International Journal of Pharmaceutics, 28 (1986) 95–101
Elsevier

IJP 00938

Research Papers

Characterization, dissolution and bioavailability in rats of ibuprofen–β-cyclodextrin complex system

DahNan D. Chow and Adel H. Karara

Division of Pharmaceutics and Medicinal Chemistry, School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209 (U.S.A.)

(Received June 26th, 1985)
(Modified version received August 15th, 1985)
(Accepted August 23rd, 1985)

Key words: ibuprofen – β-cyclodextrin – bioavailability of ibuprofen – dissolution of ibuprofen tablets

Summary

Phase solubility studies revealed a 12-fold increase in the solubility of ibuprofen and the formation of an insoluble microcrystalline complex in the presence of high concentration of β-cyclodextrin (β-CD). The complex system formed had a stoichiometric ratio of 2 : 3 (ibuprofen:β-CD) which reflected contributions from several complexes precipitating in the system. More evidence of complex formation was obtained from the analysis of UV, IR, DSC and X-ray diffraction studies. The dissolution rate of the ibuprofen was significantly enhanced by complexation. After 20 min the % of drug released was 5 and 95 for the drug powder and the complex, respectively. Increased solubility, decreased crystallinity and improved wettability probably accounted for the observed enhancement in the dissolution rate. Bioavailability studies in rats showed the extent of absorption to be the same for the free and complexed ibuprofen. However, the time to reach peak plasma concentration for the complexed ibuprofen was 2.5-fold faster than the drug alone. Results of this report indicate that β-cyclodextrin could be a useful additive to solid ibuprofen formulations as it may result in a more rapid and uniform release of the drug.

Introduction

Ibuprofen, (±)-2-(*p*-isobutylphenyl)propionic acid, belongs to the group of non-steroidal antiinflammatory agents (NSAIDs) and is widely indicated for the symptomatic relief in cases of arthritis. The drug is very slightly soluble in water and has poor wettability properties. However, ibuprofen is completely bioavailable and is relatively rapidly absorbed after oral administration with peak plasma or serum levels achieved within 2 h (Albert and Gernaat, 1984). Several reports in the literature have shown a variation in the absorption rate among ibuprofen solid oral dosage forms. Gillespie et al. (1982) conducted a bioavailability study in 18 normal volunteers and found marked variation in the absorption rate of five commercially available ibuprofen products. Stead et al. (1983) also found potential bioinequivalence problems associated with ibuprofen solid dosage forms. The pharmacokinetics of ibuprofen in man has been extensively studied by Lockwood et al. (1983a), Albert et al. (1984), Lockwood et al. (1983b) and Wagner et al. (1984). In a cross-over study design in 15 normal male subjects, absorption of ibuprofen from tablets was shown not to be simple first order as from a solution form (Wagner et al., 1984). β-Cyclodextrins and their

Correspondence: A.H. Karara, Division of Pharmaceutics and Medicinal Chemistry, School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209, U.S.A.

derivatives have been used in pharmaceutical formulations to enhance solubility, dissolution rate, stability and bioavailability. Several studies have reported interactions of β-CD with NSAIDs (Hamada et al., 1975; Kurozumi et al., 1975; Ikeda et al., 1975). Nambu et al. (1978) administered the freeze-dried product of several NSAIDs including ibuprofen to rabbits and reported higher blood levels compared with the freeze-dried drug alone. The primary objective of the present study was to investigate the possibility of improving the release properties of ibuprofen via complexation with β-cyclodextrin. The physicochemical properties and bioavailability in rats of ibuprofen–β-cyclodextrin system are reported.

Materials and Methods

Materials

Ibuprofen was obtained courtesy of the Upjohn Co. β-CD was purchased from Sigma Co. and was recrystallized from water and stored in a desiccator. All other chemicals used were of analytical grade and double distilled water was used in all studies.

