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Multicomponent Complexes of Piroxicam with Cyclodextrins and Hydroxypropyl Methylcellulose

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ABSTRACT

The purpose of the study was to investigate the effect of hydroxypropyl methylcellulose (HPMC) on the complexation of piroxicam (PX) with β-cyclodextrin (β-CD) and dimethyl-β-cyclodextrin (DM-β-CD) in solution and in the solid state. Phase solubility study revealed a positive effect of the polymer on the drug complexation. Improvement in stability constants values, K_s, of ternary complexes clearly proves the benefit of the HPMC addition for promoting higher complexation efficiency. Solid binary and ternary complexes were prepared by spray drying. Drug-CD and drug-CD-polymer interactions were studied in the solid state by differential scanning calorimetry (DSC), zeta-potential measurements, and particle size distribution. A marked increase in the PX dissolution rate was observed even in binary and ternary complexes. The presence of HPMC in ternary complexes slightly retarded the release of PX. Cyclodextrin complexation increased the PX concentration gradient over the semipermeable membrane, resulting in an increased PX flux. The retarded diffusion of PX to the membrane interface decreased the PX flux values of the ternary complexes.

Key Words: Piroxicam; Cyclodextrins; Hydroxypropyl methylcellulose; Multicomponent complexes.

INTRODUCTION

Cyclodextrins have been attracting increasing interest in the pharmaceutical field because of their ability to modify physical, chemical and biological properties of a number of hydrophobic drug molecules through the formation of inclusion complexes.[1,2]

In the last two decades, cyclodextrins have been widely used as complexing agents to modify drug solubility or improve drug stability, bioavailability or

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toxicity, by means of drug inclusion into the hydrophobic cavity of cyclodextrin. Recently, considerable interest has been focused on the incorporation of cyclodextrins into polymeric drug delivery systems such as microspheres and nanospheres.[3]

Unfortunately, the complexation efficiency of cyclodextrins is rather low and therefore a significant amount of cyclodextrins is needed to solubilise a small amount of water-insoluble compounds. However, enhanced complexation can be achieved by formation of ternary complexes (or co-complexes) between the drug molecule, cyclodextrin molecule and a third component. Moreover, recent works have shown that the addition of a suitable third component can often significantly improve both the solubilising and complexing abilities of cyclodextrins towards several drugs.[4]

Various polymers are capable of interacting with cyclodextrins and of increasing the apparent stability constants of the drug-cyclodextrin complexes. Thus, the amount of cyclodextrins that can be incorporated into the drug formulations could be limited. Polymers are believed to form ternary complexes (or co-complexes) with the drug and cyclodextrin molecules. These ternary complexes are formed in aqueous solutions at very low polymer concentrations, typically between 0.1 and 0.3% (w/v), and by heating to 120–140°C for 20–40 min. Formation of a ternary complex is not limited to a certain type of cyclodextrin or a certain type of polymer, it rather appears to be a general property of cyclodextrins and various polymers.[5] The exact nature of the polymer-cyclodextrin interaction is still unknown.[6]

Hydroxypropyl methylcellulose is one of the most frequently used polymers for this purpose. This cellulose derivative is a hydrophilic polymer, well established as a pharmaceutical excipient, which has been extensively used in controlled drug delivery systems. Hydroxypropyl methylcellulose has been previously reported to be useful in the improvement of cyclodextrin complexation.[7,8]

Most of the studies carried out to analyse the effect of hydrophilic polymers on the complex formation with cyclodextrins were done in solution, not in the solid state. Several papers have been published on the improvement of the solubility and bioavailability of drugs through the formation of binary and ternary systems with cyclodextrins.[9–15]

Piroxicam is an established NSAID in the treatment of rheumatic diseases. It can be administered by both oral and topical routes. Due to its poor water solubility, piroxicam oral administration is characterised by slow absorption. This limited solubility seems to be a problem for piroxicam bioavailability and it is a drawback for its formulation in controlled release devices. However, as piroxicam oral administration is associated with gastrointestinal side effects, it is also important to develop a therapeutic system that will minimize these effects. In this sense, the interaction of drugs with cyclodextrins is an important feature in modifying different drug properties, such as solubility, dissolution rate, bioavailability, etc. Several studies on the complexation of piroxicam with cyclodextrins have presented clear evidence of these advantages.[7,16,17]

The aim of the present work was to prepare solid multicomponent piroxicam binary and ternary complexes using hydroxypropyl methylcellulose and two cyclodextrins. Complexation efficiency and the solubilising effect of cyclodextrins by addition of a water-soluble polymer might be a useful strategy to find new ways of achieving the required release pattern from different formulations.

