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Influence of amorphous cyclodextrin derivatives on aceclofenac release from directly compressible tablets

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An inclusion complex of hydroxypropyl β-cyclodextrin (HPβCD), an amorphous, highly water soluble derivative and aceclofenac (AC), was prepared by the kneading method. The complex was further characterized by differential scanning calorimetry (DSC), X-ray powder diffractometry (XRD), fourier-transform infra red spectroscopy (FT-IR), scanning electron microscopy (SEM) and *in vitro* dissolution studies. The dissolution of AC from the inclusion complex studied by the dispersed powder technique showed significant dissolution enhancement in case of the kneaded product (KN) compared to pure AC. The complex possessed good compressibility and the tablets so compressed displayed good dissolution profile. The dissolution data were characterized by different model independent parameters such as dissolution efficiency (DE), difference factor (f_1) and similarity factor (f_2).

1. Introduction

Aceclofenac, a phenylacetic acid derivative, [(2-{2,6-dichlorophenyl)amino} phenylacetooxyacetic acid] is a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of pain and inflammation with a reduced side effect profile, especially regarding gastrointestinal events (Sweetman 2002).

Aceclofenac (AC) is practically insoluble in water. The poor aqueous solubility and wettability of AC gives rise to difficulties in pharmaceutical formulations for oral delivery which may lead to variable bioavailability. To overcome these drawbacks, increasing the aqueous solubility of AC is an important goal. The approach of complexation has been frequently used to increase the aqueous solubility and dissolution rate of water insoluble and slightly soluble drugs in an effort to increase oral bioavailability. However, in certain instances this approach can be used to increase drug stability, particularly of esters, control drug release rate, improve organoleptic properties and maximize the gastrointestinal tolerance by reducing drug irritation after oral administration. Generally speaking, cyclodextrins are potential carriers for achieving such objectives (Duchene and Wouessidjewe 1990; Bekers et al. 1991; Mishra et al. 1999).

Cyclodextrins have been extensively used to increase solubility and to improve bioavailability of poorly water-soluble drugs and have shown the ability to reduce the local irritation of many poorly soluble drugs. Hydroxypropyl β-cyclodextrin (HPβCD), a chemically modified β-cyclodextrin, is highly water soluble and does not have limitations such as the renal toxicity associated with β-cyclodextrin or higher hemolytic effect shown by methylated cyclodextrins (Kumar et al. 2005; Ugwu et al. 1999; Ventura et al. 2006; Gibaud et al. 2005).

In the present investigation, an AC−HPβCD complex was prepared in an equimolar ratio by the kneading method and was investigated for improvement in dissolution. The kneaded product (KN) was incorporated to formulate directly compressible tablets for oral administration. The physical mixture (PM) was also prepared in equimolar ratio and used for characterization. Usually, the incorporation of the higher amount of cyclodextrin for the formation of inclusion complexes is not desirable with respect to increase in the formulation bulk, difficulty to cross the biological membranes readily as well as increased cost of the formulation. These limitations were minimized as an equimolar drug to cyclodextrin ratio was able to significantly enhance drug dissolution and the complete drug release was achieved within ten minutes. To the best of our knowledge, no work has been reported on aceclofenac complexes with HPβCD.

2. Investigations and results

2.1. Phase solubility studies

The phase solubility diagram can be classified as A_L type (Higuchi and Connors 1965), as the solubility of AC increased almost linearly with an increase in the concentration of HPβCD (0–3.5 M). The increase in solubility in the systems is due to one or more molecular interactions between AC and HPβCD to form distinct species or complexes. Because the straight line had a slope less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1 : 1 complex. The apparent stability constant $K_{1:1}$ was calculated according to Eq. (1) and was found to be 356.74 M^{-1}.

$$K_s = \frac{\text{Slope}}{S_0(1 - \text{Slope})} \quad (1)$$

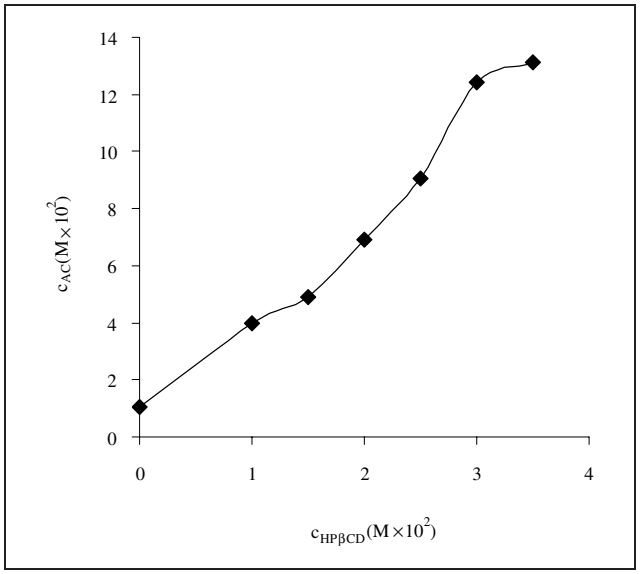

Fig. 1: Phase solubility diagram of AC−HPβCD mixtures

where S_0 is the intercept that is solubility of AC in absence of HPβCD.

The high value of stability constant indicated that AC interacted strongly with HPβCD. The phase solubility diagram is presented in Fig. 1.

