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Modification of the Dissolution Behaviour of a Water-insoluble Drug, Naftazone, for Zero-order Release Matrix Preparation*

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Abstract—The preparation of hydrophilic matrix tablets able to release naftazone, a water-insoluble drug, into an aqueous medium at a constant rate (zero-order dissolution) is described. Enhancement of dissolution rate of the drug was achieved using cross-linked carmellose sodium, β-cyclodextrin or hydroxypropyl-β-cyclodextrin. Hypromellose was used as a water-gelling polymer. Tablets could be prepared that released naftazone at a constant rate over 16 h.

Water-insoluble drugs are usually characterized by a low bioavailability, because their absorption is dissolution rate limited and consequently slow and irregular (Fincher 1968).

Furthermore, some of these drugs are also characterized by a short half-life and the preparation of oral extended release formulations could be required. However, in these cases the design of a formulation such as a hydrophilic matrix can be unsuitable owing to the poor diffusion characteristics of the drug.

We have previously described (Giunchedi et al 1993) a hydrophilic matrix capable of releasing a water-insoluble drug, carbamazepine, at a nearly constant rate for an extended time (18–24 h), using a combination of a water-swellable polymer (cross-linked carmellose sodium, CM-XL) with a water-gelling polymer (hypromellose, HPM).

CM-XL has a dual role in controlling drug release: it acts as dissolution rate enhancer of the drug (Sangalli et al 1989; Giunchedi et al 1990), which can then be incorporated, like a water-soluble drug, in a hydrophilic matrix; owing to its swellable properties (Caramella et al 1984a, b), it determines the progressive erosion of the matrix, thus overcoming the problem of decreasing rate of drug release with time as the length of the diffusion pathway increases (Ranga Rao et al 1988).

The aim of the present study was to identify materials which, like CM-XL, would be suitable for the preparation of hydrophilic matrices able to release water-insoluble drugs at a constant rate. In particular cyclodextrins were considered as good candidates. They have already been used for the dissolution rate enhancement of insoluble drugs (Saenger 1980; Uekama et al 1983), but little attention has been given to their incorporation in solid oral dosage forms (Bootsma et al 1989).

Naftazone, a haemostatic agent characterized by a low solubility in water (20 mg L^{-1}, 37°C), was chosen as a model drug.

Drug-carrier systems were prepared in which the carrier was constituted by cross-linked carmellose sodium (CM-XL), β-cyclodextrin (β-CyD) and hydroxypropyl-β-cyclodextrin (HP-β-CyD); hydrophilic matrices were obtained by mixing and then tableting the drug-carrier systems with HPM.

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Materials and Methods

Materials

Naftazone was obtained from Innothera (Arceil, France) and had a volume-surface mean diameter of 9·04 μm. Cross-linked carmellose sodium (CM-XL) was obtained as Ac-Di-Sol (FMC Corp., Philadelphia, PA, USA); the 2·0% w/w aqueous dispersion had a viscosity of 25 cP at 20°C (manufacturer value). β-Cyclodextrin (β-CyD, mol. wt 1135) was obtained as Kleptose R (Roquette, France); the solubility in water was 45 g L^{-1} (manufacturer value). Hydroxypropyl-β-cyclodextrin (HP-β-CyD, mol. wt about 1300) was obtained as Encapsin HPB from Janssen Biotech (Olen, Belgium); the solubility in water was 18·5 g L^{-1} (manufacturer value). Hypromellose (HPM) as Methocel K4M and Methocel K15M, was obtained from Colorcon (Orpington, UK) and the 2·0% w/v aqueous solutions had viscosities of 4000 and 15 000 cP, respectively (manufacturer values).

Preparation of drug-carrier systems

The systems were prepared with a ball milling technique. Naftazone and CM-XL, β-CyD or HP-β-CyD were placed in a ceramic ball mill (Staarlich, Berlin, Germany) of capacity 1 L and a cylindrical size of 12 cm. The milling was carried out for 2 h, at a speed of 70 rev min^{-1}, using ten 2-cm balls; the empty volume of the jar containing the powder mixture and the balls was about 30%. The weight of each batch of drug-carrier system prepared was 100 g. The systems prepared were designated NzXL (10% naftazone and 90% CM-XL), Nz-β-CyD and Nz-HP-β-CyD containing drug and carrier in a 1:2 molar ratio.