EXPERIMENTAL

Materials

Piroxicam (PX) was kindly donated by Belupo (Koprivnica, Croatia). β-cyclodextrin (β-CD) and dimethyl-β-cyclodextrin (DM-β-CD) with an average substitution degree per anhydroglucose unit of 1.8 were used as received (Wacker, Chemie GmbH, Munich, Germany). Hydroxypropyl methylcellulose (HPMC), Metolose®, viscosity 4000 mPa s (2% aqueous solution), was obtained from Shin-Etsu Chemical Co. Ltd., Japan. All other materials and solvents used were of analytical grade.

Methods

Phase Solubility Studies

Phase solubility studies were performed using the method previously reported by Higuchi and Connors.[18] Briefly, excess amounts of PX (0.05 g) were added to 20 ml of aqueous solutions containing various concentrations of β-CD (0 to 1.0×10^{-2} M) and DM-β-CD (0 to 4.0×10^{-2} M). The suspensions were vigorously shaken at 25±1°C for 3 days. The 3-day equilibration was considered sufficient. After equilibrium was attained, the samples were filtered through a 0.45 μm Millipore membrane filter and suitably diluted with 0.01 mol l^{-1} methanol hydrochloric acid. PX concentration was determined spectrophotometrically at 242 nm (Ultrospec Plus, LKB, Pharmacia, Sweden).

To establish the effect of the polymer on the solubility diagram, HPMC was added (0.05 and 0.1%)

to suspensions. The suspensions were sonicated in an ultrasonic bath for 1 h, at 70°C, and were then allowed to equilibrate at 25±1°C for 3 days. After equilibrium was attained, undissolved drug was removed from the samples by centrifugation (3500 rpm, 15 min) and the PX content was determined by the previously described method.

The apparent 1:1 stability constants, K_s, were calculated from the phase solubility diagrams using the equation:

$$K_s = \frac{slope}{S_0(1 - slope)}$$

where S_0 is the PX solubility in the absence of cyclodextrins or HPMC (intercept).

Preparation of Binary PX-CD Complexes

PX or equimolar amounts of PX (1.32 g) and cyclodextrins (4.54 g of β-CD or 5.32 g of DM-β-CD) were dissolved in water (400 ml) by addition of a 25% ammonium hydroxide solution. The solution was stirred for 24 hours at ambient temperature to reach complexation equilibrium, and was then subjected to spray drying. The drying conditions were as follows: flow rate 0.25 l h^{-1}, inlet temperature 110°C, outlet temperature 80°C, and air flow rate 700 Nl h^{-1}.

Percentages of PX in spray-dried systems were determined spectrophotometrically after dissolution of the product in 0.01 mol l^{-1} methanol hydrochloric acid.

Preparation of Ternary PX-CD- HPMC Complexes

For ternary products, equimolar amounts of CDs and PX were dispersed in a 0.1% HPMC solution, and a 25% ammonium hydroxide solution was added. The systems were stirred at 600 rpm for the next 24 hours to attain complexation equilibria and were subjected to spray drying. The drying conditions are described in section 2. The drug dispersion in 0.1% HPMC solution was also prepared. Percentages of PX in spray-dried systems were determined spectrophotometrically.

Differential Scanning Calorimetry (DSC)

DSC thermograms of the drug, polymer, cyclodextrins, and the prepared solid binary and ternary systems were recorded on a Perkin Elmer Pyris 1 instrument. The instrument was calibrated with indium and zinc prior to analysing the samples. All accurately weighed samples (2–5 mg) were sealed into aluminium pans and scanned at a heating rate of 10°C min^{-1} over a temperature range 30–250°C under dry nitrogen (35 ml/min).

Zeta Potential Measurement

Zeta potentials of spray-dried pure components (HPMC, β-CD and DM-β-CD) and the prepared solid binary and ternary systems were measured in 10 mmol l^{-1} NaCl, at pH=6.25, using a Malvern 3000 HS Zetasizer (Malvern, UK).

Size Distribution of the Systems

A microscopical imaging analysis technique for determination of size distribution was applied. The size and distribution were determined with an Olympus BH-2 microscope, equipped with a computer controlled image analysis system (Optomax V, Cambridge, UK).