Analysis of ibuprofen

An HPLC method was used to analyze for ibuprofen in the in vitro and in vivo studies. The conditions for the analysis were as follows: column, MicroPak MCH-10; flow rate, 1 ml/min; wavelength 264 nm; sensitivity, 0.2 a.u.f.s.; and mobile phase (methanol : 4% glacial acetic acid 85 : 15). The conditions for in vivo analysis were the same as the in vitro analysis except samples were monitored at a wavelength of 220 nm and mobile phase used was methanol : 0.4% glacial acetic acid 75 : 25. Thirty microliter samples were injected into a Varian 5000 LC equipped with a Varian UV 50 variable wavelength detector.

Phase-solubility studies

Phase-solubility studies were performed according to the method reported by Higuchi and Connors (1965). Exactly 40 mg of ibuprofen were weighed into each of 25 ml Erlenmeyer flasks, to which were added 20 ml of water containing various concentrations of β-CD (0.001–0.016 M). The sealed flasks were shaken for one day at a controlled temperature of $30 \pm 0.5°C$. After equilibrium for 2 days, an aliquot was filtered with a 0.45 μm HA-type millipore filter. The ibuprofen concentration in the filtrate was determined by HPLC.

Preparation of the solid complex

The solid ibuprofen–β-CD complex was prepared by choosing the mole ratio of the components where there was no more undissolved drug and β-CD was still within its solubility limit (that point is indicated by an arrow in Fig. 1). The precipitated complex was filtered, washed and dried in a 40°C oven overnight. Chemical analysis was performed to confirm stoichiometry of the complex system.

Ultraviolet and infrared spectroscopy

UV-spectra of 0.003 M ibuprofen in pH 7.0 phosphate buffer (1/15 M) with increasing concentrations of β-CD were recorded on an Aminco DW-2 UV-VIS spectrophotometer. The prepared solutions were shaken at 30°C and equilibrated for one day. IR-spectra were obtained using a Perkin-Elmer IR-spectrophotometer Model 257. Nujol mull technique was used since compression in potassium bromide pellets resulted in complex formation in the physical mixture samples. The amount used in samples was equivalent to 5 mg of ibuprofen.

Differential scanning calorimetry (DSC)

DSC scans were recorded on a Perkin-Elmer Model 1B apparatus equipped with a low temperature cell and nitrogen as the purging gas. The sample size was equivalent to 5 mg of ibuprofen and the scanning speed was 16°/min.

X-Ray diffraction spectroscopy

X-Ray diffractometry was carried out using a Norelco X-Ray diffractometer with a Norelco's Ni filter CuK(α) radiation detector. The scanning speed used was $1° \cdot 2\theta$/min. Additionally, the complex sample was also run at a higher sensitivity.

Dissolution rate

Dissolution studies were performed using U.S.P. dissolution apparatus (paddle method) in one liter of 0.027 N hydrochloric acid solution as the dissolution medium. The stirring rate was 100 rpm and temperature was maintained at 37°C. Dissolution samples (passed through 30 and retained on 80 mesh USP standard) contained the equivalent of 50 mg ibuprofen.

Bioavailability in rats

Bioavailability of the prepared complex and the drug was tested by administering the preparation orally to Sprague–Dawley rats. Six rats were fasted overnight and dosed in the morning with 60 mg ibuprofen equivalent/kg in 0.1% CMC solution (5 ml/kg). Blood samples were withdrawn from the tail vein at designated time intervals by the procedure described by Nerenberg and Zedler (1975). Plasma samples were frozen until analyzed. The HPLC method of Lockwood and Wagner (1982) was utilized with slight modification to analyze for unchanged ibuprofen. Probenecid was used as the internal standard. The samples were acidified with 0.1 N hydrochloric acid and methylene chloride was added for extraction. The samples were shaken for 10 min. The organic layer was then transferred to a dry culture tube and evaporated to dryness under a stream of nitrogen at 40°C. The residue was reconstituted in the mobile phase which was then injected into the HPLC. This method was used previously to analyze for ibuprofen in serum samples (Karara et al., 1984). The area under the plasma concentration–time curves (AUC) was calculated using the trapezoidal rule. The elimination half-life was estimated graphically from the terminal linear phase of the plasma concentration–time curve.

