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Solid Dispersion of Hydroxypropyl β-Cyclodextrin and Ketorolac: Enhancement of In-vitro Dissolution Rates, Improvement in Anti-inflammatory Activity and Reduction in Ulcerogenicity in Rats

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Abstract

Ketorolac, is a non-steroidal anti-inflammatory drug, with strong analgesic activity. It is practically insoluble in water and has been implicated in causing gastrointestinal ulceration. This study describes the formulation of solid dispersions of ketorolac using hydroxypropyl β-cyclodextrin (HPβ-CyD) and β-cyclodextin (β-CyD) as carriers, to improve the aqueous solubility of the drug, thus enhancing its bioavailability. Also, reduction in ulcerogenicity was anticipated.

Differential scanning calorimetry and X-ray diffraction studies indicated loss of crystalline nature of the drug, in the dispersions prepared with HPβ-CyD. NMR studies revealed a strong interaction between drug and HPβ-CyD. Solid dispersions of drug with β-CyD retained the crystalline nature of the drug. All the solid dispersions showed a remarkable improvement in the rate and extent of dissolution of ketorolac. The kneaded dispersion with HPβ-CyD prepared using a 1 : 1 alcohol–water mixture showed promise in reducing the ulcer-inducing effect of ketorolac in rats. Oral administration of this dispersion was found to inhibit carrageenan-induced paw oedema in rats to a significantly greater extent compared with ketorolac or its trometamol salt. Though β-CyD as a carrier for ketorolac gave faster release of the poorly soluble drug, HPβ-CyD proved to be superior to β-CyD, as a carrier in the kneaded dispersion prepared using 1 : 1 alcohol–water mixture.

These results suggest that solid dispersions of ketorolac with HPβ-CyD aid in faster dissolution and better bioavailability of the drug. The higher solubility of the drug in the presence of HPβ-CyD also reduces local gastrointestinal side-effects of the drug.

Ketorolac is a non-steroidal anti-inflammatory drug, which possesses analgesic, anti-inflammatory and antipyretic activity. When used clinically, it is administered as the trometamol salt, which is freely soluble in water, whereas ketorolac, the free acid, has limited aqueous solubility. The majority of adverse effects associated with ketorolac trometamol involve the gastrointestinal tract and range from mild gastric mucosal irritation to serious ulceration or haemorrhage (Gillis & Brogden 1997). Hydroxypropyl β-cyclodextrin (HPβ-CyD), a chemically modified β-cyclodextrin (β-CyD), is reported to have good potential in improving aqueous solubility, dissolution rate and bioavailability of drugs exhibiting poor aqueous solubility (Pitha et al 1986; Nagarsenker & Shenai 1996; Uekama et al 1998). Solid dispersions of non-steroidal anti-inflammatory drugs with HPβ-CyD have also been found to decrease the ulcerogenic potential of drugs (Nagarsenker et al 1997). The aim of this study was to formulate solid dispersions of ketorolac using HPβ-CyD and β-CyD as carriers and assess the advantages that they may offer over ketorolac or its trometamol salt.

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Materials and Methods

Materials

Ketorolac trometamol was obtained as a gift from Sun Pharma Exports, Dadra, India. HPβ-CyD was generously donated by Cerestar Inc., USA and

β-CyD was donated by Amaizo, USA. All the other materials used were of pharmaceutical grade.

Precipitation of ketorolac from ketorolac trometamol

Ketorolac was obtained by acidifying a solution of ketorolac trometamol. The precipitated ketorolac was checked for the absence of trometamol by the method given as an identification test for tromethamine in the USP monograph for ketorolac tromethamine.

Solubility studies

Solubility studies were performed and the association constant calculated according to the method reported by Higuchi & Connors (1965). Excess amounts of ketorolac were added to aqueous solutions containing different concentrations (5, 10, 15, 20, 25 mM) of HPβ-CyD and were shaken at room temperature for 24 h. After equilibration, the solutions were filtered and the concentration of ketorolac in the filtrate was determined spectrophotometrically at 322 nm. The association constant of ketorolac and β-CyD in water was determined by solubility studies in the same manner as reported for HPβ-CyD. Solutions containing 2, 4, 6, 8 and 10 mM of β-CyD were used.