Scanning electron microscopy (SEM)

The morphological characteristics of the raw materials and of the drug-carrier systems were studied using a Jeol JSM-35C scanning electron microscope (Japan Electron Optical Laboratory, Tokyo, Japan).

The samples were fixed on aluminium stubs with double-sided tape, sputter-coated with gold and examined in the

microscope using an accelerating voltage of 15 kV, at a working distance of 8 mm.

Differential scanning calorimetry

Differential scanning calorimetry (Mettler TA 3000, Zurich, Switzerland) was used to assess the thermal behaviour of drug, carriers and corresponding systems prepared. Samples were scanned in pierced aluminium pans, under static air atmosphere, at a heating rate of 10° min^{-1}, in the temperature range 30–220°C.

Preparation of extended release matrices

The matrices prepared were designated as follows: XL.K4 and XL.K15 (containing CM-XL), β-CyD.K4 and β-CyD.K15 (containing β-CyD); HP-β-CyD.K4 and HP-β-CyD.K15 (containing HP-β-CyD); all the matrices had 20% Methocel K4M or Methocel K15M.

To assess the influence of the materials used (polymers and cyclodextrins) on the release of the drug, the matrices were prepared without excipients.

HPM and the corresponding quantity of drug-carrier system were mixed in a Turbula apparatus (W. A. Bachofen, Basel, Switzerland) at a speed of 90 rev min^{-1} for 20 min. The total weight of the powder mixture used for the preparation of each batch was 100 g.

The matrices were prepared by direct compression of the mixtures, at compression force of about 25 kN, using a Kilian single-punch reciprocating tablet machine (Kilian, Berlin, Germany), equipped with 11·28 mm flat punches, and instrumented with two piezoelectric load-washers (Kistler 903 A) (Conte et al 1972).

All matrices contained 30 mg drug with final weights of 375 mg for those containing CM-XL, 434 mg for those containing β-CyD, and 491 mg for those containing HP-β-CyD.

Dissolution and release tests

The dissolution and release tests were carried out using a modified USPXXII no. 2 dissolution test apparatus consisting of a cylindrical vessel with a nominal capacity of 5 L; the distance between the blade of the paddle and the bottom of the vessel was 50 mm.

Tests were carried out in 5 L distilled water, at 37°C and with a stirring rate of 100 rev min^{-1}.

At the beginning of the test, each sample, naftazone (30 mg) or drug-carrier systems corresponding to 30 mg drug or matrices containing 30 mg drug, were placed directly in the dissolution medium.

Naftazone was spectrophotometrically determined at 270 nm (1 cm cell) (Spectracomp 602, Advanced Products, Milano, Italy).

Dissolution and release tests were carried out in triplicate for each batch of systems and matrices (standard deviations within 1–3%).