Results and Discussion

The phase solubility diagram shown in Fig. 1 can be classified as type Bs according to Higuchi and Connors (1965). An insoluble microcrystalline complex was formed in solution at high β-CD concentrations. Because the ascending linear portion of the diagram had a slope less than 1, it was

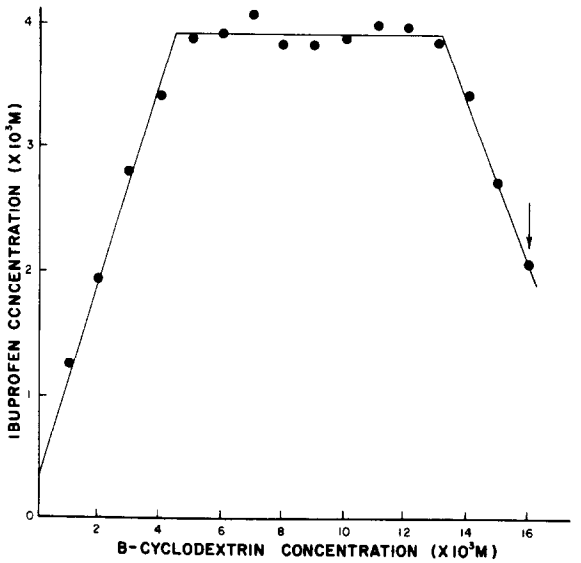

Fig. 1. Phase solubility diagram of ibuprofen–β-CD system in water at 30°C. An arrow showing experimental condition for the preparation of solid complex (see text).

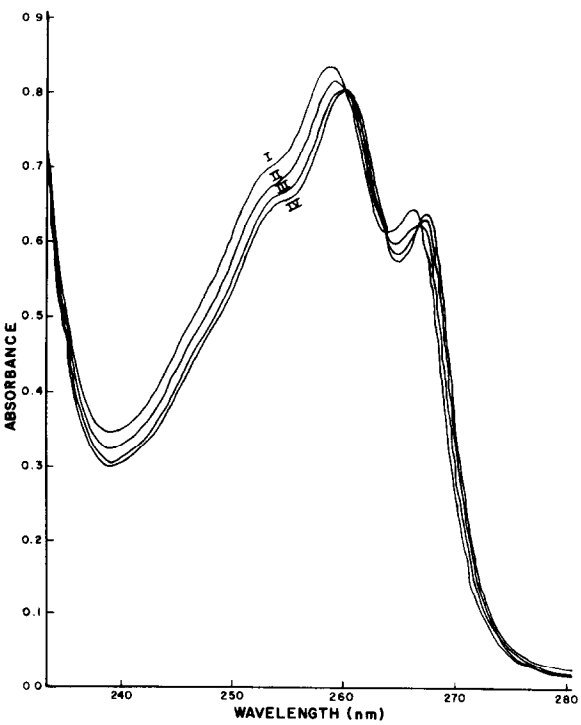

Fig. 2. Effect of β-CD on the absorption spectrum of 0.003 M ibuprofen: (I) ibuprofen alone; (II) 0.001 M β-CD; (III) 0.002 M β-CD; and (IV) 0.003 M β-CD.