Preparation of solid dispersions

Solid dispersions of HPβ-CyD and ketorolac were prepared in a molar ratio of 1 : 1. Physical mixtures of HPβ-CyD and ketorolac were prepared by simply mixing the powders together with a spatula. The kneaded dispersions were prepared by wetting the physical mixture with either 1 : 1 distilled water–alcohol mixture or acetone to obtain a dough-like mass, which was dried in a vacuum oven at 45°C for 1 h. The contents were stored overnight in a vacuum desiccator. The co-evaporated products were prepared by adding aqueous solutions of HPβ-CyD to an alcoholic solution of ketorolac or a solution of ketorolac in 25% ammonia. The resulting mixtures were stirred for 1 h and evaporated at 45–50°C until nearly dry and then stored overnight in a vacuum desiccator. The freeze-dried product was prepared by drying a 0·25% aqueous ammonia solution, containing HPβ-CyD and ketorolac in an Edward's Modulyo 4K Freeze-Drier. All the dispersions obtained were sieved through 85-mesh B.S. Solid dispersions of ketorolac and β-CyD were prepared in a molar ratio of 1 : 1. The physical mixture was prepared by mixing the powders together with a spatula and the kneaded dispersion was prepared by wetting the physical mixture with a 1 : 1 alcohol–distilled water mixture and treated in a manner similar to the kneaded dispersion with HPβ-CyD.

Characterization of solid dispersions

Differential scanning calorimetry (DSC) studies. The drug and its solid dispersions were scanned at a rate of 10°C min^{-1} on a Shimadzu DT-40 Thermal Analyzer between 30 and 300°C.

X-ray diffraction (XRD) studies. Powder X-ray diffraction patterns were recorded using a Phillips X-ray diffractometer (PW 1130/00) with a copper target, voltage 45 KV, current 30 mA, at a scanning speed of 2°C min^{-1}.

NMR studies. ^{1}H NMR spectra of pure ketorolac and dispersions with HPβ-CyD (prepared by freeze drying or physical mixture of 1 : 1 and 1 : 5 (drug: HPβ-CyD)) were recorded on a Bruker AMX-500 FTNMR at 298°K and 500 MHz. The NMR spectrum of ketorolac was recorded in CD_3OD, due to its low solubility in D_2O, whereas those of HPβ-CyD and the dispersions were recorded in D_2O.

Evaluation of solid dispersions. The dispersions were assayed spectrophotometrically and the content of ketorolac in the dispersions was determined. The in-vitro release profiles were studied according to the dispersed powder method (Uekama et al 1984) using USP type-II dissolution testing apparatus in each of 600 mL of distilled water and simulated gastric fluid pH 1·2 (SGF). A stirring rate of 50 ± 2 rev min^{-1} and a temperature of 37 ± 0·5°C were used.

Accelerated stability studies. The kneaded dispersion of ketorolac and HPβ-CyD prepared using 1 : 1 alcohol–distilled water was stored at 25°C, 37°C, 45°C and at 40°C/75% r.h. conditions and evaluated for reliability of dissolution profiles at periodic intervals over 12 weeks. The dispersions were assayed for drug content at the beginning and the end of the 12 weeks of storage at all the conditions, to establish the chemical stability of the drug in the dispersion under accelerated conditions of storage.

In-vivo studies

Reduction in ulcerogenicity. The kneaded dispersion was investigated for the possibility of reduction in ulcerogenicity of ketorolac on complexation

with HPβ-CyD. The study was carried out in Wistar rats, by the method reported by Nambu et al (1978).

A dose of 35 mg kg^{-1} of ketorolac was selected on the basis of preliminary studies. The rats were divided into 4 groups; each consisting of 4 healthy adult rats, 150–200 g. The 4 groups were administered, respectively, ketorolac, ketorolac trometamol, HPβ-CyD or the kneaded dispersion in the form of suspensions/solutions in an aqueous vehicle containing 1% sodium carboxymethylcellulose.

The rats were fasted overnight before administration. Six hours after administration, the rats were killed with chloroform and the abdomen was opened. The stomach was removed and incised along the greater curvature and gently washed with water. The degree of injury was observed, sketched and evaluated by the following numerical marks: 0·0, normal (no injury, bleeding and latent injury); 0·5, latent injury or widespread bleeding; 1·0, slight injury (2 or 3 small dotted injuries); 2·0, severe injury (continuous lined injury or 5 or 6 dotted injuries); 3·0, very severe injury (several continuous lined injuries); 4·0, widespread lined injury or widened injury.

Reduction in carrageenan-induced oedema in hindpaw of rats. Female Wistar rats, 130–200 g, were used in the study. The rats were starved overnight, and were divided into four groups. One group (n = 7) was used as the control. The remaining three groups (n = 5–7) were administered orally by means of a canula, ketorolac, ketorolac trometamol or the kneaded dispersion, respectively, dispersed/dissolved in a slurry containing 1% sodium carboxymethylcellulose in a dose of 35 mg of ketorolac per kg body-weight.

Thirty minutes later, the rats were challenged by a subcutaneous injection (0·1 mL) of a 1% solution of carrageenan in 0·9% NaCl, into the plantar site of the left hindpaw. The paws were marked with ink at the level of the lateral malleolus. The paw volumes were measured by immersing the paws up to the mark in the well of a Ugo Basile 7140 Plethysmometer, 0, 0·5, 1, 1·5, 2, 2·5, 3, 4, 5 and 6 h after administration of carrageenan.