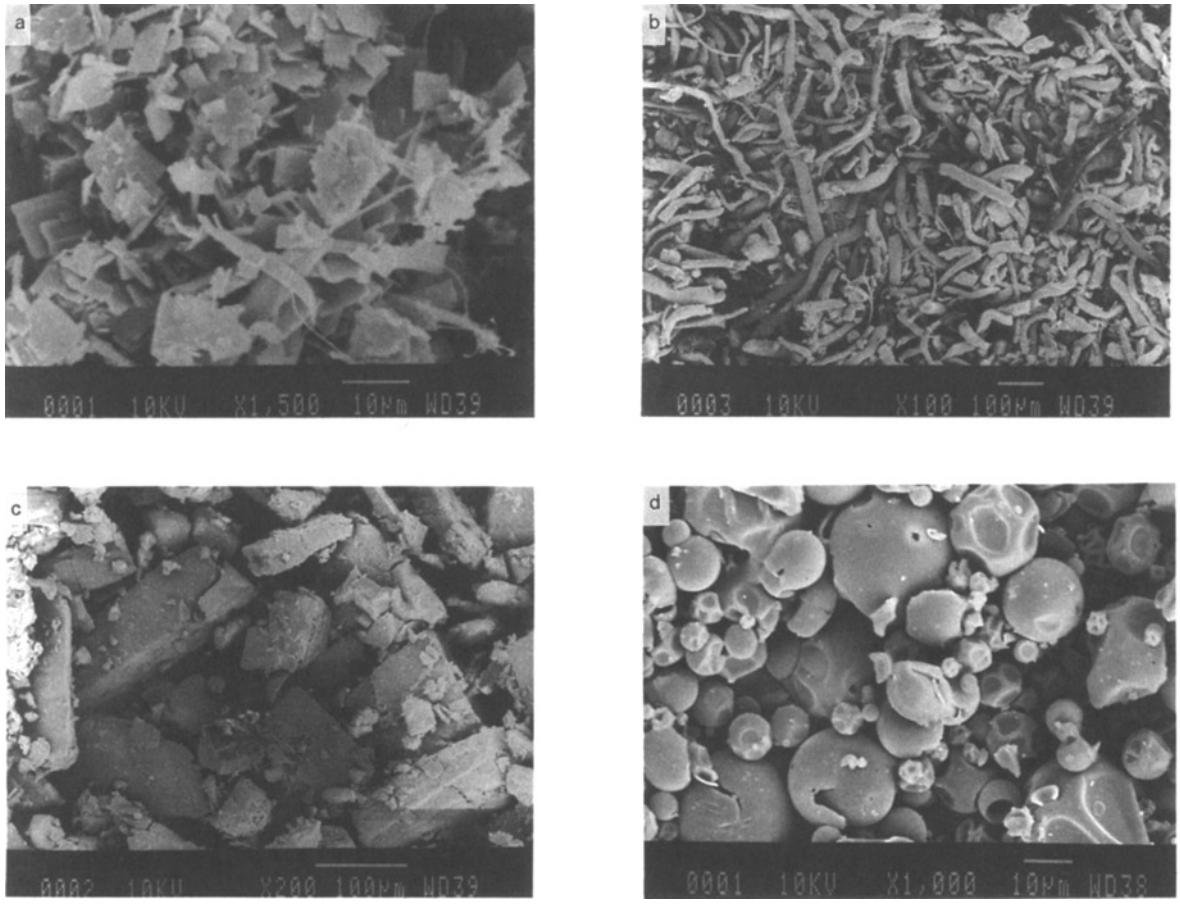

FIG. 1. Photomicrographs of a. naftazone, b. CM-XL, c. β-CyD, d. HP-β-CyD.

Erosion/release test

Erosion/release studies of the matrices were carried out, according to Ranga Rao et al (1988), using the modified dissolution test apparatus and the conditions described above. Gelled or partially eroded matrices were taken out of the medium and placed in a circulating hot air oven (65–70°C) until the residual matrix was dried to constant weight. At the same time the drug released was determined by a UV spectrophotometer.

Results and Discussion

The morphological characteristics of naftazone and of the carriers are shown in Fig. 1.

Fig. 2 shows scanning electron micrographs of the drug-carrier systems. The NzXL system has drug crystals homogenously distributed on the surface of CM-XL. Nz-β-CyD and Nz-HP-β-CyD systems show that the technique of preparation (ball milling) leads to a modification of the morphology of the starting materials with the original structures of β-CyD, HP-β-CyD and of the drug being partially destroyed.

Fig. 3 shows the thermal behaviour of the pure components compared with the thermal behaviour of the drug-carrier systems. The melting peak of naftazone has completely disappeared in the case of NzXL, while the heat involved in the melting process of naftazone in the Nz-β-CyD system is about 43% of the heat involved in the melting process of the drug alone, and is about 88% in the Nz-HP-β-CyD system, suggesting that some sort of interaction between drug and cyclodextrins occurs.

Fig. 4 shows the dissolution profiles of the drug-carrier systems compared with the drug alone. The dissolution rate improvement was particularly high in the case of the systems containing β-CyD or HP-β-CyD as carrier, with more than 80% of drug dissolved within about 6 min.

Extended drug release at a fairly constant rate, without time lag is obtained over a range of about 8–12 h in the case of the matrices containing CM-XL (Fig. 5), and over a range of about 10–20 h in the case of the matrices containing cyclodextrins (Fig. 6). In all cases the drug-release rate is dependent on the viscosity grade of HPM constituting the matrix; in fact the matrices containing HPM with the higher viscosity value (15000 cP) are always characterized by the lower drug-release rates with respect to the matrices containing the HPM with the low viscosity value (4000 cP). We suggest that in the presence of the carrier the drug had lost its characteristics of water insolubility and therefore the viscosity of the gel becomes critical in controlling the drug release rates.

