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Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions

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Abstract

Increase in the poor water solubility and dissolution rate of norfloxacin was studied. Two systems were used: solid dispersion with PEG 6000 prepared using the fusion method and inclusion complexes with cyclodextrins (β-cyclodextrin and HP-β-cyclodextrin) obtained by freeze-drying. IR spectrophotometry, X-ray diffractometry, and differential scanning calorimetry showed differences between norfloxacin/cyclodextrin complexes and their corresponding physical mixtures, but not between norfloxacin/PEG 6000 solid dispersions and their corresponding physical mixtures. The solubility and dissolution rate of norfloxacin were significantly increased with PEG solid dispersions and cyclodextrin complexes as well as with norfloxacin-CD physical mixtures. However, enhancement was not statistically different either among various cyclodextrin complexes, or between solid dispersions and cyclodextrin complexes.

Keywords: Norfloxacin; β-Cyclodextrin; Hydroxypropyl-β-cyclodextrin; Complexation; Poly(ethylene glycol) 6000; Solid dispersion

1. Introduction

Norfloxacin, a fluoroquinolone carboxylic acid, is an antimicrobial agent widely used in the treatment of urinary tract infections. It has a low bioavailability, mainly attributed to its low aqueous solubility.

Norfloxacin is poorly soluble in water: 0.45 mg ml^{-1} at pH 7.5 (Swanson et al., 1983) and 0.40 mg ml^{-1} at pH 7 (Ross and Riley, 1990).

In aqueous solutions, norfloxacin exists in four protonation forms. The zwitterionic form, which is predominant at the isoelectric point of the molecule at pH close to 7, has the lowest solubility (Takács-Novák et al., 1992).

In order to improve the solubility and bioavailability of poorly water soluble drugs many methods are used. Solid dispersions (Chiou and Riegelman, 1970; McGinity et al., 1984; Duchêne et al., 1985) and cyclodextrin inclusion complexes

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(Duchêne and Wouessidjewe, 1990a; Szejtli, 1991) are actually among the most frequently used.

Polyoxyethylene glycols (PEG) are used extensively as carriers for dispersions due to their low melting point and their hydrophilic environment.

β-Cyclodextrin (β-CD) is known to form inclusion complexes with many pharmaceutical compounds (Kurozumi et al., 1975; Duchêne and Wouessidjewe, 1990b) while hydroxypropyl-β-cyclodextrin (HP-β-CD) appears to possess promising properties for the improvement of drug release, since it has the complexing properties of cyclodextrins and much greater solubility in water than β-cyclodextrin. HP-β-CD is also useful in the formulation of parenteral preparations due to its low cytotoxicity, weak haemolytic activity and only minor irritating effect (Uekama and Otagiri, 1987; Duchêne and Wouessidjewe, 1990a).

Moreover, where storage leads to a decrease in solubility and bioavailability of systems such as solid dispersions (SD) (Chiou and Riegelman, 1971; Duchêne, 1985), it has been shown that the process of storage does not affect the biopharmaceutical behaviour of drug/CD inclusion complexes (Torres-Labanderia et al., 1994).

Several methods have been used to prepare SD and CD inclusion complexes. In both types of product, it was found that the dissolution kinetics were dependent on the nature of the carrier and the preparation method (Chiou and Riegelman, 1971; Ford, 1986; Lin et al., 1991; Conte et al., 1993; El Moussaoui et al., 1994).

The aim of this work was to investigate the influence of dispersion in PEG 6000 and complexation with cyclodextrins on the physico-chemical characteristics and dissolution rate of norfloxacin. For this purpose, a comparative study on the dissolution rate of norfloxacin was carried out on SD of norfloxacin vs physical mixtures of norfloxacin/PEG 6000 and on inclusion complexes of norfloxacin vs physical mixtures of norfloxacin/cyclodextrins.

In order to analyze the prepared products, selective physical determinations based on X-ray diffractometry, IR spectroscopy and differential scanning calorimetry (DSC) were used. Solubility diagrams and dissolution studies were also carried out.

2. Materials and methods

2.1. Materials

Norfloxacin was obtained from Sigma Chemicals Co (St Louis, MO, USA), polyethylene glycol (PEG) 6000 was purchased from Merck (Hohenbrunn, Germany), and β-cyclodextrin (Kleptose®, Mol. Wt 1135) and hydroxypropyl-β-cyclodextrin (MS = 0.45, Mol. Wt = 1300–1400) were kindly supplied by Roquette Frères (Lestrem France). All other materials were of analytical reagent grade.

2.2. Preparation of solid dispersions and physical mixtures of norfloxacin / PEG 6000

Four SD preparations containing different weight ratios of norfloxacin and PEG 6000 (10:90, 20:80, 30:70, 50:50, respectively) were prepared by the melting method (Francès et al., 1991). SD containing higher proportions of norfloxacin could not be prepared in this way, since the final products were not homogeneous.

