buffered solution which was used as dissolution medium.

2.2. Preparation of solid dispersions

Appropriate amounts of indomethacin and polymers (1:9 w/w) were dissolved in ethanol at the final total concentration of 40 mg ml^{-1}. In the case of the blend, equal amounts of the two polymers were utilised. The solvent was removed under vacuum in a rotary evaporator at 50°C. The residue was dried for 4 days at 40°C and sieved; the size range selected was between 75 and 250 μm.

2.3. Content uniformity

An exactly weighed amount of solid dispersion powder was dissolved in ethanol, sonicated for 10 min to destroy any agglomerates, and assayed spectrophotometrically (Perkin-Elmer 552, thoroughness = 0.005 Å) at 320 nm.

2.4. DSC analysis

Differential scanning calorimetry was performed with a Mettler TA 4000 equipped with a DSC11 cell calibrated with indium. Samples were weighed in aluminium pans, hermetically sealed and scanned at 10°C per min.

2.5. Drug release study

Drug release was carried out on compressed powders using the rotating disk method described elsewhere (Nicklasson and Brodin, 1982). A weighed amount (about 250 mg) of powder was compressed into a disk using a 1.3 cm diameter flat-face die in an I.R. press (Perkin-Elmer) and a force of 10 tons. For the preparation of tablets, no lubricant was used. Tablets were fixed onto a stainless steel disk with the aid of molten paraffin and were coated on the circumference using the same product to keep a constant surface. The

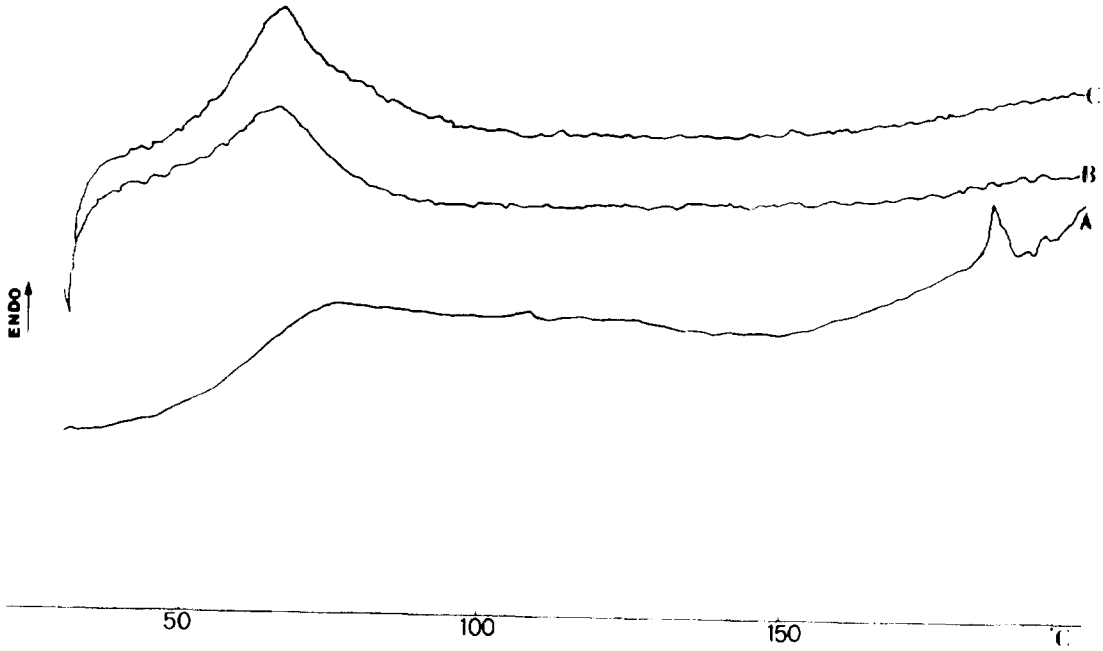

Fig. 1. DSC thermograms of the indomethacin-Eudragit RS system at different times of storage: A, $t = 45$ days at 50°C; B, $t = 2$ years at RT; and C, $t = 3$ years at RT.