The release profiles of the matrices containing CM-XL are characterized by some differences with respect to the matrices containing β-CyD or HP-β-CyD: there is an initial burst effect (about 10% of drug released in the first hour) which is missing in the case of the matrices containing cyclodextrins, and furthermore, they have higher release rates.

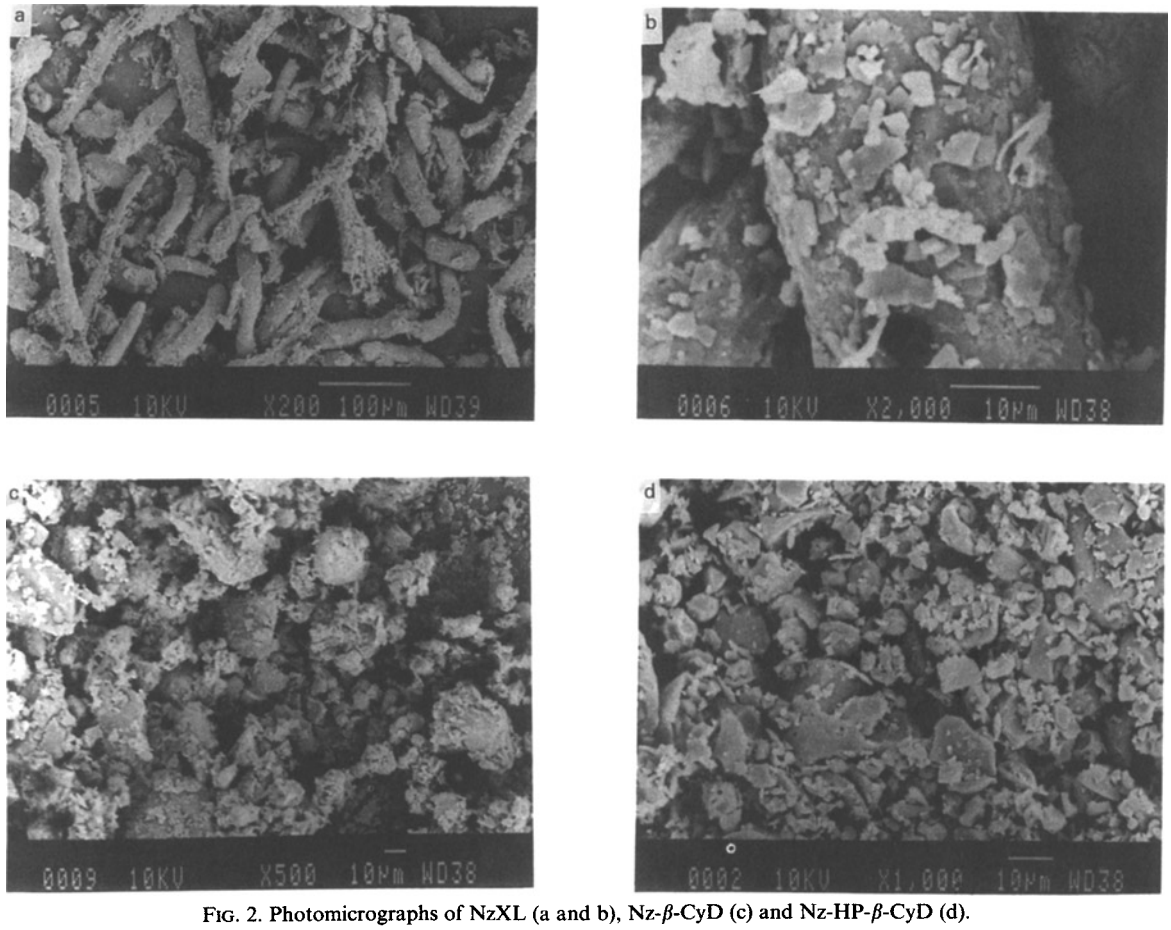

FIG. 2. Photomicrographs of NzXL (a and b), Nz-β-CyD (c) and Nz-HP-β-CyD (d).