The carrier (PEG 6000) was melted in a water bath at 70° C, the drug was added in the solid state and the mixture stirred until homogeneity was attained. The mixture was then allowed to cool slowly at room temperature (slow cooling preparation of dispersion with PEG 3000 as carrier gave an unchanged dissolution rate during 10 months storage (Sjokvist Saers et al., 1993)).

After solidification, the product was ground in a mortar. The resulting powder was sieved smaller than 180 μm.

In addition, norfloxacin and PEG 6000 were weighed accurately, pulverized and then mixed thoroughly by light trituration in a mortar until a homogeneous mixture was obtained. The mixture was passed through a 180 μm sieve. Thus, four norfloxacin/PEG 6000 physical mixtures in the same ratios as the SD were prepared.

2.3. Preparation of inclusion complexes and physical mixtures of norfloxacin / cyclodextrins

The norfloxacin inclusion complexes with β-CD and HP-β-CD were prepared by freeze-drying (Brewster et al., 1991).

Norfloxacin and CD (β-CD or HP-β-CD) in two different norfloxacin/CD molecular ratios (1:1 and 1:2) were mixed by magnetic stirring in aqueous solution (pH 7 ± 0.1) for 24 h at room temperature. Preparations were then filtered through a 0.8 μm cellulose acetate/cellulose nitrate membrane in order to remove a possible excess of norfloxacin not included in the complex. The filtrate was freeze-dried for 24 h (Serail freeze drier, France).

Physical mixtures of appropriate amounts of norfloxacin and CD (β-CD or HP-β-CD) were obtained by pulverizing and then mixing both solids in a mortar. In each case, the resulting powder was passed through a 180 μm sieve.

2.4. Physicochemical determinations of the interaction

2.4.1. X-ray analysis

The physical state of norfloxacin in the various preparations was evaluated by X-ray diffraction. Powder X-ray diffractometry was carried out with a Philips X-ray diffractometer (PW 1050/PW 1710) using Ni-filtered, CuK_α radiation ($\lambda = 1.5418$ Å), a voltage of 40 kV and a current of 40 mA. The scanning rate was 6°/min over a 2θ range of 5–60°, chart speed 10 mm/min and count range 1000 cps.

2.4.2. IR analysis

The IR spectra of the samples were taken on an IR spectrophotometer (Shimadzu IR 470) using the KBr disk technique (sample concentration: 1.5 mg in 200 mg KBr).

2.4.3. DSC

Thermal analysis was performed using a Mettler TA 4000 system with a differential scanning calorimeter equipped with a computerized data station (Mettler model DSC 30, Mettler-Toledo AG, Switzerland).

All samples were weighed (8–10 mg) and heated at a scanning rate of 10° C min^{-1} between 30 and 300° C. Aluminium pans and lids were used for all samples. Temperature calibrations were performed periodically using indium as a standard.

The results presented were the means of three determinations.

2.4.4. Solubility measurement of norfloxacin

Solubility study was carried out according to the method of Higuchi and Connors (1965). Excess norfloxacin (30 mg) was introduced into a 25 ml bottle containing a mixture of 10 ml of deionized water (pH 7 ± 0.1) and various amounts of β-CD or HP-β-CD. On the other hand, norfloxacin SD with different quantities of PEG 6000 were placed in bottles of 25 ml containing 10 ml of deionized water. All suspensions were protected from the light by wrapping the vials with aluminium foil (light has a significant effect on the stability of norfloxacin solution (Nangia et al., 1991)) and rotated for 24 h at room temperature. The content of each bottle was then filtered through a 0.8 μm membrane. The filtrate was then diluted in distilled water and assayed spectrophotometrically at 274 nm (Beckman model 34 spectrophotometer, USA). There was no interference from PEG 6000 or CD at this wavelength.

Each solubility was determined in triplicate.

2.5. Dissolution studies

Dissolution studies were performed using USP XXII apparatus 2 (rotating paddle method; Erweka model DT, Germany).

Pure norfloxacin and all the other products (physical mixtures, SD and inclusion complexes) prepared as described above were included in this study. Samples of each preparation equivalent to 10 mg of norfloxacin were spread over the surface of the dissolution medium (1000 ml of deionized water, maintained at a temperature of 37 ± 1° C and at pH 7.0 ± 0.2). The dissolution medium was stirred with a rotating paddle (200 rpm).

The aqueous solutions were filtered (filter-fitted teflon tubing) and continuously pumped (peristaltic pump Gilson Minipuls 2, France) to a flow cell in the UV spectrophotometer, so that the absorbance was monitored automatically at 274 nm.

The dissolution tests were carried out for 60

min. The results were computed with a standard calibration curve of the drug ($r = 0.999$).

All experiments were carried out in triplicate.

2.6. Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA). To determine whether or not the observed differences between the dissolution profiles obtained were significant, the Scheffé test was applied to the experimental values. A significance level of $p = 0.05$ was chosen. The Scheffé method was interesting to carry out after ANOVA, since it permitted a posteriori comparison of multiple results and isolation of the sources of significant differences (Scheffé, 1953).