Percentage inhibition of oedema at any time, t, was calculated as:

$$\% \text{ Inhibition} = 100 \times \left[1 - \frac{A - x}{B - y}\right] \qquad (1)$$

where A is mean volume of the treated rats after administration of carrageenan at time t, x is mean volume of treated rats before administration of carrageenan, B is mean volume of control rats after administration of carrageenan at time t and y is mean volume of control rats before administration of carrageenan.

Results and Discussion

Solubility studies

The phase solubility diagram for the complex formation between ketorolac and HPβ-CyD is shown in Figure 1A and that between ketorolac and β-CyD is shown in Figure 1B. An A_L type of diagram (Higuchi & Connors 1965) was obtained in both cases, indicating formation of complex with ketorolac. The slope of the solubility diagram was less than unity, suggesting a 1 : 1 complex stoichiometry of ketorolac with HPβ-CyD and β-CyD on a molar basis. Values of the association constants for complex with HPβ-CyD and β-CyD were found to be 1186 M^{-1} and 1130 M^{-1} respectively. Values falling within the range of 200–5000 M^{-1} are

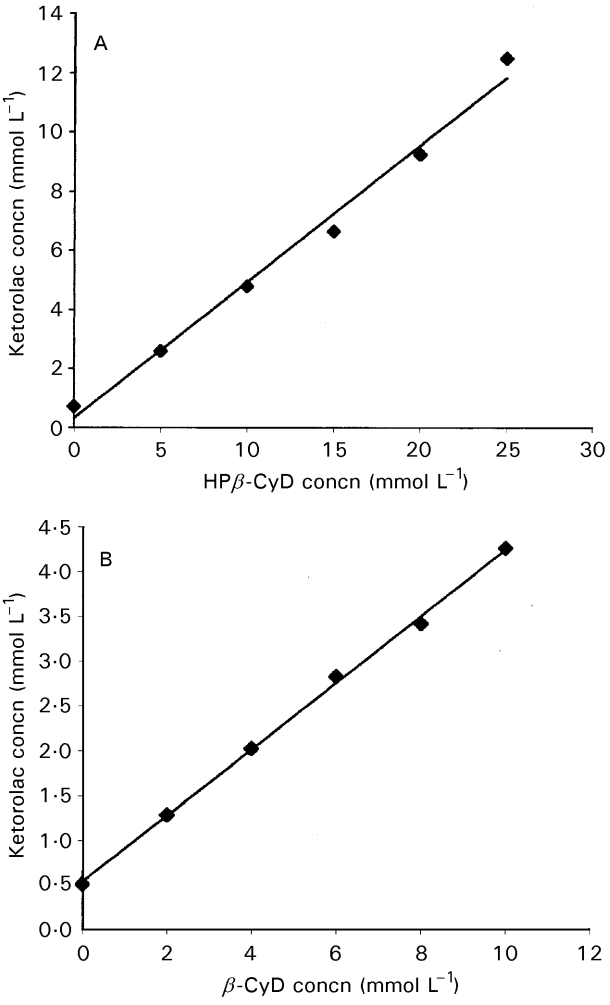


Figure 1. Solubility diagrams. A. Plot of concentration of ketorolac vs concentration of HPβ-CyD. B. Plot of concentration of ketorolac vs concentration of β-CyD.

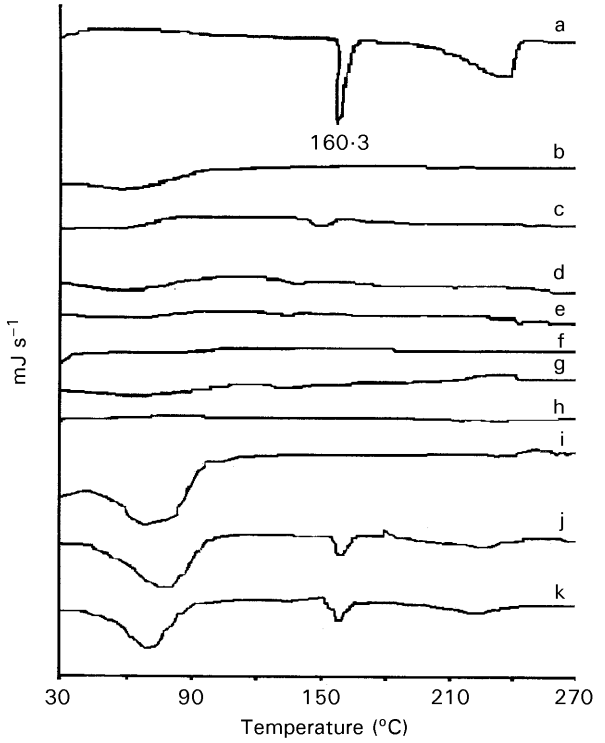


Figure 2. DSC thermograms of ketorolac (a), HPβ-CyD (b), β-CyD (i), dispersions with HPβ-CyD: physical mixture with HPβ-CyD (c), kneaded with alcohol (d), kneaded with acetone (e), co-evaporated with alcohol (f), co-evaporated with ammonia (g) and freeze-dried (h) dispersions with β-CyD: physical mixture with β-CyD (j) and kneaded with alcohol (k).