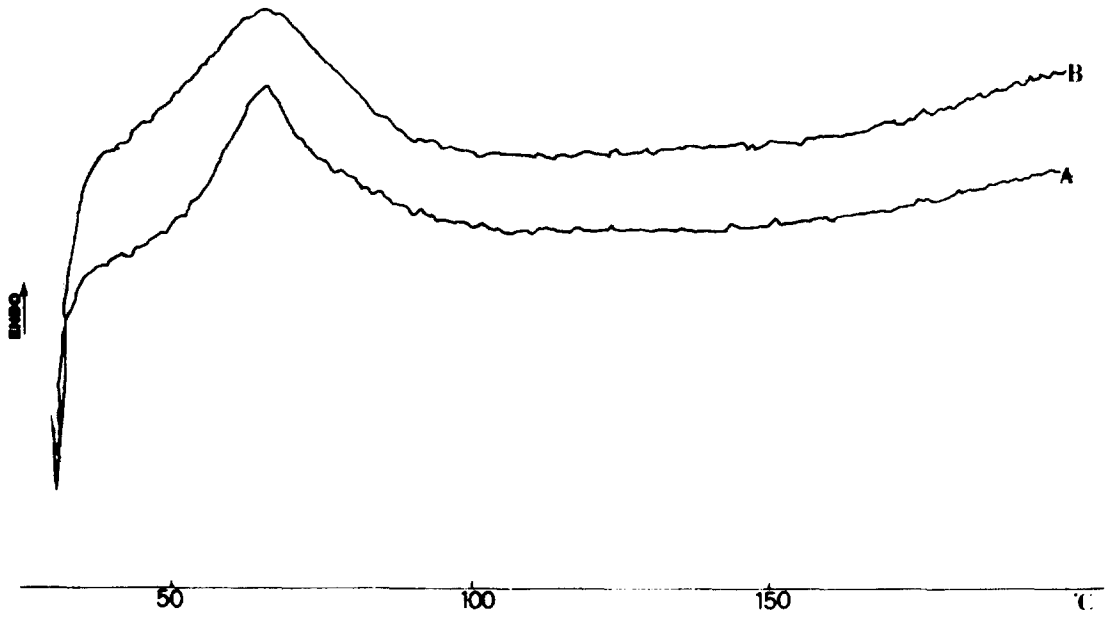

Fig. 2. DSC thermograms of the indomethacin-Eudragit RS system after 3 years of storage: A, before compression; and B, after compression.

rotating disk was centred 2.5 cm above the bottom of the glass beaker. The stirring rate was 900 rpm and the experiments were carried out at 37 ± 0.1°C. The dissolution medium was the USP phosphate buffer at pH 7.4.

Aliquots of solution (5 ml) were taken out for analysis at predetermined times and were immediately replaced with fresh phosphate buffer. The concentration in the dissolution medium was recorded spectrophotometrically in a 1 cm quartz cell at 320 nm. Each experiment was performed in duplicate and the c.v.% was less than 3.