3. Results and discussion

3.1. Physico-chemical properties of solid dispersions and complexes

3.1.1. Solubility

Phase solubility profiles of norfloxacin with PEG and CD are shown in Fig. 1.

The solubility of norfloxacin in water at pH 7 ± 0.1 without PEG or CD was found to be 1.084 mM (0.377 mg ml^{-1}). The values reported by Ross and Riley (1990) (0.40 mg ml^{-1} at 25° C and pH 7) and by Swanson and co-workers (1983) (0.45 mg ml^{-1} at 25° C and pH 7.5) were slightly higher.

The solubility of norfloxacin increased as a function of CD concentration. This function is linear in the case of β-CD. Probably because of its higher solubility in water, HP-β-CD was more efficient in solubilizing norfloxacin. The phase solubility profiles of norfloxacin in β-CD and HP-β-CD aqueous solutions could be classified as being of the A_n and A_l type, respectively, as defined by Higuchi and Connors (1965). Similar results had previously been reported by Brewster and co-workers (1991) for carbamazepine/CD complexes but with a quadratic function for the CD concentration.

In contrast, PEG does not increase the solubil-

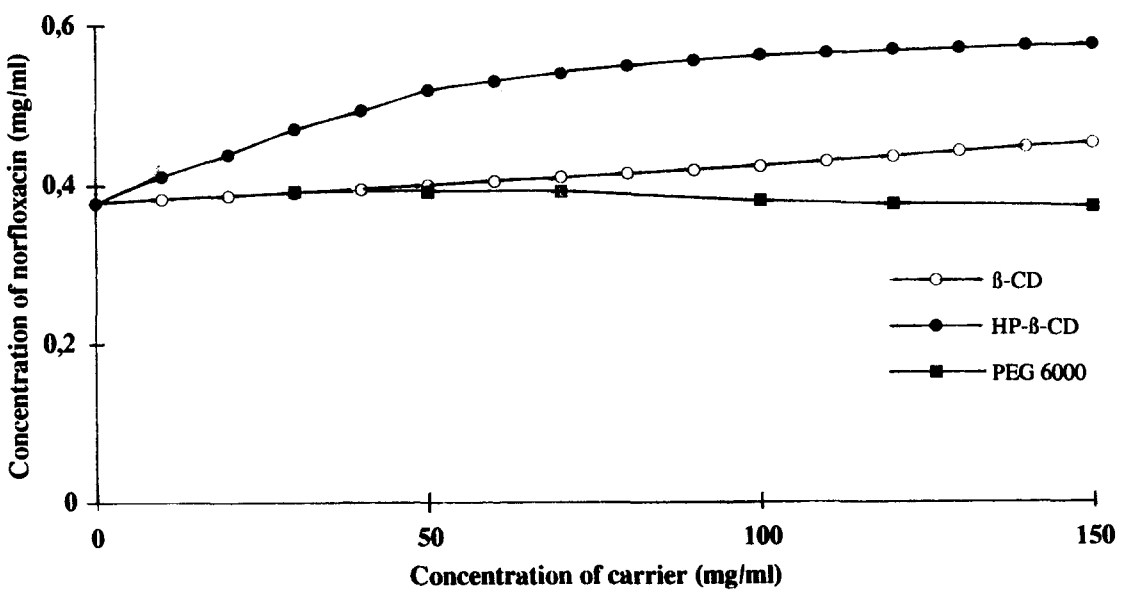

Fig. 1. Phase solubility diagrams of norfloxacin with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and PEG 6000 in aqueous solution at room temperature (25° C).

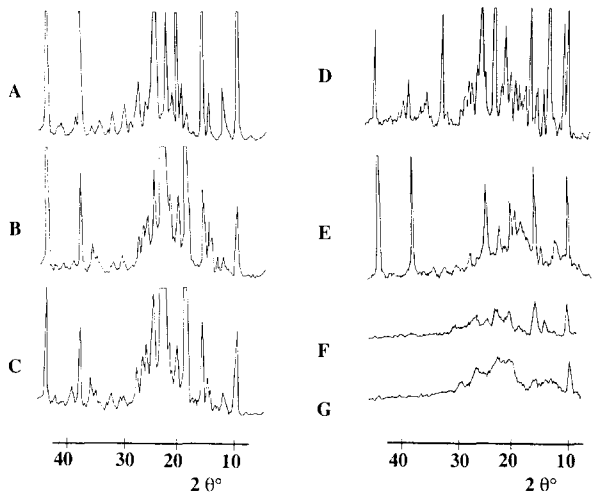

Fig. 2. Powder X-ray diffraction patterns of norfloxacin and its various combination forms with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) or PEG 6000. (A) Norfloxacin crystals; (B) physical mixture of norfloxacin/PEG 6000 (30–70); (C) solid dispersion of norfloxacin/PEG 6000 (30–70); (D) physical mixture of norfloxacin/β-CD (1:1); (E) physical mixture of norfloxacin/HP-β-CD (1:1); (F) freeze-dried complex of norfloxacin/β-CD (1:1); (G) freeze-dried complex of norfloxacin/HP-β-CD (1:1).

ity of norfloxacin significantly. Maximum norfloxacin dissolution (0.392 mg ml^{-1}) was produced by norfloxacin/PEG (30–70) SD.