In Vitro Dissolution Studies

Dissolution studies were performed in sink conditions according to the dispersed amount method by adding the solid systems, equivalent to 50 mg of PX, to 500 ml of water thermostated at 37°C±0.5°C, and stirred at 50 rpm with a glass three-blade propeller centrally immersed in the baker. At fixed time intervals, samples were withdrawn with a filter-syringe (0.45 μm) and assayed spectrophotometrically for the drug content, as in phase solubility studies. A correction was applied for the cumulative dilution caused by replacement of the sample with an equal volume of fresh medium.[7]

In Vitro Permeation Study

Effects of the HPMC and cyclodextrins on PX diffusion through the cellophane membrane (Medicell Dialysis Tubing MW CO 600) were investigated using the Franz diffusion cell (Perme Gear, USA) with a diffusion area of 10.18 cm^2 and acceptor compartment volume of 100 ml. The acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer. The samples (equivalent to 50 mg of PX in 10 ml of water for the binary and ternary complexes prepared) were placed into the donor compartment thermostated at 37°C (non-sink conditions).

The amount of the drug permeated through the membrane was determined by removing aliquots at fixed time intervals from the acceptor compartment. The aliquots were replaced with a fresh medium. The

PX concentration was determined spectrophotometrically as in the phase solubility studies. PX flux through the membrane was calculated using the equation:

$$J = dQ/A\ dt$$

where J is the steady-state flux, Q is amount of diffused drug and A is the diffusion area.

RESULTS AND DISCUSSION

Binary and Ternary Complexes of PX in the Solution

Phase solubility studies of PX in binary and ternary systems with cyclodextrins and HPMC were performed to obtain more information about the drug solubilisation and multicomponent complex formation in solution. Phase solubility diagrams of PX in aqueous β-CD and DM-β-CD solutions in the presence or absence of HPMC are shown in Fig. 1. In all cases, the diagrams can be included in the A_L-type according to the Higuchi and Connors classification.[18] Slopes of the diagrams were lower than 1, suggesting the formation of 1:1 molar stoichiometry. HPMC enhanced significantly the solubilising effect of cyclodextrins but did not affect the type of the phase solubility diagram obtained for binary systems. The apparent stability constants, K_s, of PX-β-CD and PX-DM-β-CD binary and ternary complexes were calculated from the slopes of the phase solubility diagrams, assuming a 1:1 stoichiometry. The K_s values of PX-CD binary and ternary complexes and PX solubility values in solutions of different composition are presented in Table 1.

Stability constants of the complexes showed, in both cases, an enhancement in the presence of HPMC. The drug-CDs binding constants increased as the concentration of HPMC increased. The observed

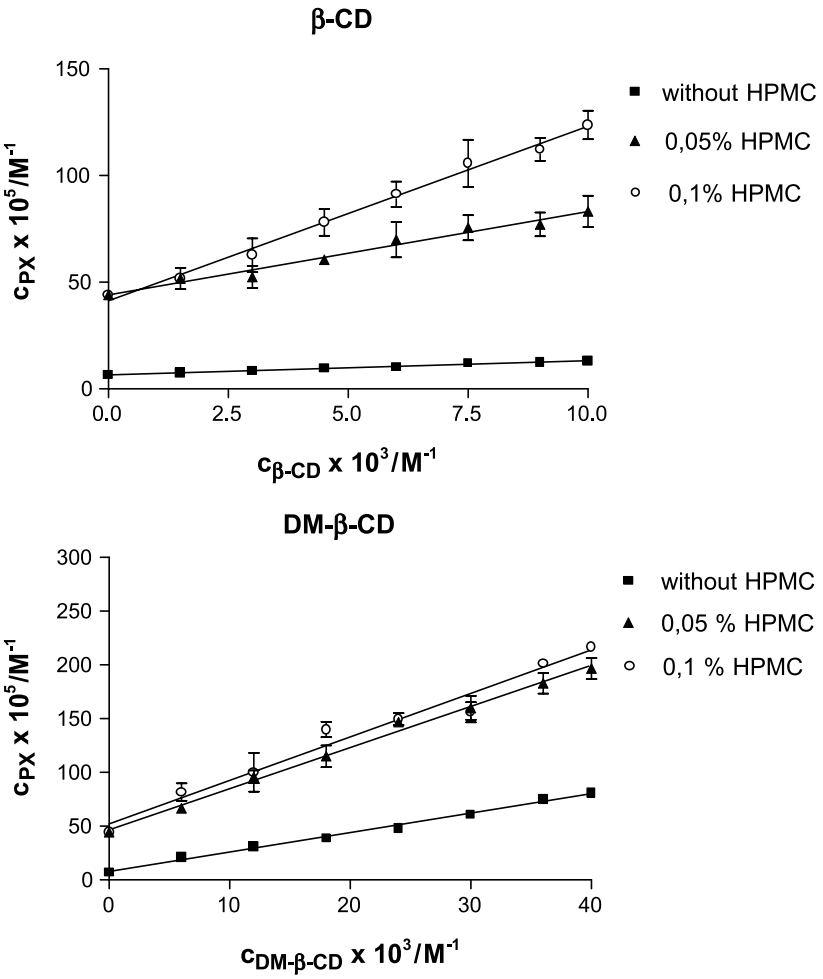

Figure 1. Phase solubility diagrams of PX-CD systems at 25°C, with and without HPMC (mean ± SD, n = 5).