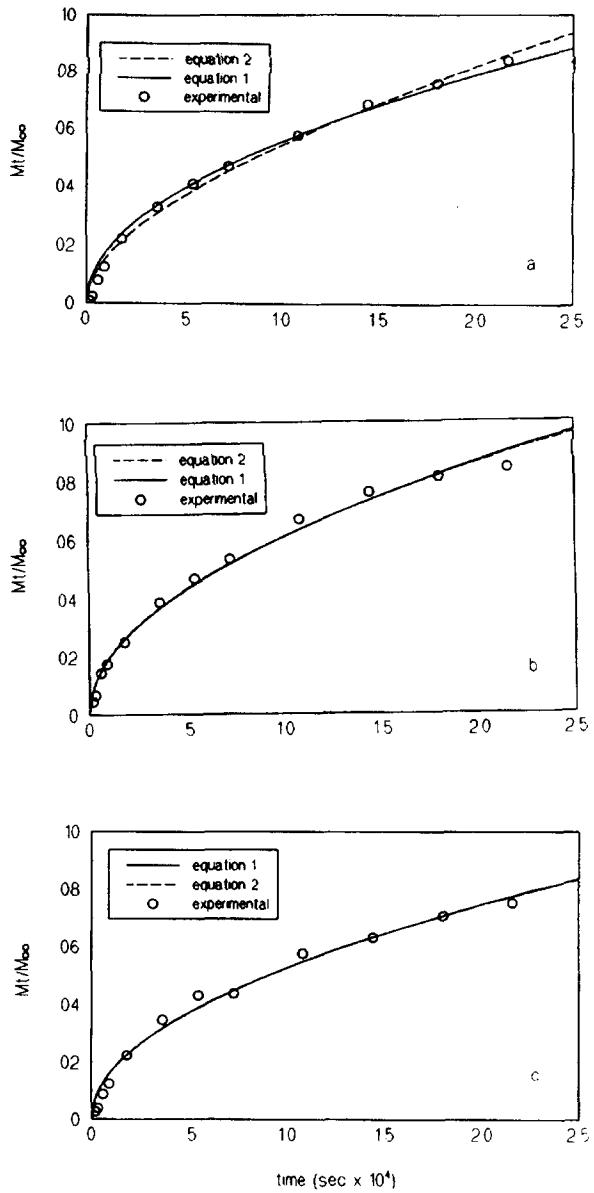

Fig. 3. Graphical plot representing the fits of Eqs. 1 and 2 to the indomethacin-Eudragit RS system at different times of storage: A, $t = 0$; B, $t = 2$ years; and C, $t = 3$ years.

2.6. Data analysis

Assuming that the amount of drug loading was lower than the solubility of indomethacin in the polymers, and considering the experimental conditions, the following equations have been used for dissolution data treatment (Lee, 1992):

$$\frac{M_t}{M_\infty} = \frac{4}{L}\left[\frac{Dt}{\pi}\right]^{0.5} \quad (1)$$

$$\frac{M_t}{M_\infty} = \frac{4}{L}\left[\frac{Dt}{3}\right]^{0.5} + \frac{2Bt}{L} \quad (2)$$

where M_t/M_∞ is the drug fraction released at time t, D is the diffusion coefficient (cm sec^{-2}), L is the matrix thickness (cm), and B is the inward macromolecular relaxation front rate (cm sec^{-1}). Both the equations were satisfied for $0 \leq M_t/M_\infty \leq 0.6$.

3. Results and discussion

3.1. Indomethacin-Eudragit RS

Thermal analysis was performed on pure Eudragit and drug/polymer systems. No significant modification of the T_g value was observed in the freshly prepared samples; in fact, the T_g found for the pure polymer was 61.5°C, while this value was 60.4°C for the drug/polymer solid dispersion.

In Fig. 1 the thermograms of coprecipitates stored for 45 days at 50°C, and after 2 and 3 years of storage at room temperature, have been shown.

As can be seen from Fig. 1, no endothermic peak of indomethacin was detected, indicating that no relevant phase separation takes place during storage. The most important observation was the appearance of a peak at the T_g value of the polymer in the samples stored for longer periods of time, but this peak does not appear for samples stored at 50°C for 40 days. These peaks were attributed to a phenomenon known as enthalpic relaxation (Riesen and Wyden, 1982) which is generally observed in polymers during storage,

Table 1
Data obtained from Eq. 1

Polymer	Storage time (years)	Diffusion coefficient ($cm^2\ sec^{-1}$)	Error^2
RS	0	5.52×10^{-9}	1.64×10^{-4}
	2	6.58×10^{-9}	9.77×10^{-4}
	3	4.95×10^{-9}	1.21×10^{-4}
E	0	8.25×10^{-9}	2.26×10^{-4}
	2	1.58×10^{-8}	6.77×10^{-4}
	3	6.06×10^{-12}	2.51×10^{-7}
Blend	0	1.06×10^{-8}	1.6×10^{-3}
	2	3.40×10^{-9}	2.99×10^{-4}
	3	4.02×10^{-10}	8.18×10^{-5}