3.1.2. X-Ray diffraction

Fig. 2 shows the powder X-ray diffraction patterns of norfloxacin and its physical mixtures, SD and CD inclusion complexes.

PEG 6000, β-CD and HP-β-CD (not shown) are amorphous whereas pure norfloxacin is crystalline as demonstrated by the sharp and intense diffraction peaks.

The powder X-ray diffraction patterns of the norfloxacin/PEG (30:70) SD and the physical mixtures of norfloxacin/PEG and norfloxacin/CD showed several peaks corresponding to the crystalline form of norfloxacin.

The observed variations in some peaks may result from behavioural changes of norfloxacin/PEG solid dispersions. However, crystallinity of the systems does not seem to be affected. Similar results were reported using hot-stage microscopy with ciprofloxacin and PEG 6000 (Francès et al., 1991).

In contrast, samples of norfloxacin/CD (β-CD or HP-β-CD) inclusion complexes showed a halo pattern, indicating that norfloxacin/CD complexes were in the amorphous state. Similar results have been reported for *p*-boronophenylalanine/β-CD or HP-β-CD inclusion complexes prepared by freeze-drying (Hatanaka et al., 1993). Moreover, the presence of diffraction peaks in the X-ray diffraction patterns of physical mixtures containing the same quantities of norfloxacin and CD indicates that the loss of drug peaks with the complex is not the result of a dilution effect.

These data are indicative of the transformation of norfloxacin from the crystalline to the amorphous state by formation of an inclusion complex with β-CD or HP-β-CD. The formation of an amorphous state proves that the drug was dispersed in a molecular state with the CD (Nakai et al., 1990).

3.1.3. IR spectrophotometry

Fig. 3 demonstrates the spectra of pure norfloxacin, norfloxacin/PEG 6000 SD, norfloxacin/CD inclusion complexes and their corresponding physical mixtures.

Physical mixtures of norfloxacin/PEG or norfloxacin/CD and SD of norfloxacin/PEG show spectra corresponding to a superposition of their parent products (norfloxacin/PEG or norfloxacin/CD).

In contrast, the IR absorption peak of COOH at 1720 cm^{-1} disappeared in the norfloxacin/CD complexes. These results suggest that the carboxylic portion of the norfloxacin is predominantly included within the apolar cavity of β-CD or HP-β-CD. Similar results were obtained for an other drug/CD complex prepared by freeze-drying (Hatanaka et al., 1993).

3.1.4. DSC

Thermograms of norfloxacin, PEG, their physical mixtures and SD are shown in Fig. 4.

Pure norfloxacin exhibits two endothermic peaks (at 100 and 222° C) which represent the loss of adsorbed water and melting of the sample,

respectively. The end of the thermogram corresponds to break up of norfloxacin (probably by decomposition).

Norfloxacin/PEG preparations containing less than 50% of norfloxacin show one endothermic peak at 62° C due to the melting of PEG, without an appreciable endothermic peak in the melting region of norfloxacin. However, an endothermic peak at 221° C corresponding to the melting of norfloxacin is displayed when the concentration of the drug either in the SD or in the physical mixtures was 50%. These data indicate the absence of interaction of PEG with norfloxacin and are in agreement with the IR and X-ray diffraction data.

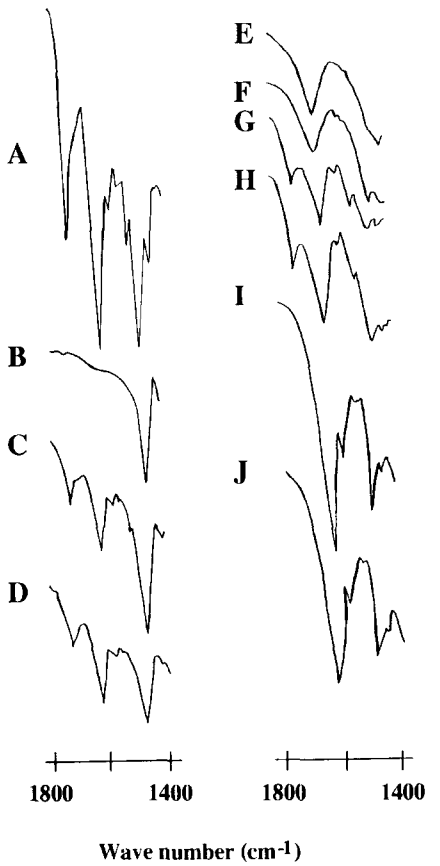

Fig. 3. IR spectra of norfloxacin, PEG 6000, β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and their various combination forms. (A) Norfloxacin crystals; (B) PEG 6000; (C) physical mixture of norfloxacin/PEG 6000 (30–70); (D) solid dispersion of norfloxacin/PEG 6000 (30–70); (E) β-CD; (F) HP-β-CD; (G) physical mixture of norfloxacin/β-CD (1:1); (H) physical mixture of norfloxacin/HP-β-CD (1:1); (I) freeze-dried complex of norfloxacin/β-CD (1:1); (J) freeze-dried complex of norfloxacin/HP-β-CD (1:1).