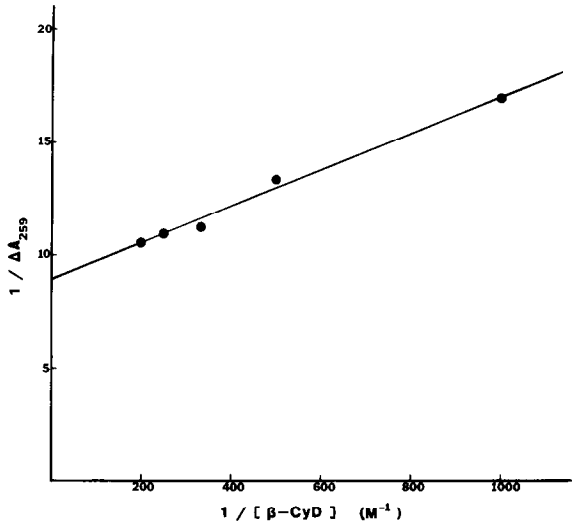

Fig. 3. Benesi-Hildebrand plot for the effect of β-cyclodextrin on the absorbance of ibuprofen at 259 nm.

assumed that the increase in the solubility observed (approximately 12-fold) was due to the formation of a 1 : 1 complex. The apparent formation constant calculated from the initial segment was approximately 1.0×10^4 M^{-1}. The stoichiometry of the complexes precipitating from solution can be calculated from the plateau segment of the diagram. It appeared that 5.8×10^{-3} mole of ibuprofen reacted with 8.6×10^{-3} mole of β-CD, indicating a 2 : 3 (ibuprofen:β-CD) stoichiometric ratio. This stoichiometric ratio probably reflects contributions from several complexes precipitating in the descending portion of the solubility diagram (Higuchi and Connors, 1965). Because of the complexity of the system, the calculated apparent formation constant $K_{2:3}$ had a large unrealistic value. Chemical assay of precipitated complex confirmed the observed stoichiometry. Anderson and Bundgaard (1984) reported a similar stoichiometry for the metronidazole–β-CD complex system.

UV-spectra of ibuprofen solutions in increasing concentration of β-CD are shown in Fig. 2. From the spectra, it appears that both λ_{max} peaks of ibuprofen, at 258.5 and 266 nm showed a bathochromic shift as a result of complex formation. The intensity of the absorption maxima slightly decreased with increasing β-CD concentration. The shift in UV absorption maxima may be explained by a partial shielding of the

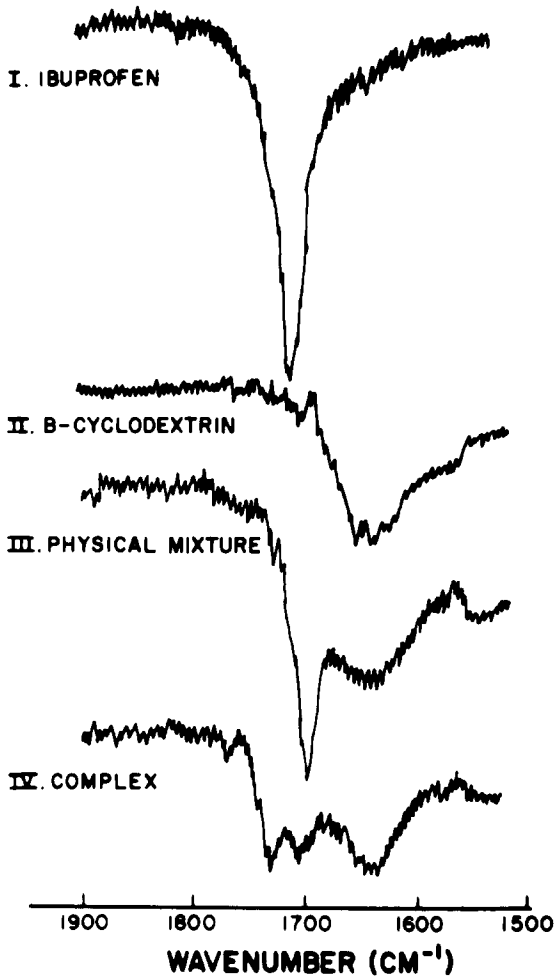

Fig. 4. IR spectra of: (I) ibuprofen alone; (II) β-CD alone; (III) physical mixture of ibuprofen and β-CD (2:3 in mole ratio); and (IV) complex system of ibuprofen with β-CD.