Table 1. Apparent stability constants, K_s, and PX solubility in binary and ternary complexes (mean ± SD, n = 5).

	β-CD			DM-β-CD		
HPMC	K_s/M^{-1}	K_T/K_B*	S_1/S_2**	K_s/M^{-1}	K_T/K_B*	S_1/S_2**
No polymer	103.5 ± 7.4	–	–	237.5 ± 9.3	–	–
0.05%	622.1 ± 15.8	6.01	1.16	521.8 ± 17.2	2.19	1.42
0.1%	1359.9 ± 18.3	13.14	1.07	603.8 ± 12.8	2.54	1.38

*$K_T/K_B - K_s$ ratio for ternary and binary complexes.
**S_1/S_2 PX solubility ratio obtained in ternary complexes and correspondingly sum of values in CD and polymer solution.

enhancement of K_s upon addition of the polymer showed that HPMC was able to interact with drug-CDs binary complexes. The effect could be explained as being a result of a ternary complex formation, which increased the complexation efficiency of both CDs.

DM-β-CD proved to have better solubilising and complexing properties for PX than the parent β-CD, which could be deduced from the higher K_s value obtained for the binary complex. Methylated CDs are surface active. This fact should be considered in the solubilising property of DM-β-CD.

Addition of HPMC to the CDs solutions resulted in a K_s increase, which varied from a minimum of 119% to a maximum of 1214% depending on the CD and polymer concentration.

Interestingly, it was also demonstrated that PX-β-CD ternary systems were more stable than those with DM-β-CD. Probably the substituent methyl groups of DM-β-CD in the presence of HPMC do hamper inclusion of PX molecules into the cavity via steric hindrance. It is known that methylation increases the height of the cavity but at the same time the inner diameter of the cavity is decreased.[19]

Consequently, a synergistic effect on PX solubility was observed in the presence of CDs and HPMC. The solubility values obtained in the presence of both CDs and HPMC were higher than the sum of the contribution solubility values obtained with the CD and HPMC solutions. The influence of HPMC on the solubilising effect of CDs toward PX is not simply additive. Addition of HPMC resulted in a 7–42% increase in PX solubility (Table 1).

Preparation and Characterisation of Solid Binary and Ternary PX Complexes

Solid binary and ternary complexes were obtained by spray drying from the equimolecular PX-CD solutions, as found in the phase solubility study, and HPMC concentration in ternary complexes was 0.1%.

DSC was used to characterise the multicomponent solid system prepared. DSC thermograms of pure components and various binary and ternary complexes are shown in Fig. 2. The DSC curve of PX (A) showed a single sharp endothermic peak at 200.8°C ($\Delta H = 108.12\ Jg^{-1}$), indicating a cubic polymorph form (Polymorph I).[20] DSC thermogram of HPMC (B) showed a wide endothermic band, which was correlated to the exit of the adsorbed moisture or solvent from the molecule (35–110°C). A small exothermic event was noticed in the region from 170–216°C, indicating a phase transition. Thermogram of the PX-HPMC (C) complex showed a small endothermic peak at 73°C (exit of solvent) followed by an exothermic peak at 113°C, which indicated a crystallisation process. The endothermic melting peak of PX was observed at 198°C. The position and shape of the peak indicated the interaction of PX and HPMC, and partial transformation of the PX polymorph I (cubic form) to polymorph II (needle form). DSC thermogram of β-CD (D) indicated dehydration, seen as a wide endothermic peak (54.5–97.3°C). Thermogram of DM-βCD (G) showed dehydration (37–74.4°C) followed by the exothermic peak at 159°C, indicating phase transition.

PX-β-CD binary complex (E) in the region from 34–119°C showed the solvent exit followed by an endothermic event with peaks at 160.5°C ($\Delta H = 16.18\ Jg^{-1}$) and at 223.1°C ($\Delta H = 9.8\ Jg^{-1}$), assigned to phase transition and melting of the PX molecule incorporated in β-CD, respectively. DSC curve of the PX-DM-β-CD complex (H) showed the solvent exit from DM-β-CD molecules (33.6–85.6°C). In the regions from 123.3–140°C and 165.3–179.8°C, there were other small endothermic events with peaks at 130.1°C ($\Delta H = 1.97\ Jg^{-1}$) and 176.3°C ($\Delta H = 1.06\ Jg^{-1}$). Shifting of the melting peak of the PX molecule to a lower temperature confirms the interaction between PX and CDs.