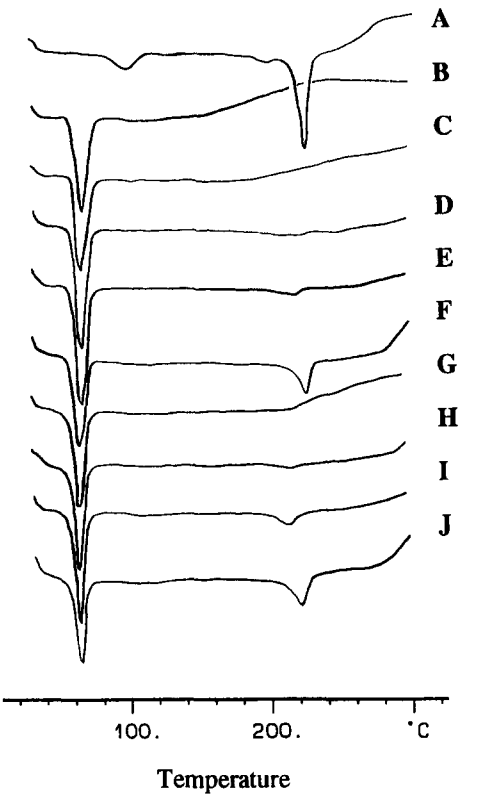

Fig. 4. DSC thermograms of norfloxacin with PEG 6000. (A) Norfloxacin crystals; (B) PEG 6000; (C) physical mixture of norfloxacin/PEG 6000 (10–90); (D) physical mixture of norfloxacin/PEG 6000 (20–80); (E) physical mixture of norfloxacin/PEG 6000 (30–70); (F) physical mixture of norfloxacin/PEG 6000 (50–50); (G) solid dispersion of norfloxacin/PEG 6000 (10–90); (H) solid dispersion of norfloxacin/PEG 6000 (20–80); (I) solid dispersion of norfloxacin/PEG 6000 (30–70); (J) solid dispersion of norfloxacin/PEG 6000 (50–50).

The broadening and disappearance of the endothermic peak corresponding to fusion of norfloxacin in both systems at low norfloxacin concentrations can be explained by the complete or partial dissolution of norfloxacin crystals in the PEG 6000 melt. Francès and co-workers (1991) reported similar results with ciprofloxacin/PEG systems and confirmed the dissolution of ciprofloxacin crystals in the PEG 6000 melt by hot-stage microscopy. More recently, the same

phenomenon was reported for fenofibrate/PEG 6000 SD (Sheu et al., 1994).

Fig. 5 presents thermograms of norfloxacin, CD, their physical mixtures and inclusion complexes.

The DSC curves of norfloxacin/CD physical mixtures show peaks resulting from the simple superposition of their separated component DSC curves.

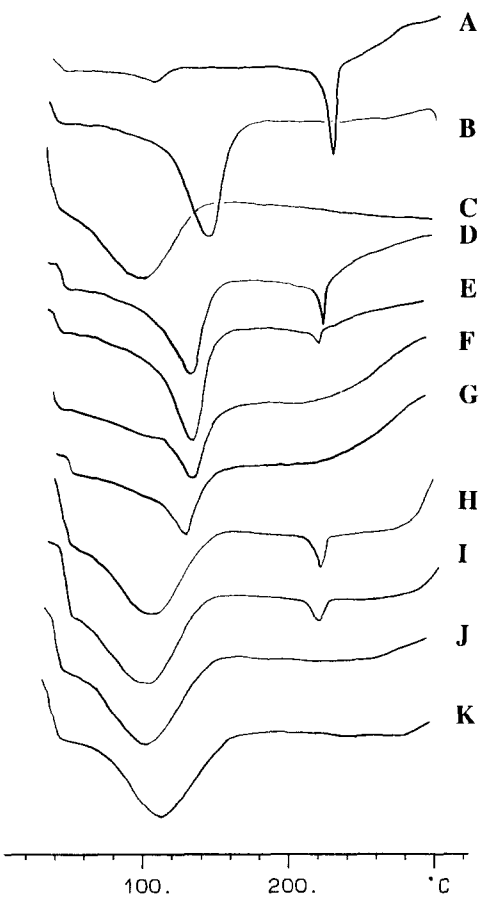

Fig. 5. DSC thermograms of norfloxacin with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD). (A) Norfloxacin crystals; (B) β-CD; (C) HP-β-CD; (D) physical mixture of norfloxacin/β-CD (1:1); (E) physical mixture of norfloxacin/β-CD (1:2); (F) freeze-dried complex of norfloxacin/β-CD (1:1); (G) freeze-dried complex of norfloxacin/β-CD (1:2); (H) physical mixture of norfloxacin/HP-β-CD (1:1); (I) physical mixture of norfloxacin/HP-β-CD (1:2); (J) freeze-dried complex of norfloxacin/HP-β-CD (1:1); (K) freeze-dried complex of norfloxacin/HP-β-CD (1:2).