Table 2
Data obtained from Eq. 2

Polymer	Storage time (years)	Diffusion coefficient ($cm^2\ sec^{-1}$)	Macromolecular relaxation rate ($cm\ sec^{-1}$)	Error^2
RS	0	3.40×10^{-9}	1.21×10^{-7}	1.11×10^{-4}
	2	7.21×10^{-9}	-1.33×10^{-8}	9.28×10^{-5}
	3	4.74×10^{-9}	-5.31×10^{-9}	1.21×10^{-4}
E	0	2.52×10^{-9}	1.57×10^{-7}	1.36×10^{-4}
	2	1.92×10^{-8}	-1.57×10^{-7}	5.86×10^{-4}
	3	5.54×10^{-12}	5.25×10^{-10}	2.50×10^{-7}
Blend	0	1.74×10^{-9}	5.87×10^{-7}	3.26×10^{-4}
	2	1.04×10^{-9}	2.48×10^{-7}	7.25×10^{-5}
	3	4.22×10^{-11}	1.31×10^{-7}	1.88×10^{-5}

and which is related to a transition from a disordered glassy state to a more ordered one; the enthalpy values found were 23 J g^{-1} for samples stored for 2 years and 40 J g^{-1} for those stored for 3 years. Since the release experiments were performed on compressed drug powders, while the samples were stored as powders, we controlled the influence of compression on the T_g peak. Results indicated that, after compression, the T_g peak was still present (Fig. 2).

In Fig. 3(a, b and c), the experimental release data and relative fittings obtained from Eqs. (1) and (2) are shown, while the diffusion coefficient of indomethacin from solid dispersions with Eudragit RS is listed in Table 1 and Table 2. Observing data derived from these equations, one can conclude that the diffusion coefficient does not show significative differences, even after 3 years of storage. However, results obtained from Eq. (2) indicated a time-dependent physical behaviour of those systems. At $t = 0$, a significant B value, that takes into consideration phenomena such as erosion and dissolution, was observed; in the case of an insoluble polymer, this fact can attributed to an inward front rate of macromolecular relaxation during the release process. In the samples after 2 and 3 years storage, this parameter had no physical meaning. A possible interpretation of these data was that this relaxation depended on the ability of the polymer to undergo local readjustment. Glassy polymers probably densified during ageing, thus a longer period of time was required for local readjustment to be established.

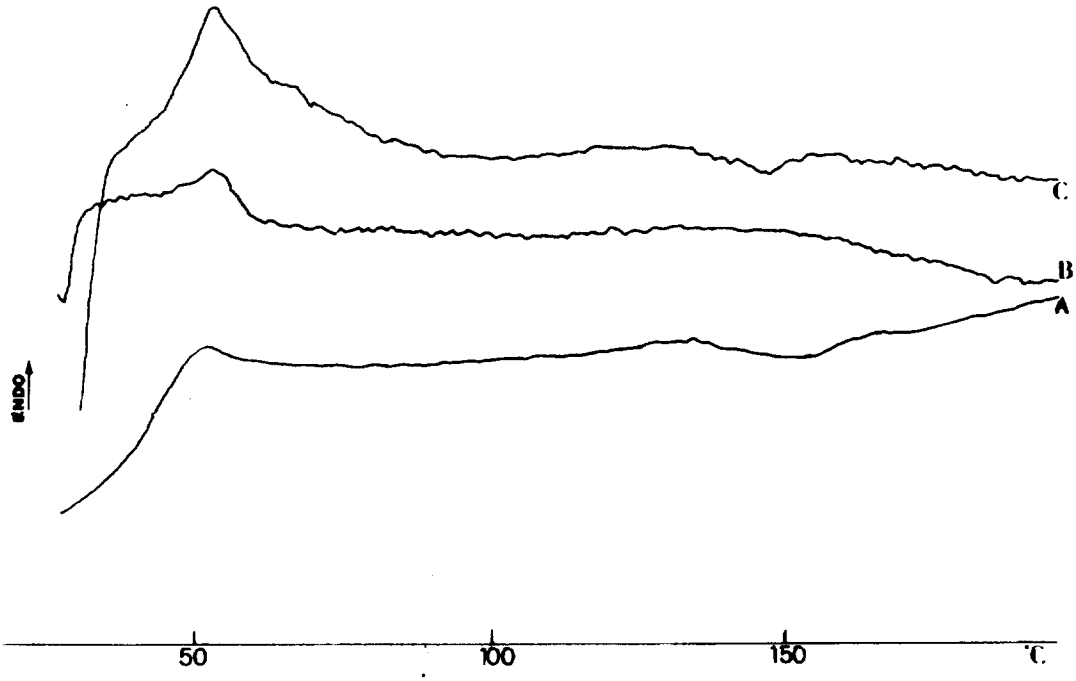

Fig. 4. DSC thermograms of the indomethacin-Eudragit E system at different times of storage: A, $t = 45$ days at 50°C; B, $t = 2$ years at RT; and C, $t = 3$ years at RT.