excitable electrons in the cyclodextrin cavity (Szejtli, 1982). Similar shifts in UV maxima have been observed with β-CD complexes of mefenamic acid (Ikeda et al., 1975) and salicyclic acid, vitamin K3 and vitamin D3 (Szejtli, 1982). Because the molar absorptivities of the complex and the drug differed at the same wavelength it was possible to determine the stability constant from the spectral data (Connors and Mollica, 1966). The apparent $K_{1:1}$ stability constant was determined from the following equation (Benesi and Hildebrand, 1949):

$$\frac{1}{\Delta A} = \frac{1}{K_{1:1} \times S_t \times \Delta a \times L} + \frac{1}{S_t \times \Delta a}$$

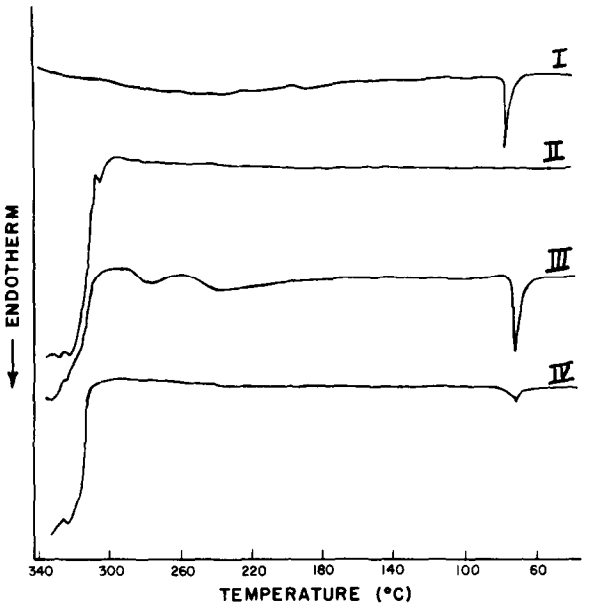

Fig. 5. Differential scanning calorimetry of: ibuprofen (I); β-CD (II); the physical mixture of ibuprofen and β-CD (2:3) (III); and the complex system of ibuprofen with β-CD (IV).

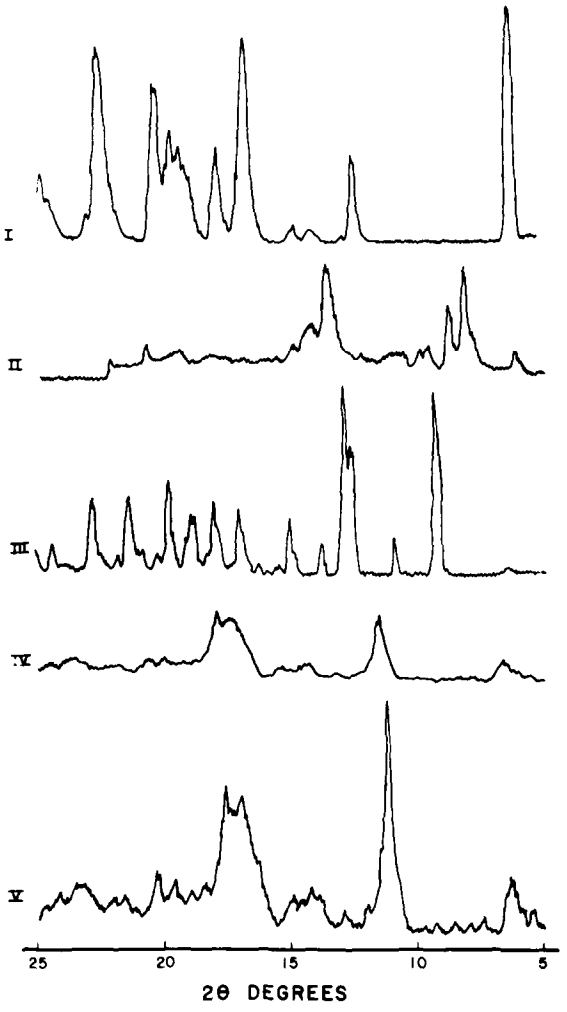

Fig. 6. Powder X-ray diffraction patterns of: ibuprofen (I); β-CD (II); the physical mixture of ibuprofen and β-CD (2:3) (III); the complex of ibuprofen with β-CD (IV) and the same sample as IV with a 5-fold higher relative intensity (V).