In contrast, no endothermic peak corresponding to fusion of norfloxacin was observed in the DSC curves of norfloxacin/CD complexes. The disappearance of this peak is due to the interaction of norfloxacin with CD and formation of inclusion complexes (Kurozumi et al., 1975). DSC thermograms indicate the existence of a new compound and confirm the X-ray diffraction and IR spectral data concerning the presence of norfloxacin in an amorphous state, dissolved or homogeneously dispersed in the CD. From these data, one can conclude that the interaction of norfloxacin either with CD (in complexes) or with PEG (in SD) was completely different.

3.2. Dissolution tests

Fig. 6 illustrates the dissolution profiles plotted from the experimental values of pure norfloxacin, and its physical mixtures and SD with PEG 6000. Two groups of curves can be distinguished.

In the first group, the dissolution profiles from pure norfloxacin and its physical mixtures with PEG 6000 are included. These profiles do not show any significant difference either in the dissolved amount, at the same time, or in the dissolution rate of norfloxacin. As would be expected, the extent of pure norfloxacin release was found to be low due to the hydrophobic nature of the drug.

The second group of curves includes the dissolution profiles of norfloxacin from SD. These binary systems exhibit faster dissolution rates. Complete dissolution of samples was achieved within 30 min with SD, 60 min with physical mixtures and 80 min with pure norfloxacin. Within 30 min, 91.8 and 93.7% were dissolved from pure norfloxacin and its physical mixtures, respectively. SD show only a 1.1-fold increase in the initial dissolution rate of norfloxacin.

Among SD, the dissolution kinetics of norfloxacin/PEG 6000 (30:70 and 20:80) seem to be more greatly enhanced with time. Thus, to obtain the maximal dissolution rate of the drug from SD, optimal weight fractions of polymer should be necessary. Similar findings have been reported with several SD such as sulfathiazole/PVP, car-

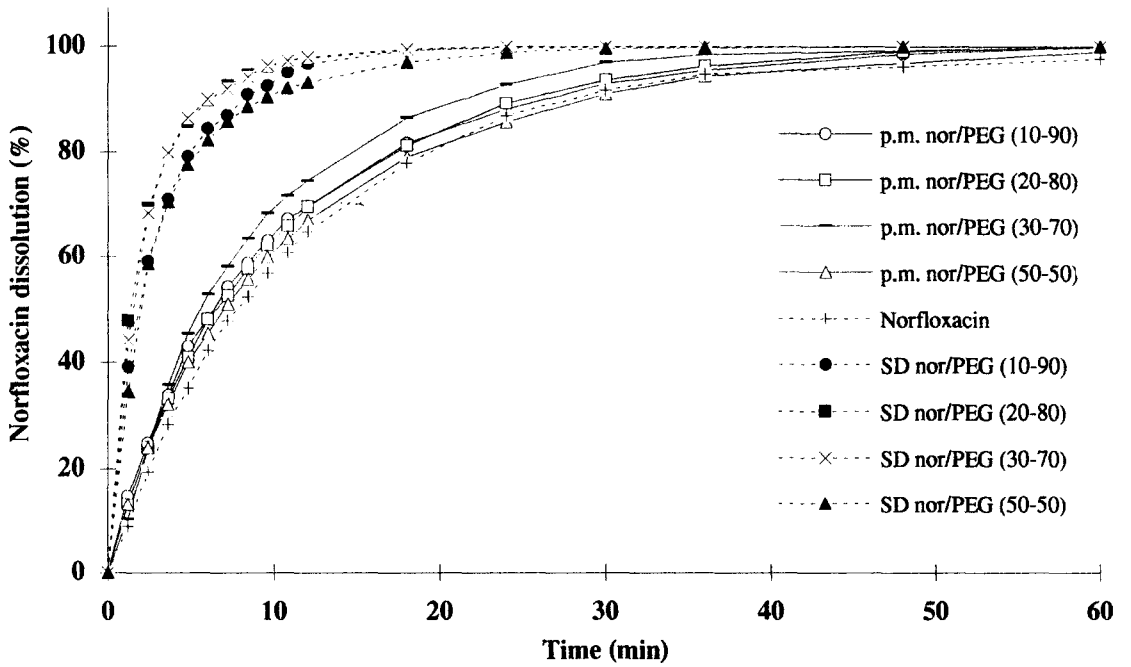

Fig. 6. Dissolution profiles of norfloxacin, physical mixtures of norfloxacin/PEG 6000 (p.m. nor/PEG) and solid dispersions of norfloxacin/PEG 6000 (SD nor/PEG).