3.2. Indomethacin-Eudragit E

The presence of indomethacin (10%) does not modify significantly the T_g value of the polymer. The value found for the pure polymer was 45.3°C, while the T_g value for the drug/polymer system was 43.3°C. In Fig. 4, the DSC thermograms of coprecipitates stored for 45 days at 50°C, (above the T_g value), and after 2 and 3 years of storage at room temperature, have been reported.

As it can be observed, no indomethacin peak was detected, and we can conclude that, for this system, phase separation does not take place. The only difference seen with respect to Eudragit RS was the less pronounced enthalpic recovery for this polymer. The enthalpic values were 2.7 J g^{-1} and 11.5 J g^{-1} for 2 and 3 years of storage, respectively.

In Fig. 5(a, b and c) the results of fitted experimental release data at pH 7.4 have been shown.

The numerical results listed in Tables 1 and 2 show some differences with respect to Eudragit RS. At $t = 0$, the drug diffusion coefficient for the two polymers was not significatively different. This fact was expected because, at this pH value, the Eudragit E was present in its unprotonated form and its solubility was similar to that of Eudragit RS, i.e., very low. The higher B value for Eudragit E can be attributed to the fact that at 37°C, which was the experimental condition for release in the study, macromolecular motion was higher for the polymer showing the lower T_g. After 2 years of storage, the diffusion coefficient in Eudragit E was slightly increased and the B value became negative. This can be explained, as in the same way for Eudragit RS, by the higher densification of the polymeric network due to ageing, and hence, macromolecular relaxation in solution would take a longer period of time to occur. The most important observation was a drastic reduction in the drug diffusion coefficient in Eudragit E, with respect to Eudragit RS, after 3 years of storage. This fact can probably be attributed to a chemical interaction between in-

domethacin and Eudragit E, i.e., the basic amine group of the polymer can strongly interact with the acidic function of the indomethacin. This hypothesis was supported by the fact that this interaction did not occur with Eudragit RS, whose structure carries a quaternary ammonium salt. In the above mentioned hypothesis at pH 7.4, indomethacin will be involved in an ionic complex with Eudragit E and the equilibrium will be shifted to that of the complex form. However this interaction does not take place at $t = 0$; one of the reasons could be that the solvent (ethanol) effect on hydrogen bonding during the preparation process would prevent the formation of such a complex in solution. In a solid polymer, indomethacin will take more time to rearrange in order to form this strong interaction.