DSC thermogram of the ternary β-CD complex (F) exhibited a wide endothermic peak of dehydration in the temperature region 30–120°C, with the onset temperature at 49°C ($\Delta H = 151.6\ Jg^{-1}$). DSC of the

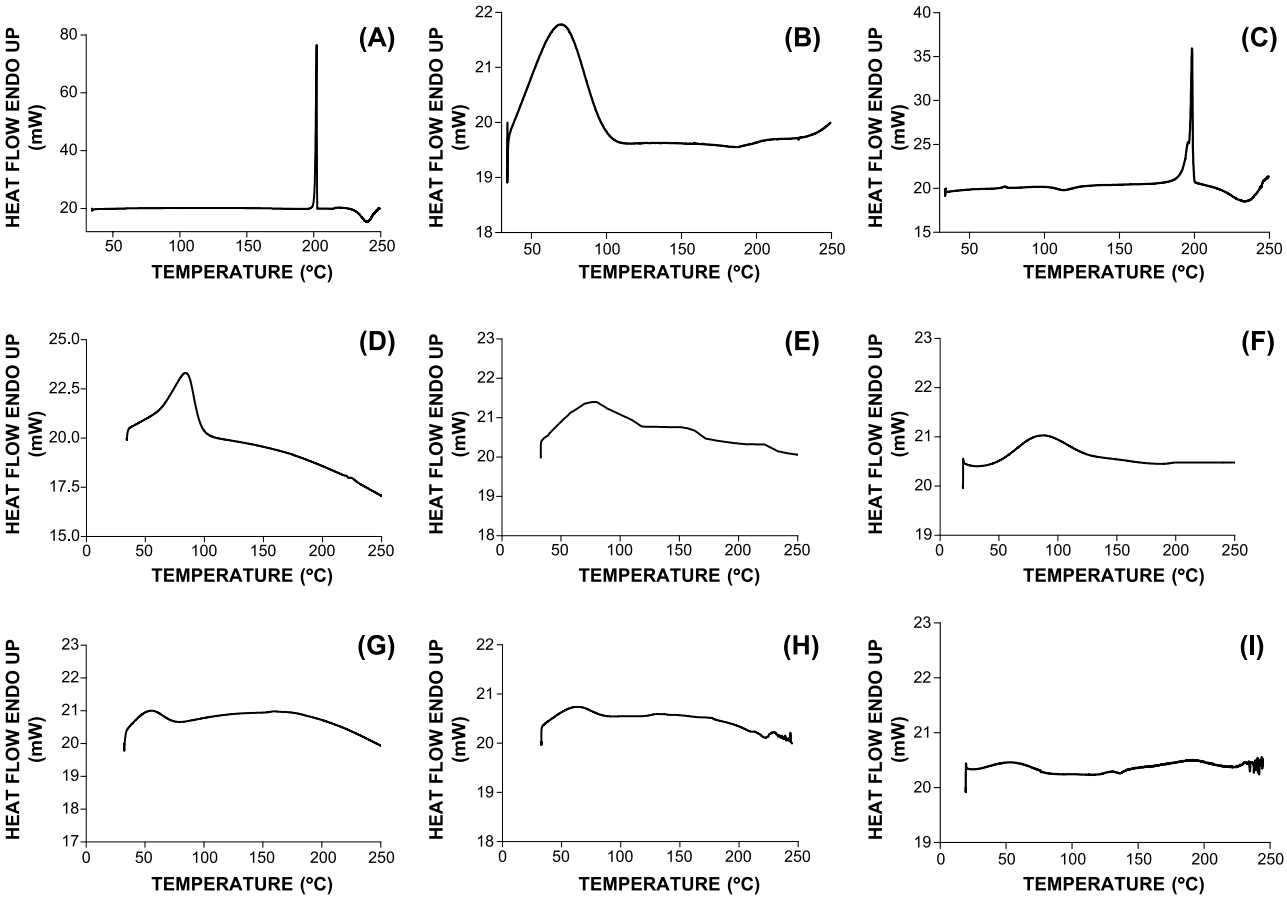

Figure 2. DSC thermograms of components and binary and ternary complexes: PX (A), HPMC (B), PX-HPMC (C), β-CD (D), PX-β-CD (E), PX.β-CD-HPMC (F), DM-β-CD (G), PX-DM-β-CD (H), PX-DM-β-CD-HPMC (I).

DM-β-CD ternary PX (I) complex exhibited a wide endothermic peak in the region from 25–75°C, with the onset temperature at 38.9°C ($\Delta H = 23\ Jg^{-1}$) corresponding to dehydration. Further heating led to complex degradation.