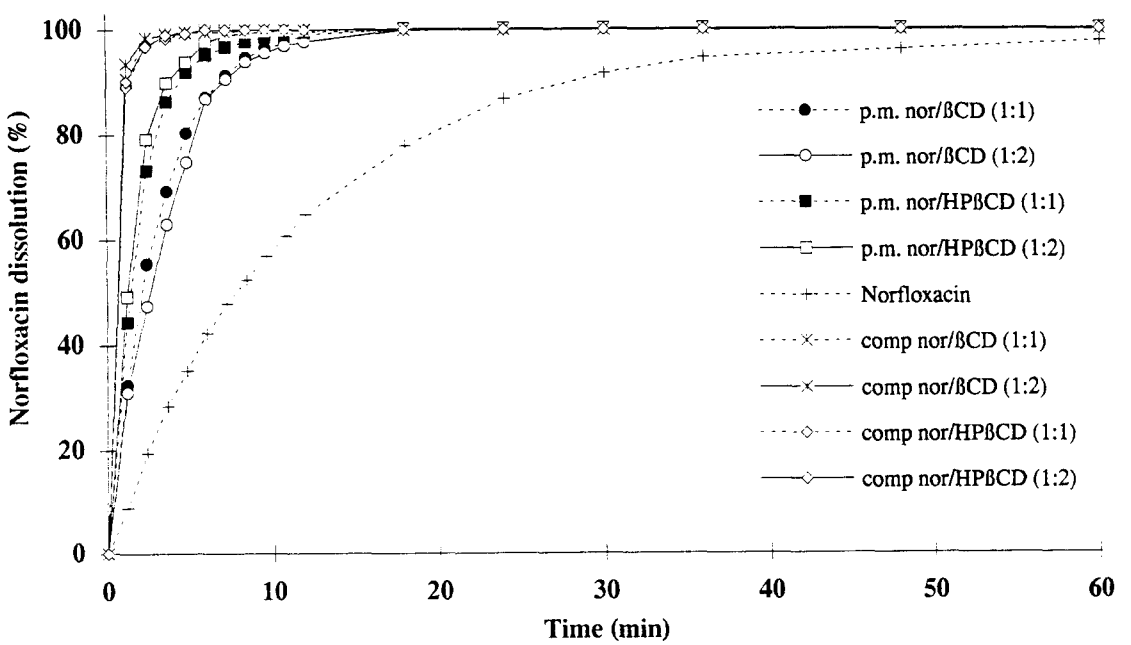

Fig. 7. Dissolution profiles of norfloxacin, physical mixtures of norfloxacin/cyclodextrins (p.m. nor/βCD or nor/HPβCD) and complexes of norfloxacin/cyclodextrins (comp nor/βCD or nor/HPβCD).

bamazepine/PVP/PVA, ciprofloxacin/PEG 6000 and alkyl *p*-aminobenzoate/PEG 6000 (Simonelli et al., 1969; Francès et al., 1991; Sjokvist Saers and Craig, 1992; Zingone and Rubessa, 1994). In order to explain this behaviour, many mechanisms were proposed: formation of a polymer outer layer controlling drug release (Simonelli et al., 1969), formation of a continuous drug layer (Dubois and Ford, 1985) and release of intact particles, from which dissolution occurs over a large area (Sjokvist Saers and Craig, 1992).

However, the DSC curves of norfloxacin SD lead us to believe that a fraction of norfloxacin was dissolved in the PEG 6000 during preparation of SD. Thus, a proportion of norfloxacin in the final product may be dispersed in the molecular state. A similar result has been reported from ciprofloxacin/PEG 6000 SD (Francès et al., 1991).

The increase in dissolution rate was significant ($p < 0.05$) with all the melt SD as compared to pure norfloxacin and its physical mixtures. In contrast, no significant difference (Scheffé test) was noted among the SD, leading to the formulation into one group of the SD, and into the other of the pure drug and its physical mixtures. Faster dissolution rates of drugs from SD as compared to physical mixtures have recently been reported (Francès et al., 1991; Sheu et zal., 1994).