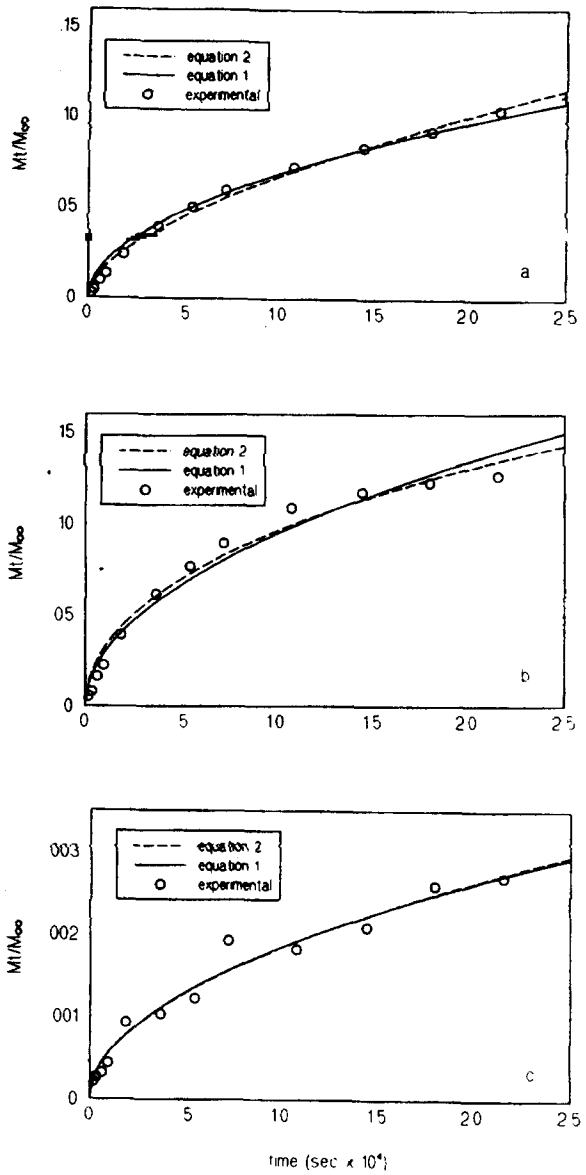

Fig. 5. Graphical plot representing the fits of Eqs. 1 and 2 to the indomethacin-Eudragit E system at different times of storage: A, $t = 0$; B, $t = 2$ years; and C, $t = 3$ years.

3.3. Indomethacin-Eudragit RS/Eudragit E

Thermograms of the system containing the polymer blend are shown in Fig. 6. The main observation that can be drawn is the appearance, after 3 years of storage, of two separated peaks (corresponding to the enthalpic recovery of the polymers) suggesting that the polymer mixture produced a slow phase separation. Furthermore, indomethacin does not crystallise out and solvent was not present. Enthalpic attribution was difficult due to peak overlapping.

In Fig. 7(a, b and c), the experimental data and relative fittings are reported. From these figures it is evident that the best fit is given by Eq. (2), so our hypothesis is based on the numerical data listed in Table 2. The values indicate that macromolecular relaxation takes place and that the drug diffusion coefficient is the same at $t = 0$ as at after 2 years of storage. After 3 years of storage, the diffusion coefficient was highly reduced. This result can be attributed to the fact that indomethacin was more soluble in Eudragit E than in Eudragit RS, thus the drug concentration in Eudragit E would be higher than in Eudragit RS and, since these two polymers were separated in the blend, the mechanism of drug release will be similar to that of Eudragit E. Also, in this case, drug/polymer interaction will take place, thus influencing the release parameters of the drug.

4. Conclusions

The conclusion from this study was that the indomethacin-Eudragit RS (1:9 w/w) system was