where ΔA is the difference in absorbance at 259 nm, Δa is the difference in the molar absorptivities between free and complexed drug, S_t is the total ibuprofen concentration and L is the concentration of free β-CD. The stability constant obtained from the intercept/slope ratio of Fig. 3 was calculated to be 10,800 which is in good agreement with the estimate from the solubility study. The IR spectra shown in Fig. 4 show distinctive changes in the region of the carbonyl absorption. The characteristic carbonyl stretching band at 1709 cm^{-1} appeared in both the drug and physical mixture samples; conversely, the band was shifted to 1736 cm^{-1} with a markedly decreased intensity in the inclusion complex sample. One possible explanation of the shift to higher wavenumber may be the breakdown of the intermolecular hydrogen bonding associated with the ibuprofen molecules and the establishing of less weak forces in the complex system (Bellamy, 1958). The observed decrease in intensity of the carbonyl band may have resulted from its restriction within the β-cyclodextrin cavity. The shift of the carbonyl stretching band was also observed in the complex system of steroid hormones studied by Uekama et al. (1982). More evidence of complex formation was obtained from the differential scanning calorimetry (DSC) thermograms (Fig. 5). The endothermic peak at 76°C equivalent to ibuprofen almost disappeared in the inclusion complex system.

The X-ray diffraction analysis of powder samples revealed less crystallinity in the complex system as evidenced by fewer and broader peaks of lower intensity. The diffraction patterns obtained for the complex and physical mixture are shown in

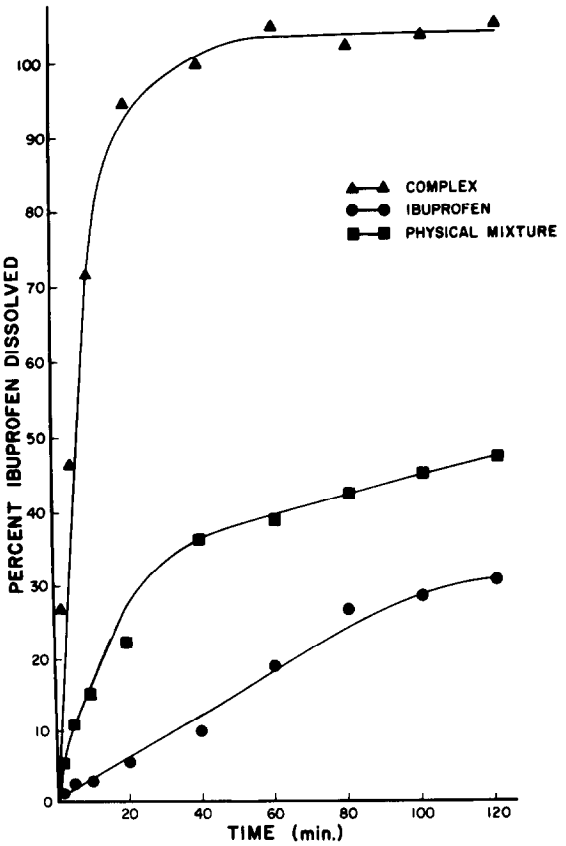

Fig. 7. Dissolution profiles of ibuprofen and its β-CD complex in 0.027 N hydrochloric acid solution at 37°C by U.S.P. dissolution apparatus (paddle method).