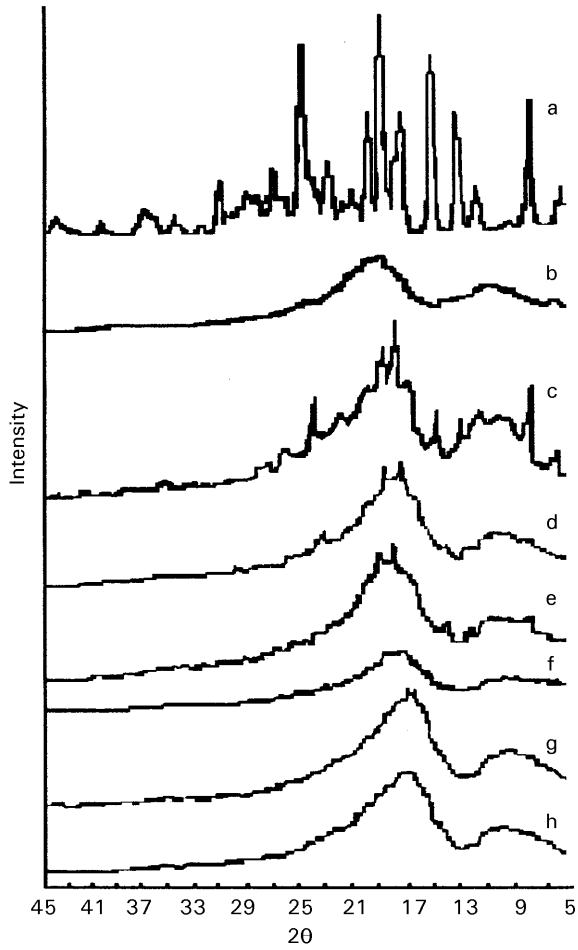


Figure 3. X-ray diffraction patterns of ketorolac (a), HPβ-CyD (b) and its dispersions: physical mixture with HPβ-CyD (c), kneaded with alcohol (d), kneaded with acetone (e), co-evaporated with alcohol (f), co-evaporated with ammonia (g) and freeze-dried (h).

considered by various authors to be adequate for the formation of inclusion complex, which may contribute to improved bioavailability of poorly water-soluble drugs (Moyano et al 1995).

Characterization of solid dispersions

The DSC thermograms in the temperature range of 30–270°C are shown in Figure 2. The water content calculated from the broad endotherm observed in the thermograms was found to be around 1% for HPβ-CyD and the kneaded dispersion with HPβ-CyD and 6–7% for β-CyD and the kneaded dispersion with β-CyD. The DSC curve of ketorolac showed a sharp melting endotherm at 160°C. A complete disappearance of the melting endotherm of ketorolac was seen in the co-evaporated and freeze-dried dispersions with HPβ-CyD, which is due to amorphisation of the drug or inclusion complex formation, or both. In the kneaded dispersions with HPβ-CyD, a shallow endotherm was seen at around 130–140°C, which indicated a lesser extent of amorphisation or interaction. The DSC thermogram of the physical mixture showed a broad endotherm in the range of 140·4–157·8°C, accounting for least interaction between the drug and HPβ-CyD in the physical mixture. The characteristic melting endotherm of the drug was observed in DSC thermograms of the physical mixture as well as the kneaded dispersion of the drug with β-CyD.

The X-ray diffraction pattern of ketorolac exhibited sharp characteristic peaks indicating the crystalline nature of the drug, as seen in Figure 3. The X-ray diffraction pattern of the physical mixture of ketorolac and HPβ-CyD was simply a superimposition of each component, with the peaks having lower intensity. The freeze-dried and co-evaporated dispersions showed diffused spectra with broad peaks in the interplanar distance range of HPβ-CyD suggesting the possibility of inclusion or amorphisation (or both) of ketorolac in these dispersions. The dispersions prepared by kneading showed some of the peaks as seen in the diffraction pattern of the drug which were, however, not very conspicuous. The dispersion kneaded with 1 : 1