As shown in Fig. 7, freeze-dried inclusion complexes of norfloxacin exhibit instantaneous dissolution. 100% dissolution from all CD complexes was reached within 6 min. At this time, dissolution of norfloxacin was only 42.3% from pure drug and 95.5% from its physical mixtures. Thus, norfloxacin freeze-drying complexation with β-CD and HP-β-CD led to a 2.4-fold increase in the initial dissolution rate. The surfactant-like properties of CD were postulated in some cases to explain the higher dissolution rate of the complexes (Lin and Kao, 1989; Yazan and Sumnu, 1994). CD can reduce the interfacial tension between the solid particles of norfloxacin and the dissolution medium, leading to a greater rate of dissolution. Moreover, the smaller size and amorphous state of norfloxacin particles in CD com-

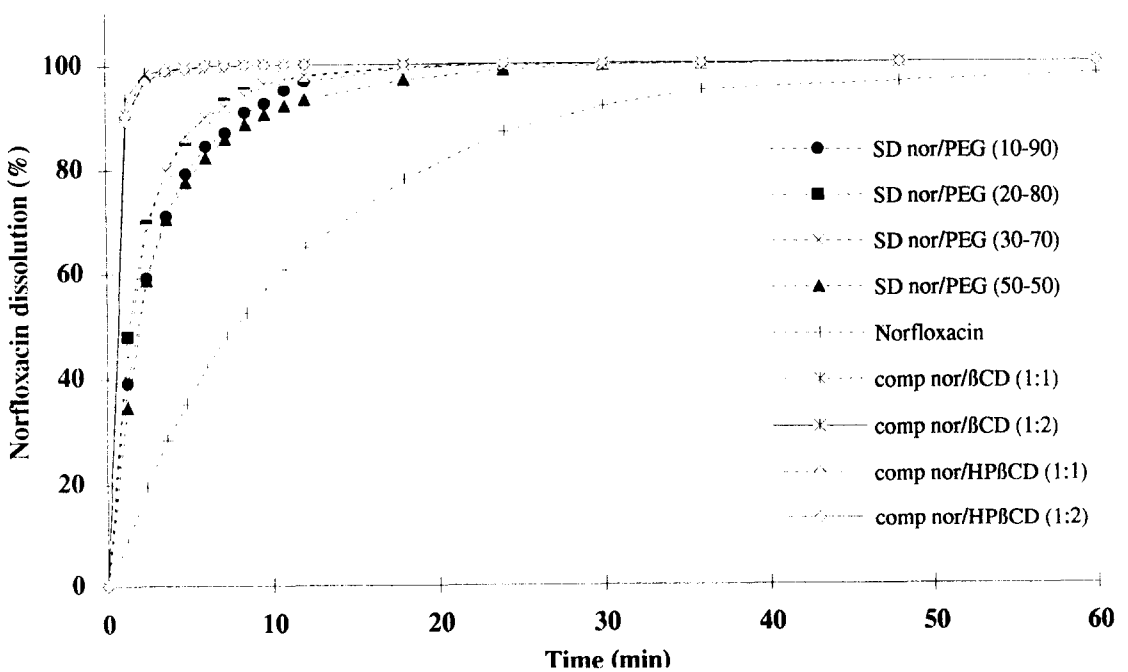

Fig. 8. Dissolution profiles of norfloxacin, solid dispersions of norfloxacin/PEG 6000 (SD nor/PEG) and complexes of norfloxacin/cyclodextrins (comp nor/βCD or nor/HPβCD).

plexes led to an increase in the rate of dissolution (Erden and Celebi, 1988; Lin and Kao, 1989; Yazan and Sumnu, 1994). The improvement in dissolution rate of norfloxacin from CD complexes is in agreement with the results of the solubility study (Fig. 1).

Dissolution profiles of norfloxacin CD physical mixtures show an increase in dissolution rate as compared to pure drug. This can be attributed to hydrophilization of norfloxacin by CD (Yazan and Sumnu, 1994) and improvement of its wettability.

No significant difference ($p < 0.05$) was observed among the dissolution rates of various norfloxacin/CD complexes. Also, no significant difference was noted between the mean dissolution rate of norfloxacin CD complexes and that of their physical mixtures.

Furthermore, CD complexes and PEG 6000 SD increase significantly the dissolution rate of norfloxacin as compared to pure drug. On the other hand, CD complexes were more efficient than PEG SD (Fig. 8) since at 6 min, the increase in rate of dissolution was 2.4- and 1.1-fold, respectively. These results confirm those reported by Kedzierewicz et al. (1990) for tolbutamide.

4. Conclusion

The increase in dissolution rate of norfloxacin might be achieved either with PEG 6000 solid dispersion or by inclusion complexation with CD (β-CD and HP-β-CD). An increase in the proportion of PEG 6000 does not significantly improve dissolution.

The results of the dissolution study showed that norfloxacin/CD complexes and norfloxacin/PEG SD had a faster dissolution rate than norfloxacin itself.

In contrast with PEG 6000, it seems that an interaction of the inclusion complexation type occurred between norfloxacin and CD. The results from the phase solubility diagrams and dissolution rate studies such as the data obtained by physical determinations (IR spectrophotometry, thermography (DSC) and X-ray diffractometry) suggested that such an interaction may occur irrespective of the preparation method.

However, further studies should be performed concerning storage and bioavailibility of norfloxacin in SD and inclusion complexes.

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