The strong reduction of intensity of the PX melting endotherm observed in the binary complexes and its total disappearance in the ternary complexes account for the presence of marked interactions between the components, leading to drug complexation. More

Table 2. Formulation characteristics and PX flux (J) through semipermeable membrane of the prepared spray-dried binary and ternary complexes.

System	Drug loading %	Mean diameter μm	J/mg cm^{-2} h^{-1} mean ± SD
PX	–	2.34	20 ± 1
PX-HPMC	85.98	2.17	21 ± 1
PX-β-CD	22.68	2.22	428 ± 21
PX-DM-β-CD	18.55	2.41	452 ± 19
PX-β-CD-HPMC	24.04	2.22	216 ± 13
PX-DM-β-CD-HPMC	19.33	2.14	321 ± 19

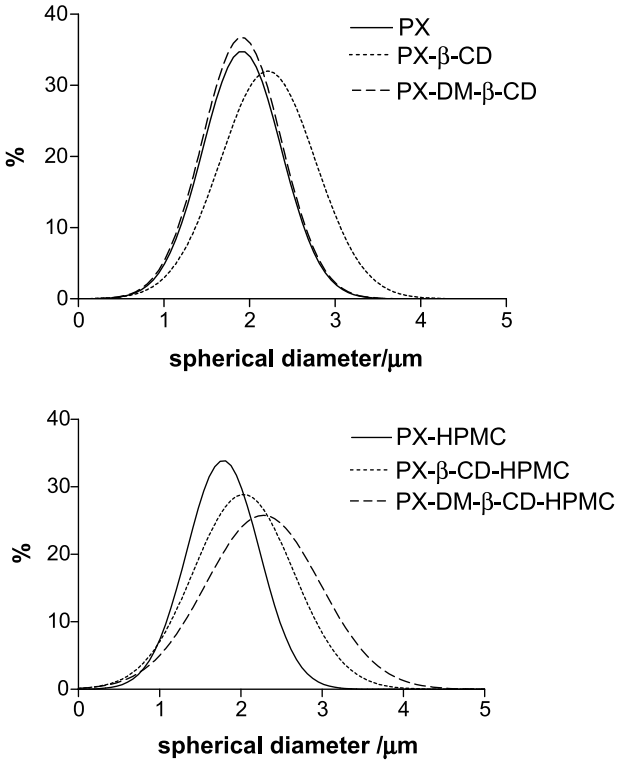

Figure 3. Particle size distribution of the complexes.

information about inclusion complex structure can be reached by other analytical methods, such as single crystal X-ray structure determination of ^{13}C-NMR solid state spectroscopy.

Table 2 shows the mean spherical diameters of the complexes prepared. The presence of HPMC and CD complexation did not substantially influence the particle size. Figure 3 represents the size distribution of the complexes. The analysis indicated a narrow logarithmic—normal distribution for all samples, with more than 70% of particles having a spherical diameter ranging from 1–3 μm.

Zeta potential measurement is an important surface characterisation technique, which provides information about the surface charge of the particles. From zeta potential measurements we can roughly know the dominant component of the particle surface. Figure 4 shows the determined zeta potential values of spray-dried pure components and their binary and ternary complexes.

Depending upon pH, PX can exist in cationic, neutral or anionic forms. Under our experimental conditions (pH$\sim$6.25), only the anionic form of PX was present, and the zeta potential of PX had a negative value ($-$15.5 mV). Cyclodextrin complexation led to a decrease in the negative value of the zeta potential. In the presence of cyclodextrin and HPMC, the particles maintained a less negative zeta potential, suggesting that the drug was mainly enclosed in the CD cavity or dispersed within the polymer matrix. Since CDs are non-ionic, the observed surface charge demonstrated the presence of CD which shifted the negative surface charge of PX to a larger distance. The zeta potential values for the binary and ternary complexes did not differ significantly. Less negative potential values from $-$1.4 to $-$3.48 mV may correspond to a small amount of drug adsorbed on the surface of complex particles.