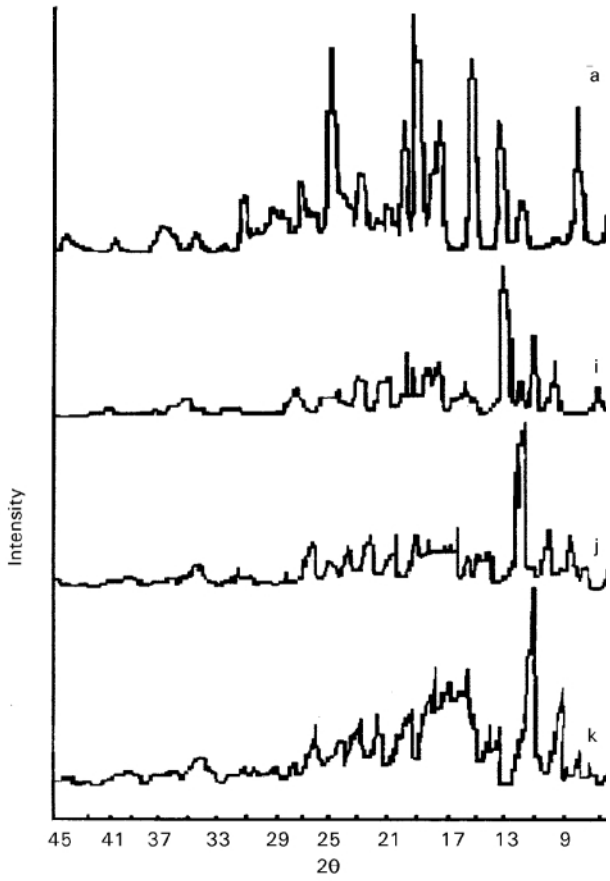


Figure 4. X-ray diffraction patterns of ketorolac (a), β-CyD (i) and its dispersions: physical mixture with β-CyD (j) and kneaded with alcohol (k).

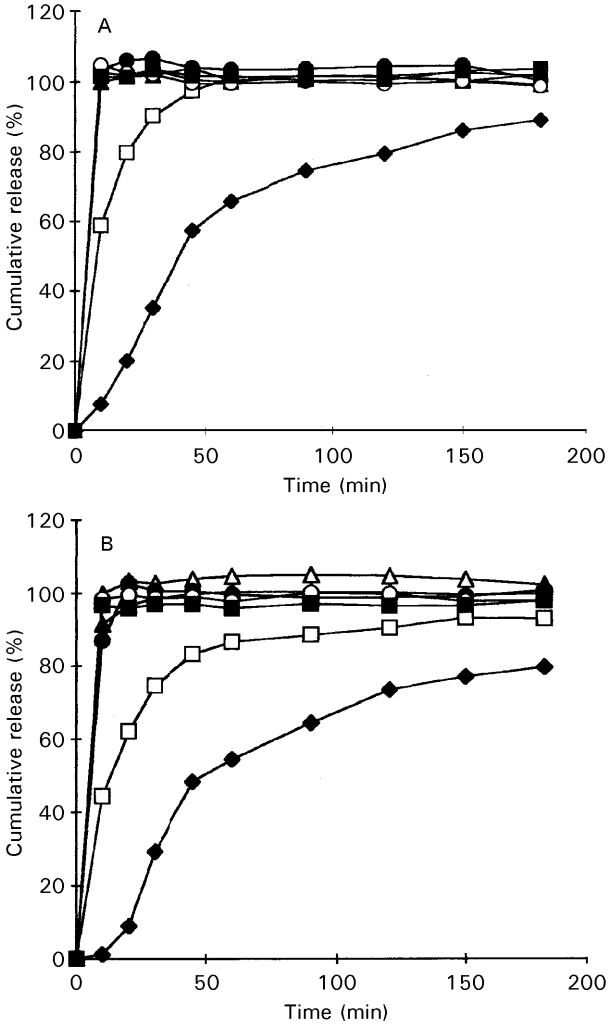


Figure 5. A. Dissolution profile of ketorolac (◆), physical mixture with HPβ-CyD (□) and solid dispersions: kneaded with alcohol (△), kneaded with acetone (●), co-evaporated with alcohol (▲), co-evaporated with ammonia (○) and freeze-dried (■) in distilled water. B. Dissolution profile of ketorolac (◆), physical mixture with HPβ-CyD (□) and solid dispersions: kneaded with alcohol (△), kneaded with acetone (●), co-evaporated with alcohol (▲), co-evaporated with ammonia (○) and freeze-dried (■) in simulated gastric fluid.

alcohol–water showed a lesser number of characteristic peaks of the drug with reduced intensity, as compared with the dispersion kneaded with acetone. The X-ray diffractograms of the physical mixture, as well as the solid dispersion with β-CyD (Figure 4), showed peaks corresponding to the drug and the carrier, at the characteristic 2θ values indicating that ketorolac retained its crystalline nature even when formulated as a solid dispersion with β-CyD.

The chemical shifts of the drug protons from the NMR spectra of all the samples are shown in Table 1. The peaks for all the drug protons were found to shift in the presence of HPβ-CyD by up to 0·3 ppm (approx.), which could be, in part, because of different solvents used for recording the spectra of the drug. This indicated an interaction between the drug and HPβ-CyD, and a possible formation of a complex.