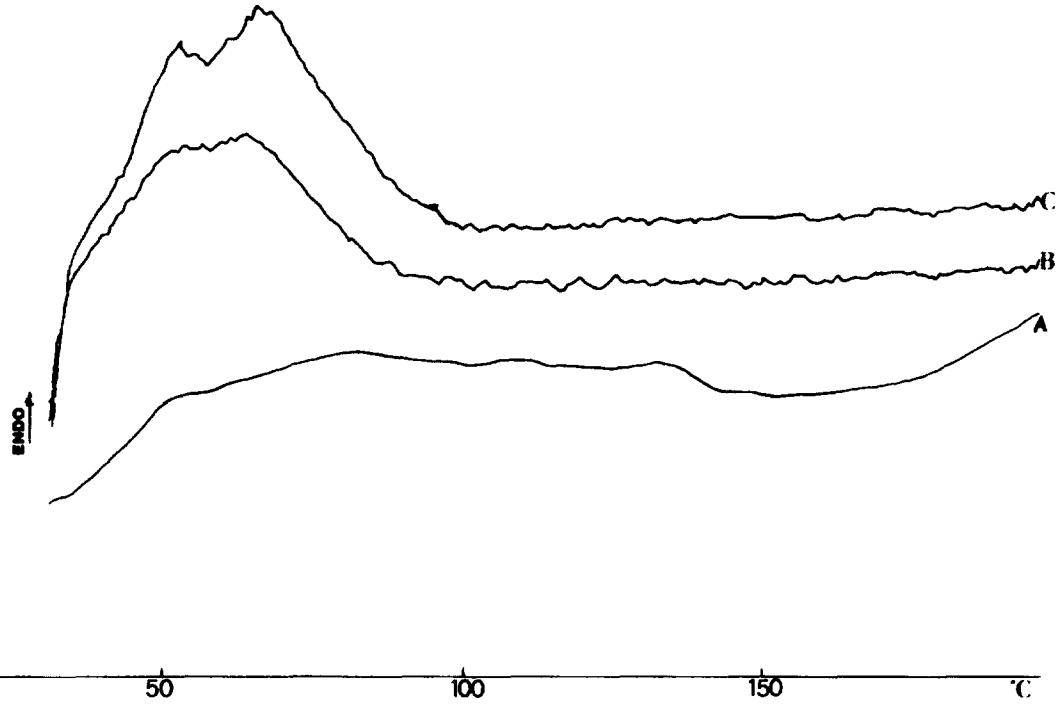

Fig. 6. DSC thermograms of the indomethacin-blend system at different times of storage: A, $t = 45$ days at 50°C; B, $t = 2$ years at RT; and C, $t = 3$ years at RT.

stable for at least three years. The diffusion coefficient of indomethacin through the polymer does not change with ageing, although the polymer undergoes local rearrangement. This result can reinforce the hypothesis that, for this system, the driving force for water uptake was the presence of ionic groups. This proves that the physical parameters (free volume, short range order) of glassy polymers do not influence the diffusion. Indomethacin and Eudragit E can form a strong interaction that can lead to a drastic reduction in the diffusion coefficient after 3 years of storage. The acidic function of the drug and the polymeric amine group might be responsible for this interaction which would not take place in the solvent used for the preparation of coprecipitate.

Physical ageing does not modify the diffusion coefficient of indomethacin in the considered polymers. The decrease of this coefficient obtained with Eudragit E cannot be attributed to a polymer physical ageing phenomenon, but to an interaction between the acidic group of the drug and the amine group of the polymer. Thus, particular attention should be placed upon the solid state chemistry of a drug with an acidic function in the presence of a polymer with basic groups.

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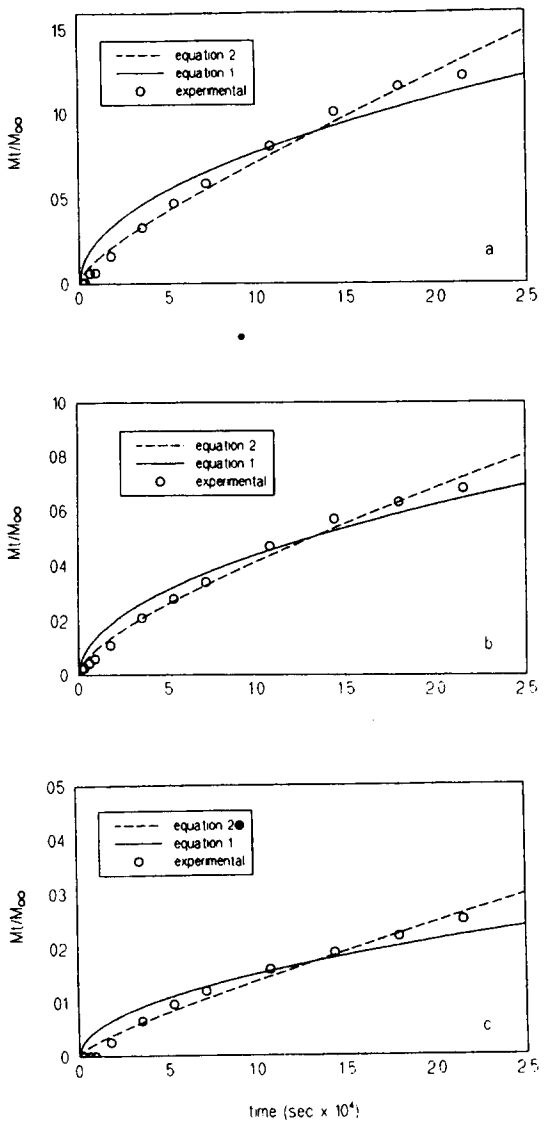

Fig. 7. Graphical plot representing the fits of Eqs. 1 and 2 to the indomethacin-blend system at different times of storage: A, $t = 0$; B, $t = 2$ years; and C, $t = 3$ years.

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