Fig. 6 and indicate the less crystalline nature of the complex system. The latter pattern is consistent with previously published patterns for β-CD inclusion compounds. From the freeze-dried products, Kurozumi et al. (1975) observed two broad peaks in the diffraction patterns of inclusion compounds at interplanar distances around 7.2–7.7 Å and 4.8–5.0 Å. The corresponding values obtained in the current work were 7.6 Å and 5.0 Å, are in good agreement.

Fig. 7 shows the dissolution profiles of ibuprofen from β-CD complex and ibuprofen powders. It is evident that the release of ibuprofen was significantly enhanced by complexation. After 20 min, the percent of drug released was approximately 5% and 95% for the powdered drug and the complex samples, respectively. Additionally, in this

TABLE 1

MEAN BIOAVAILABILITY PARAMETERS OBTAINED AFTER SINGLE ORAL DOSES OF IBUPROFEN OR IBUPROFEN–β-CD COMPLEX IN AQUEOUS SUSPENSION IN RATS

Parameter	Mean (S.E.)	
	Ibuprofen	Ibuprofen–β-CD complex
Peak plasma concentration (μg/ml)	120(10)	112(3)
Time to peak concentration (h)	0.92(0.05)	0.37(0.03) *
AUC_{0-8h} (μg/ml·h)	311(45)	321(38)
Elimination rate constant (h^{-1})	0.275(0.046)	0.254(0.036)

* Significantly different from the drug alone, $P < 0.05$.
Each value is the mean ± S.E. of 6 rats.

study, the improved wettability of ibuprofen in the complex samples was obvious during the dissolution process. The enhanced dissolution rate is probably due to increased solubility, decreased crystallinity and improved wettability. Table 1 shows the results of the bioavailability experiment in the rat. It is evident that the drug is completely available in the complex form in spite of the predicted large stability constant for the complex. This finding is interesting since Tokumura et al. (1985), recently attributed the lack in increase in the bioavailability of cinnarizine from its β-CD complex to its large stability constant (6.2×10^3 M^{-1}). The areas under the plasma concentration time curves (0–8 h) and the peak plasma concentration following the administration of ibuprofen and the complex form were not significantly different (Table 1). However, the time to reach plasma concentration for the complexed ibuprofen was about 2.5-fold greater than that for the drug alone. This enhancement in drug absorption is probably due to the fast dissolution rate of the complex. At all time intervals, the standard error of the plasma concentration values for the complex samples were found to be much smaller than those for ibuprofen samples. The results of this study indicate that ibuprofen is completely availa-

ble from its complex with β-CD and that β-CD could be a useful additive to solid ibuprofen formulations as it may result in a more rapid and uniform release of the drug.

Acknowledgements

The authors wish to thank Dr. Kenneth J. Miller, Department of Chemistry and Dr. Rene A. DeHon, Department of Geosciences, Northeast Louisiana University for their help with the DSC and X-ray diffraction studies, respectively. The authors are grateful to the Upjohn Company for the generous gift of ibuprofen.

References

Albert, K.S. and Gernaat, C.M., Pharmacokinetics of ibuprofen. Am. J. Med., 77 (1984) 40–46.

Albert, K.S., Gillespie, W.R., Wagner, J.G., Pau, A. and Lockwood, G.F., Effects of age on the clinical pharmacokinetics of ibuprofen. Am. J. Med., 77 (1984) 47–50.

Andersen, F.M. and Bundgaard, H., Inclusion complexation of metronidazole benzoate with β-cyclodextrin and its depression of anhydrate–hydrate transition in aqueous suspensions. Int. J. Pharm., 19 (1984) 189–197.

Bellamy, L.J., The infra-red spectra of complex molecules. John Wiley, New York, 1958, p. 166.

Benesi, H.A. and Hildebrand, J.H., A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbons. J. Am. Chem. Soc., 71 (1949) 2703–2707.

Connors, K.A. and Mollica, J.A., Theoretical analysis of comparative studies of complex formation. J. Pharm. Sci., 55 (1966) 772–780.