The release profiles of PX from binary and ternary complexes are shown in Fig. 5. A marked increase in the dissolution rate of PX was evident even in binary and ternary complexes and can be attributed to the formation of readily soluble complexes in the dissolution medium. Figure 5 also shows the burst effect of PX release from all complexes. This fact is most likely due to the reduced particle size and consequent increase of the surface area of the drug-carrier powder, and to the improved wettability due to the intimate

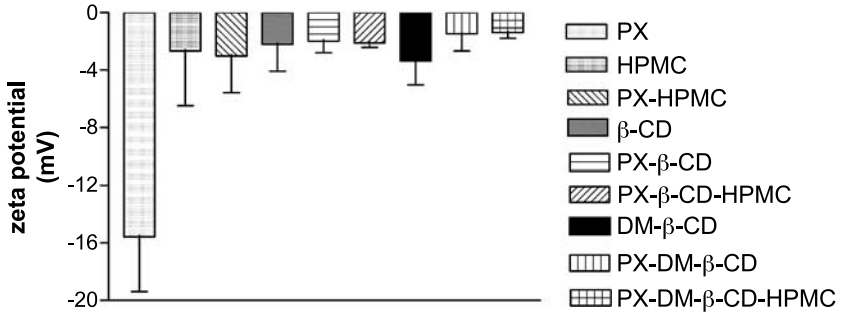

Figure 4. Zeta potential values of components and binary and ternary complexes.

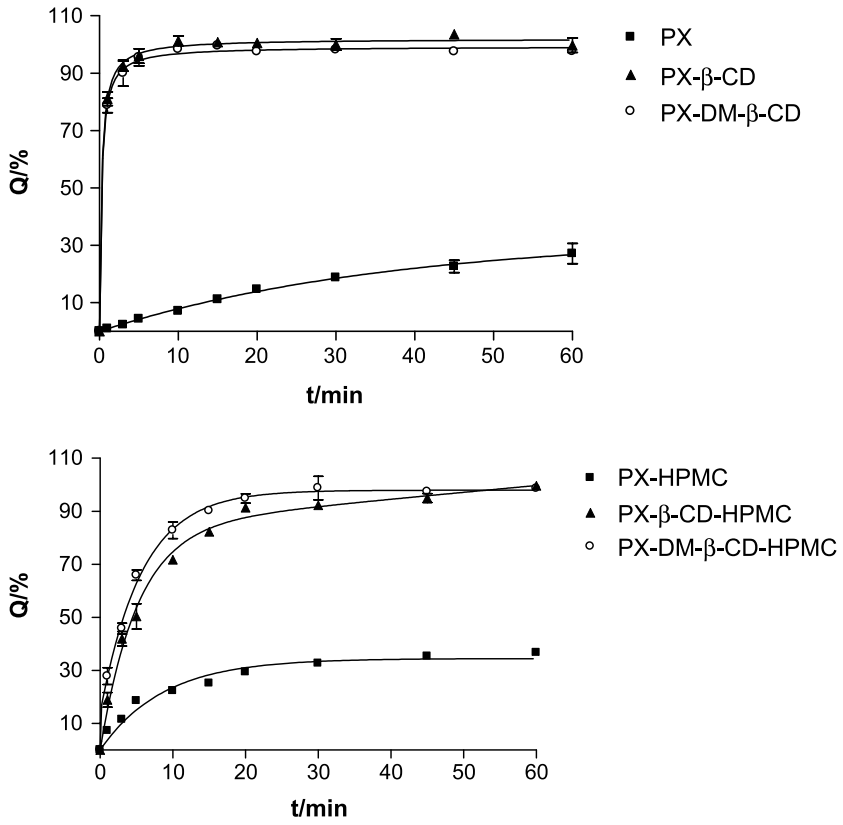

Figure 5. In vitro release of PX in water from the complexes (mean ± SD, n = 5).

contact with the hydrophilic carrier. The PX reduction in crystallinity, caused by spray drying, enhanced also its dissolution rate.

The presence of HPMC in ternary complexes slightly retarded the release of PX. This small retardant effect of HPMC could be explained by the slow diffusion of PX through the more hydrophilic HPMC/CD matrix layer around the lipophilic drug. When the complex made contact with the dissolution medium, HPMC swelled and controlled the drug release. Phase solubility diagrams revealed the positive effect of the polymer on the complexation of the drug in the solution. In solid state binary inclusion complex enhanced the dissolution behaviour of PX but from the ternary complexes the polymer controlled the release of the drug. HPMC is matrix forming polymer and it tends to sustain the drug release.

The permeation test was aimed to investigate the drug passage through the semipermeable membrane. Profiles of PX permeation from the complexes are shown in Fig. 6. Flux values were determined from the steady state region of the diffusion profiles (Table 2). Differences in the flux values of PX from the complexes could be attributed to the cyclodextrin-polymer complexation. When PX molecules diffused from an aqueous donor phase through a semipermeable membrane to an acceptor phase, two processes were occurring: PX diffusion in the aqueous donor phase and the diffusion through the membrane. Both processes made a contribution to the overall diffusion rate. PX diffusion in the aqueous diffusion layer (donor phase) was increased by improving the diffusible form of the drug species through complexation. Though the complex did not penetrate the membrane, the drug in the complex was in rapid dynamic equilibrium with the ''free'' drug, thus continuously supplying PX molecules to the membrane in a diffusible form. Cyclodextrin complexation increased the drug concentration gradient over the membrane, which resulted in increased PX flux. The stability constant values for the β-CD and DM-β-CD binary complexes differed but did not significantly affect the drug diffusivity. DM-β-CD was shown to have better solubilising and complexing properties for PX than β-CD, as it could be deduced from the higher K_s value obtained for binary complexes. DM-β-CD reduced the