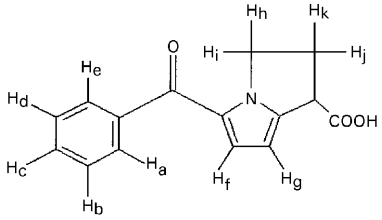
Evaluation of solid dispersions

The content of ketorolac from different dispersions, estimated by UV spectroscopy, matched with the amount of ketorolac incorporated in these dispersions.

Figure 5A shows the dissolution profiles of the different dispersions with HPβ-CyD in distilled water. Due to the low aqueous solubility of ketorolac, it exhibited a slow rate of dissolution with only 65·71% being released in the first hour and 88·43% released at the end of three hours. The physical mixture of ketorolac with HPβ-CyD released the drug at a much faster rate, releasing the entire amount of drug in one hour. All the dispersions released the entire drug rapidly in 10 min.

The dissolution profiles of the dispersions were studied in SGF with the aim of differentiating between the dissolution behaviour of the disper-

Table 1. NMR studies: chemical shifts for ketorolac protons in different dispersions.



Protons	Ketorolac	Freeze-dried dispersion (1 : 1)	Physical mixture with HPβ-CyD 1 : 1	Physical mixture with HPβ-CyD 1 : 5
Ha, He	7·549–7·573	7·731–7·841 (0·225)	7·819–7·832 (0·265)	7·822–7·836 (0·268)
Hb, Hc, Hd	7·260–7·382	7·603–7·760 (0·360)	7·604–7·819 (0·391)	7·615–7·740 (0·357)
Hf	6·619–6·637	6·899–6·905 (0·274)	6·879–6·886 (0·255)	6·885–6·902 (0·266)
Hg	5·934–5·942	6·241–6·256 (0·310)	6·322–6·353 (0·399)	6·225 (0·287)
Hi, Hh	4·159–4·327	4·337–4·577 (0·214)	4·415–4·630 (0·280)	4·350–4·575 (0·220)
Hj, Hk	2·575–2·699	2·850–2·918 (0·247)	2·915 (0·278)	2·801–2·891 (0·209)

Figures in parentheses indicate the change in the chemical shifts.

sions and to gain information about the dissolution of the drug in the acidic conditions of the stomach, which would have an influence on the ulcerogenic potential of the drug. Figure 5B shows the dissolution profiles in SGF. Ketorolac powder dissolved more slowly in SGF than in water, with only 54·5% being released in the first hour and 79·63% released at the end of three hours. The physical mixture showed an improved rate of drug dissolution, with 86·5% of the drug being released in one hour; only about 93% of the drug was released at the end of 3 hours from the physical mixture. All the dispersions released the entire amount of drug in 20 min.

Figure 6 shows the release profiles of the physical mixture and the kneaded dispersion of drug with β-CyD in 600 mL distilled water and 600 mL SGF. In water, the physical mixture released the entire amount of drug in 30 min, with the kneaded dispersion releasing the entire amount of drug in 20 min. In SGF, the physical mixture released drug relatively slowly, with only 69% being released in 30 min and approx. 96% being released at the end of 3 hours. The kneaded dispersion had a faster initial drug-release rate than the physical mixture, with 100% released in 30 min.

All the dispersions prepared were studied for particle size distribution by optical microscopy before the dissolution studies. The arithmetic-mean particle sizes for all the dispersions were found to be in a narrow range of 14–22 μm, which ruled out the effect of particle size differences on drug-release profiles from the dispersions.

Dispersions of ketorolac prepared by kneading showed slightly improved dissolution rates in the initial stages of the dissolution study when HPβ-CyD was used as carrier. This could be related to the slightly higher association constant of the drug with HPβ-CyD as compared with β-CyD, and greater loss of crystallinity of the drug as indicated by thermal and X-ray diffraction studies.

The kneaded dispersion with HPβ-CyD exhibited excellent improvement in dissolution equivalent to the freeze-dried and the co-evaporated dispersions. Kneading being a simpler method and amenable to scale-up, the kneaded dispersion with 1 : 1 alcohol–distilled water was chosen for further evaluation of stability and in-vivo performance.