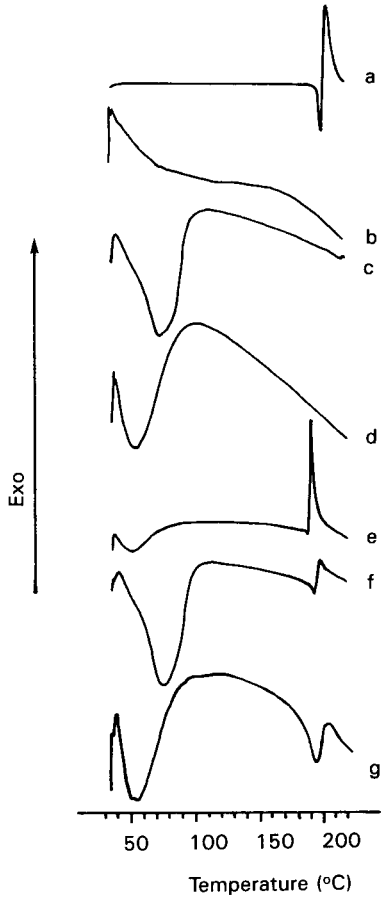

FIG. 3. Differential scanning calorimetry of a. naftazone, b. CM-XL, c. β-CyD, d. HP-β-CyD, e. NzXL, f. Nz-β-CyD, g. Nz-HP-β-CyD.

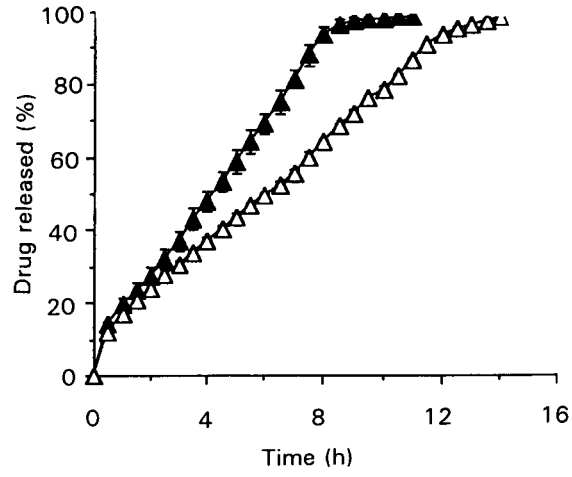

FIG. 5. Release profiles (n = 3 ± s.d.) of matrices: ▲ XL.K4 and △ XL.K15 (containing CM-XL).

In matrices containing either CM-XL or cyclodextrins, the matrices are subjected during the release tests both to a gelation process, due to the presence of HPM, and to an erosion process, which is due in the first case to the swellable properties of CM-XL and in the second case to the solubility in water of the cyclodextrins. The initial burst effect and the higher release rates from CM-XL matrices demonstrate that the swelling of CM-XL has a high capacity in determining the erosion of the gelled HPM matrix.

At the same HPM viscosity grade, β-CyD matrices are always characterized by lower release rates, with respect to HP-β-CyD matrices. This can be due to the different water solubility of the two cyclodextrins.

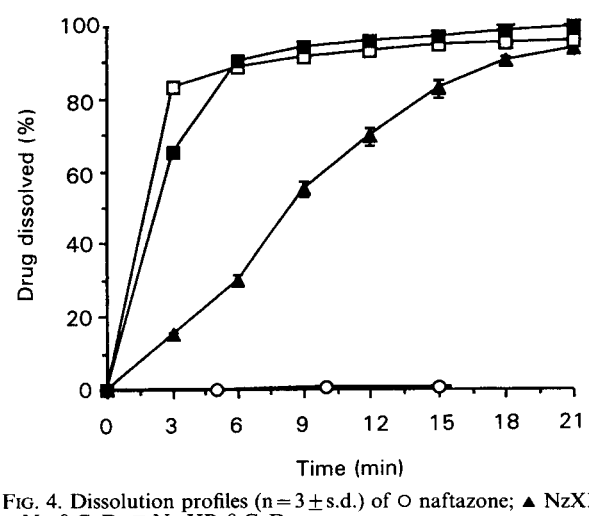

FIG. 4. Dissolution profiles (n = 3 ± s.d.) of ○ naftazone; ▲ NzXL; □ Nz-β-CyD; ■ Nz-HP-β-CyD.