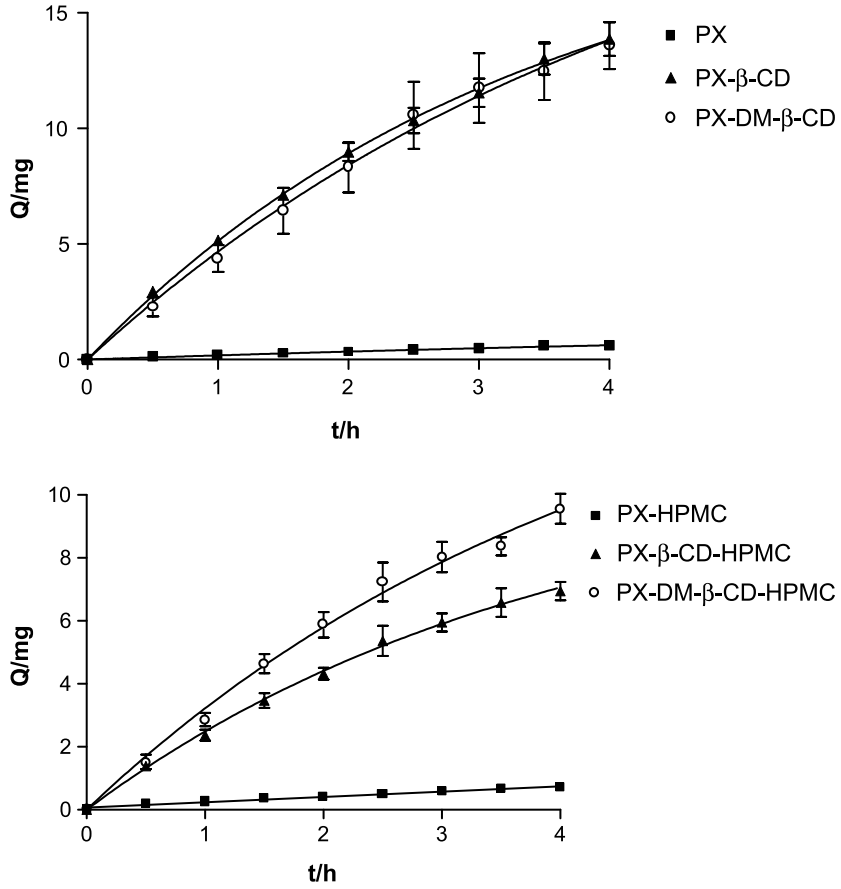

Figure 6. Cumulative amount of diffused PX across semipermeable membrane from the complexes as a function of time (mean ± SD, n = 5).

flux by preventing the PX-DM-β-CD complex from dissociation into free PX and CD by shifting the equilibrium towards association rather than dissociation of the complex.

The stability constant of PX ternary complexes was higher for β-C, which resulted in a reduced flux compared to DM-β-CD. The retarded diffusion of PX to the membrane interface could decrease the flux values of the ternary complexes. The complexed PX molecules permeated at a much slower rate than the free molecules in solution.

CONCLUSIONS

The solubility of PX can be increased by inclusion complexation with β-CD and DM-β-CD. The results showed that HPMC could enhance the complexation of PX with cyclodextrins in the solution. The presence of HPMC improved the stability constants, K_s, promoted higher complexation efficiency, and clearly proved the benefid of the polymer addition.

Cyclodextrins are unable to form inclusion complexes with polymers if their effective diameter is greater than that of the cavity (HPMC). Solid PX ternary complexes can be obtained by spray drying and their formation has been proved using DSC tehnique, and suggested the formation of new solid phases. The interaction between HPMC and cyclodextrin occured probably through intramolecular polymeric hydrogen bond formation. The dissolution and permeation rated of the drug were lower from the ternary complexes comparing with binary. When solid ternary complex made contact with the dissolution media HPMC swelled and controlled the release of PX. PX solid ternary complexes containg matrix forming polymer (HPMC) tend to controlle drug release.

So, pharmaceutical usefulness of cyclodextrins may be substantially improved by co-administration of a water soluble polymer. It might be a useful

strategy for decreasing the amount of cyclodextrins needed in dosage forms.

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