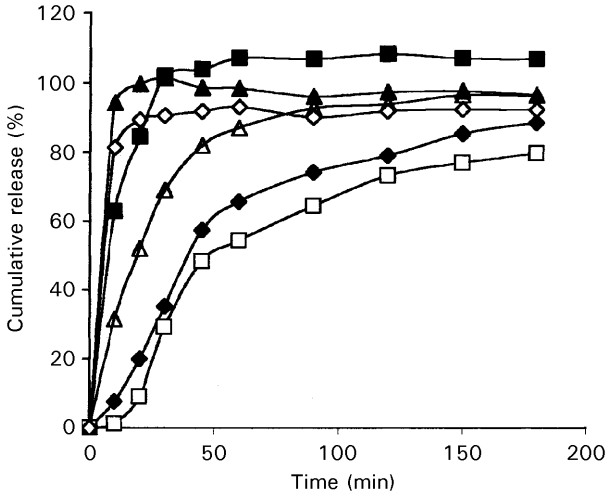


Figure 6. Dissolution profile of β-CyD dispersions: ketorolac in distilled water (◆), ketorolac in simulated gastric fluid (□), physical mixture in distilled water (■), physical mixture in simulated gastric fluid (△), kneaded dispersion in distilled water (▲), kneaded dispersion in simulated gastric fluid (◇).

Table 2. Values of t50% and t80% (time for 50% and 80% in-vitro dissolution) for kneaded dispersion after storage.

Temperature	t50% (min)				
	Initial	2 Weeks	4 Weeks	8 Weeks	12 Weeks
25°C	5·27	5·60	5·60	5·60	5·21
37°C	5·27	5·90	5·33	5·27	5·27
45°C	5·27	5·30	5·54	5·15	5·18
			t80% (min)		
25°C	8·43	8·15	8·15	8·15	8·30
37°C	8·43	8·10	9·60	8·45	8·42
45°C	8·43	8·90	9·30	8·21	8·30

Accelerated stability studies

The solid dispersion was stable with respect to drug content after storage at 25°C, 37°C and 45°C for 12 weeks. The dispersion was found to exhibit reproducible drug-release behaviour throughout the period of storage at all the conditions. The t50% (time for 50% release of ketorolac) and the t80% values (time for 80% release of ketorolac) are shown in Table 2. Analysis of variance at 1% significance level revealed no significant difference for t50% and t80% values, between temperature conditions (25°C, 37°C and 45°C) or between time periods (2, 4, 8 and 12 weeks). However uptake of moisture by the dispersion was observed, when stored at higher humidity conditions. These dispersions or their dosage forms should therefore be stored in moisture-resistant packing to prevent uptake of moisture by the dispersion.

In-vivo studies

Reduction in ulcerogenicity. The scores assigned to the extent of injury following administration of ketorolac, ketorolac trometamol, HPβ-CyD and the kneaded dispersion to rats are given in Table 3. The mean score for the degree of injury was found to be 2·875 ± 0·71 for ketorolac, the free acid. This is partly because the drug, which is poorly soluble in the acidic conditions of the stomach, remains in contact with the stomach wall for a longer period of time. This results in a high local concentration, leading to local irritation of the stomach wall and finally to ulceration. Local irritation by the drugs in the stomach allows back-diffusion of acid into the mucosa and causes tissue damage. The ulcer score for ketorolac trometamol was 2·375 ± 0·95, which was slightly lower than that of the free acid and could be because of reduction in local irritation to the gastric mucosa, owing to higher solubility of the salt.

Table 3. Degree of injury to the stomach of the rats.

Sample	Degree of injury
HPβ-CyD	0·000 ± 0·000
Ketorolac	2·875 ± 0·710
Ketorolac trometamol	2·375 ± 0·950
Kneaded dispersion	1·500 ± 0·580

The kneaded dispersion was found to reduce the ulcerogenicity of the drug and gave a lower ulcer-score value of 1·5 ± 0·58, due to reduction in the local irritant effect of the drug. The kneaded dispersion gave a significant reduction in ulcer-inducing effect by *t*-test at a 5% level of significance. The ability of the solid dispersions to promote rapid dissolution of the drug would mean that there would be no insoluble particles of the poorly soluble drug, adhering to the stomach wall for long periods. Moreover, the drug will not come into direct contact with the stomach wall in the crystalline form, since until it is dissolved, it remains encapsulated within the cyclodextrin matrix, thus reducing the local irritant effect of the drug on the mucosa of the stomach (Szejtli 1985). The solid dispersions would therefore aid in reducing the ulcerogenic potential of the drug. The ulcers produced in the rats treated with kneaded dispersion could be mainly due to the systemic effect of the drug. The drug inhibits synthesis of prostaglandins PGI_1 and PGE_2, which have a protective action on the gastric mucosa.