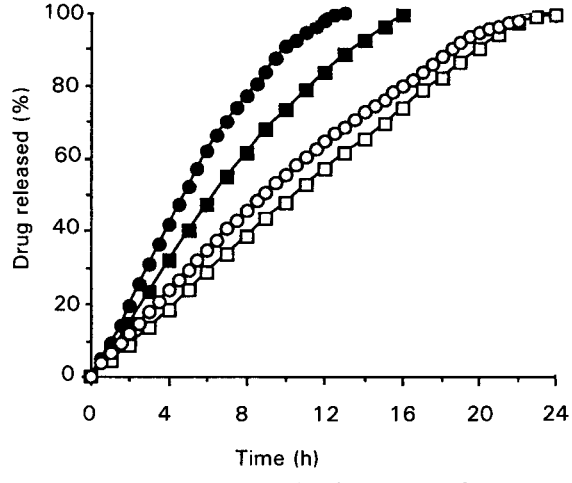

FIG. 6. Release profiles (n = 3 ± s.d.) of matrices: ■ β-CyD.K4 and □ β-CyD.K15 (containing β-CyD); ● HP-β-CyD.K4 and ○ HP-β-CyD.K15 (containing HP-β-CyD).

Table 1. Exponents (n) and coefficients of determination (r^2) according to $M_t/M_\infty = Kt^n$ for hydrophilic matrices containing CM-XL, β-CyD or HP-β-CyD.

Matrix	n	r^2
XL.K4	0·928	0·999
XL.K15	0·900	0·995
β-CyD.K4	1·080	0·996
β-CyD.K15	1·032	0·999
HP-β-CyD.K4	1·050	0·999
HP-β-CyD.K15	0·998	0·999

The drug release data were fitted to the following equation (Ritger & Peppas 1987):

$$M_t/M_\infty = Kt^n$$

where M_t/M_∞ is the fractional release of the drug at time, t, K is a constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. The data were fitted for 70% of drug released.

The values of n and the coefficient of determination r^2 obtained are listed in Table 1. All matrices had values of n very close to unity, particularly in the case of the matrices containing cyclodextrins, indicating that these matrices behave as zero-order release systems.

Erosion/release tests were carried out on XL.K15, chosen as an example of a matrix containing CM-XL, and on β-CyD.K15, chosen as an example of a matrix containing a cyclodextrin (Fig. 7). These results show in both cases that the matrix erosion process follows a linear profile, which corresponds with the linear release profile of the drug. The constant drug release could be due to a combination of the two processes, with the lengthening of the diffusional pathway balanced by the corresponding erosion of the matrix.

Our studies show that the combination of hypromellose with cross-linked carmellose sodium, β-cyclodextrin or hydroxypropyl-β-cyclodextrin is suitable for the preparation of zero order-release hydrophilic matrices for water-insoluble drugs.

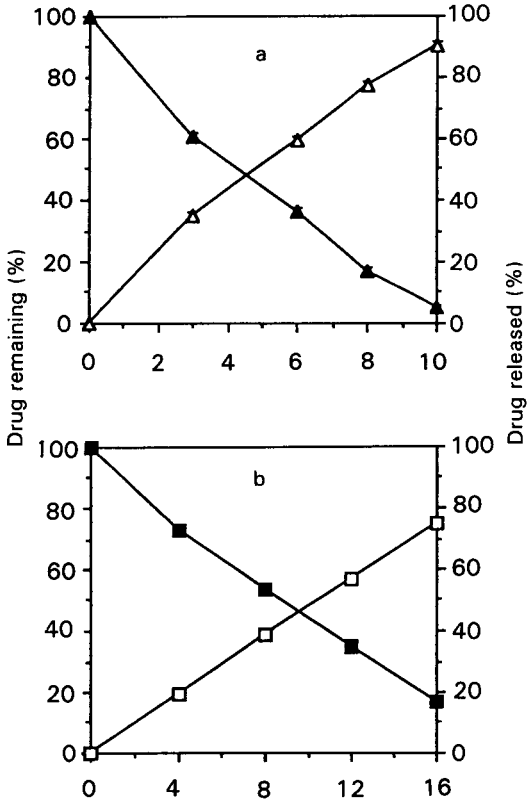

FIG. 7. a. Erosion/release studies of the XL.K15 matrix (n = 3 ± s.d.); ▲ % matrix residue; △ % drug released. b. Erosion/release studies of the β-CyD.K15 matrix (n = 3 ± s.d.): ■ % matrix residue, □ % drug released.

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