Gillespie, W.R., DiSanto, A.R., Monovich, R.E. and Albert, K.S., Relative bioavailability of commercially available ibuprofen oral dosage forms in humans. J. Pharm. Sci., 71 (1982) 1034–1038.

Hamada, Y., Nambu, N. and Nagai, T., Interactions of α- and β-cyclodextrin with several non-steroidal antiinflammatory drugs in aqueous solution. Chem. Pharm. Bull., 23 (1975) 1205–1211.

Higuchi, T. and Connors, K.A., Phase solubility techniques. In C.N. Reilley (Ed.), Advances in Analytical Chemistry and Instrumentation, Interscience, New York, 1965, p. 132.

Ikeda, K., Uekama, K. and Otagiri, M., Inclusion complexes of β-cyclodextrin with antiinflammatory drugs fenamates in aqueous solutions. Chem. Pharm. Bull., 23 (1975) 201–208.

Karara, A.H., Chow, D.N., Gandhi, R.B. and Medon, P.J., Preparation and evaluation of a prolonged release ibuprofen suppository dosage form. Presented before the APhA 37th National Meeting in Philadelphia, PA, October 28–November 1, 1984.

Kurozumi, M., Nambu, N. and Nagai, T., Inclusion compounds of non-steroidal antiinflammatory and other slightly water soluble drugs with α- and β-cyclodextrins in powdered form. Chem. Pharm. Bull., 23 (1975) 3062–3068.

Lockwood, G.F. and Wagner, J.G., High-performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. J. Chromatogr., 232 (1982) 335–343.

Lockwood, G.F., Albert, K.S., Gillespie, W.R., Bole, G.G., Harkcom, T.M., Szpunar, G.J. and Wagner, J.G., Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. Clin. Pharmacol. Ther., 34 (1983a) 97–103.

Lockwood, G.F., Albert, K.S., Szpunar, G.J. and Wagner, J.G., Pharmacokinetics of ibuprofen in man III. Plasma protein binding. J. Pharmacokin. Biopharm., 11 (1983b) 469–482.

Nambu, N., Shimoda, M., Takahashi, Y., Ueda, H. and Nagai, T., Bioavailability of powdered inclusion compounds of nonsteroidal antiinflammatory drugs with β-cyclodextrin in rabbits and dogs. Chem. Pharm. Bull., 26 (1978) 2952–2956.

Nerenberg, S.T. and Zedler, P., Sequential blood samples from the tail vein of rats and mice obtained with modified Liebig condenser jackets and vacuum. J. Lab. Clin. Med., 85 (1975) 523–526.

Stead, J.A., Freeman, M., John, E.G., Ward, G.T. and Whiting, B., Ibuprofen tablets: dissolution and bioavailability studies. Int. J. Pharm., 14 (1983) 59–72.

Szejtli, J., Cyclodextrins and Their Inclusion Complexes. Akademiai Kiado, Budapest, 1982, p. 177.

Tokumura, T., Tsushima, Y., Kayano, M., Machida, Y. and Nagai, T., Enhancement of bioavailability of cinnarizine from its β-cyclodextrin complex in oral administration with DL-phenylalanine as a competing agent. J. Pharm. Sci., 74 (1985) 496–497.

Uekama, K., Fujinaga, T., Hirayama, F., Otagiri, M. and Yamasaki, M., Inclusion complexations of steroid hormones with cyclodextrins in water and solid phase. Int. J. Pharm., 10 (1982) 1–15.

Uekama, K., Oh, K., Otagiri, M., Seo, H. and Tsuruoka, M., Improvement of some pharmaceutical properties of clofibrates by cyclodextrin complexation. Pharm. Acta Helv., 58 (1983) 338–342.

Wagner, J.G., Albert, K.S., Szpunar, G.J. and Lockwood, G.F., Pharmacokinetics of ibuprofen in man IV: Absorption and disposition. J. Pharmacokin. Biopharm., 12 (1984) 381–399.