Reduction in carrageenan-induced oedema in hindpaw of rats. The plot of percentage inhibition vs time for the three groups treated with ketorolac, ketorolac trometamol or the kneaded dispersion is shown in Figure 7. The percentage inhibition values for the group treated with kneaded disper-

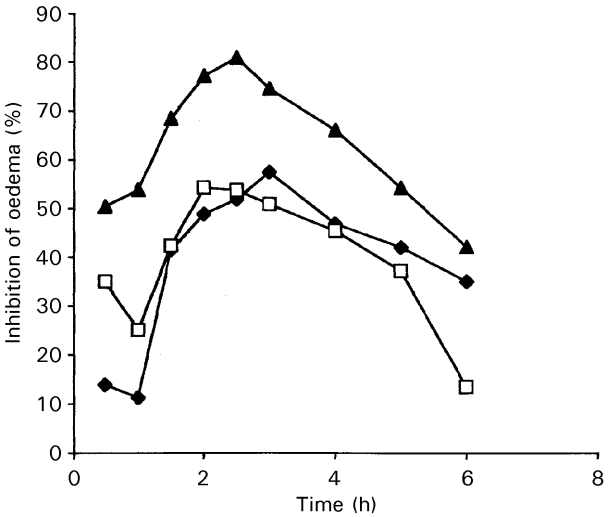


Figure 7. Plot or percentage inhibition of rat hindpaw oedema vs time for ketorolac (◆), ketorolac trometamol (□) and kneaded dispersion with HPβ-CyD (▲).

sion were the highest, indicating maximum inhibition of oedema in the group treated with the solid dispersion. A peak inhibition of 80·9% in the kneaded-dispersion group was obtained at 2·5 h (3 h after drug administration); for ketorolac, the peak inhibition of 57·4% was obtained at 3 h (3·5 h after drug administration) and for ketorolac trometamol, the peak inhibition of 54·4% was obtained at 2 h (2·5 h after drug administration).

The highest peak value of percentage inhibition for the kneaded dispersion, which was attained at an earlier time than for ketorolac, indicates an improvement in the rate and extent of absorption of the drug when given as a solid dispersion with HPβ-CyD. This implies an improvement in bioavailability of the drug due to enhancement in the solubility of the drug.

Conclusion

Solid dispersions with HPβ-CyD improved solubility of ketorolac. The NMR studies indicated a strong interaction between drug and HPβ-CyD. DSC and X-ray diffraction patterns revealed complete loss of crystallinity of the drug in the co-evaporated and freeze-dried dispersions. All the dispersions showed a remarkable improvement in the dissolution rate and extent of ketorolac released and the dissolution profiles of the solid dispersions were reliable even after storage for 12 weeks at 25°C, 37°C and 45°C. The kneaded dispersion showed a promising performance in reducing the ulcer-inducing effect of ketorolac. Oral administration of the kneaded dispersion was found to inhibit carrageenan-induced paw oedema in rats to a greater extent than either ketorolac or its trometamol salt.

The physical mixture and kneaded dispersion of ketorolac prepared using β-CyD as a carrier improved the solubility and dissolution rate of the drug, although their DSC and X-ray diffraction patterns indicated retention of the crystalline nature of the drug. However, HPβ-CyD as a carrier proved to be superior to β-CyD in the dispersions prepared by kneading.

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References

Gillis, J., Brogden, N. (1997) Ketorolac, a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs 53: 139–188

Higuchi, T., Connors, K. A. (1965) Phase solubility techniques. Adv. Anal. Chem. Inst. 4: 117–212

Moyano, J. R., Gines, J. M., Arias, N. J., Robasco, A. M. (1995) Study of the dissolution characteristics of oxazepam via complexation with β-cyclodextrin. Int. J. Pharm. 114: 95–102

Nagarsenker, M. S., Shenai, H. (1996) Influence of hydroxypropyl β-cyclodextrin on solubility and dissolution profiles of ketoprofen in its solid dispersions. Drug Dev. Ind. Pharm. 22: 987–992

Nagarsenker, M. S., Tantry, J. S., Shenai, H. (1997) Influence of hydroxypropyl β-cyclodextrin on the dissolution of ketoprofen and on the irritation to gastric mucosa after oral administration in rats. Pharm. Sci. 3: 443–445

Nambu, N., Kikuchi, K., Kikuchi, T., Takahashi, Y., Ueda, H., Nagai, T. (1978) Influence of inclusion of non steroidal anti-inflammatory drugs with β-cyclodextrin on the irritation to stomach of rats upon oral administration. Chem. Pharm. Bull. 26: 3609–3612

Pitha, J., Milecki, T., Fales, H., Pannell, L., Uekama, K. (1986) Hydroxy propyl β-cyclodextrin: preparation and characterization, effect on solubility of drugs. Int. J. Pharm. 29: 73–83

Szejtli, J. (1985) Molecular entrapment and release properties of drugs by cyclodextrins. In: Smolen, V. F., Ball, L. (eds) Controlled Drug Bioavailability: Bioavailability Control By Drug Delivery System Design. Vol. 3. Wiley Interscience Publication, New York, pp 365–415

Uekama, K., Hirayama, F., Fujise, A., Otagiri, M., Inaba, K., Saito, H. (1984) Inclusion complexation of prostaglandin F_{2a} with γ-cyclodextrin in solution and solid phase. J. Pharm Sci. 73: 382

Uekama, K., Hirayama, F., Irie, T. (1998) Cyclodextrin drug carrier systems. Chem. Rev. 98: 2045–2076