2.2. DSC studies

Supporting evidence for complex formation was also obtained from DSC studies. The DSC Thermograms showed endothermic peak of AC at 150 °C, which corresponded to its melting point, while the HPβCD exhibited a typical broad endothermic peak between 50° and 100 °C assigned to its dehydration. The disappearance or shifting of endo- or exothermic peaks of drugs is mostly an indication of the formation of inclusion complexes. The characteristic peak due to AC almost disappeared in case of the kneaded product indicating a strong evidence of the inclusion of the drug into the cyclodextrin cavity whereas the endothermic peak of HPβCD considerably broadened in the kneaded product. The thermogram of the physical mixture was merely a combination of thermogram of pure AC and HPβCD (Prahlad and Kumar 2004; Mura et al. 2002). DSC thermograms are presented in Fig. 2.

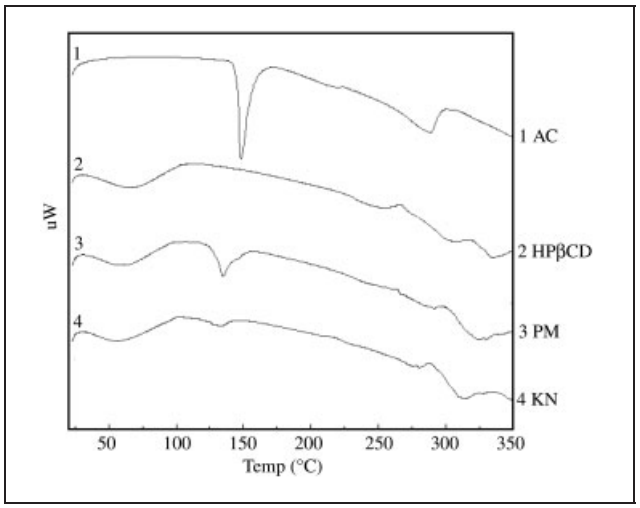

Fig. 2: DSC thermograms of AC and its binary systems with HPβCD

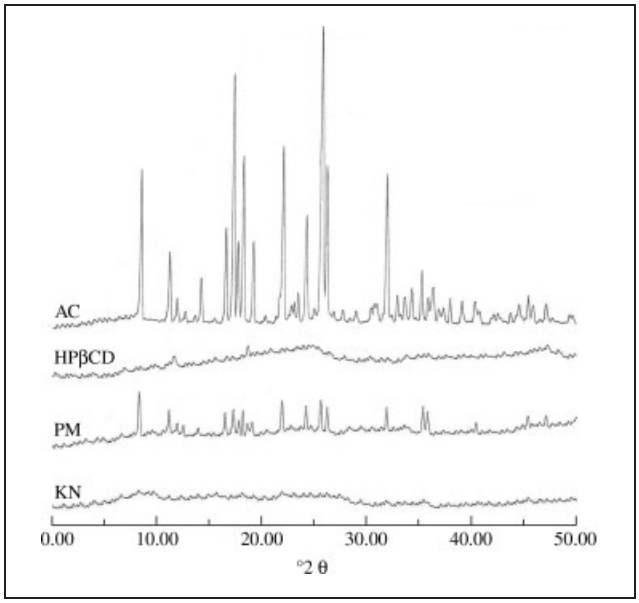

Fig. 3: X-ray diffractograms of pure AC, HPβCD, PM and KN

2.3. XRD studies

X-ray diffraction patterns revealed the crystalline nature of the pure AC as well as the amorphous nature of the HPβCD. The X-ray diffraction pattern of the PM can be interpreted as a superimposition of the AC and HPβCD. The PM showed diffraction peaks corresponding to drug but were less intense than those of the drug. The diffractogram of the KN showed no AC crystal signals, demonstrating the amorphous nature of the product (Lopez et al. 2000). X-ray diffractograms are given in Fig. 3.

2.4. FT-IR studies

Formation of inclusion complex was indicated by appearance of a band of medium intensity at 808.5 cm^{-1} (out-of-plane (oop) C−H bending of aromatic protons of 2,6-dichloro phenyl ring bearing three adjacent protons) in IR spectra of AC which shifted to 811.7 cm^{-1} in case of PM and was absent in case of KN. For another aromatic ring having four adjacent protons, oop C−H bending appeared at 757.8 cm^{-1} in case of drug but was shifted to 770.1 cm^{-1} and 776.5 cm^{-1} for PM and KN respectively. Moreover, reduced intensity and shifting of the weak band from 3052.6 cm^{-1} (C−H stretching of aromatic protons) to 3098.8 cm^{-1} in IR spectra of AC and KN respectively, further supports the involvement of aromatic protons in inclusion complex formation. The spectrum of AC showed skeleton bands at 1588.7 cm^{-1}, 1579.3 cm^{-1}, 1476.5 cm^{-1}, 1461.6 cm^{-1} from which the band at 1476.5 cm^{-1} disappeared and other skeletal bands of aromatic rings shifted from their positions in case of KN. Further, in-plane C−H bending appeared at 1128.6 cm^{-1} and 1153.2 cm^{-1} due to aromatic protons in AC, shifted with much reduced intensity in case of KN and band at 1294.8 cm^{-1} present in case of AC was absent in KN. In IR spectra of AC, C−Cl aromatic stretch appeared at 1089.4 cm^{-1} for AC, was shifted to 1098.6 cm^{-1} in case of KN. Based on these facts, it is suggested that the 2,6-dichloro phenyl ring of the AC is preferably involved in the inclusion process. However, the possibility of another phenyl ring with four adjacent protons to be involved in complexation can not be neglected for which additional characterization with

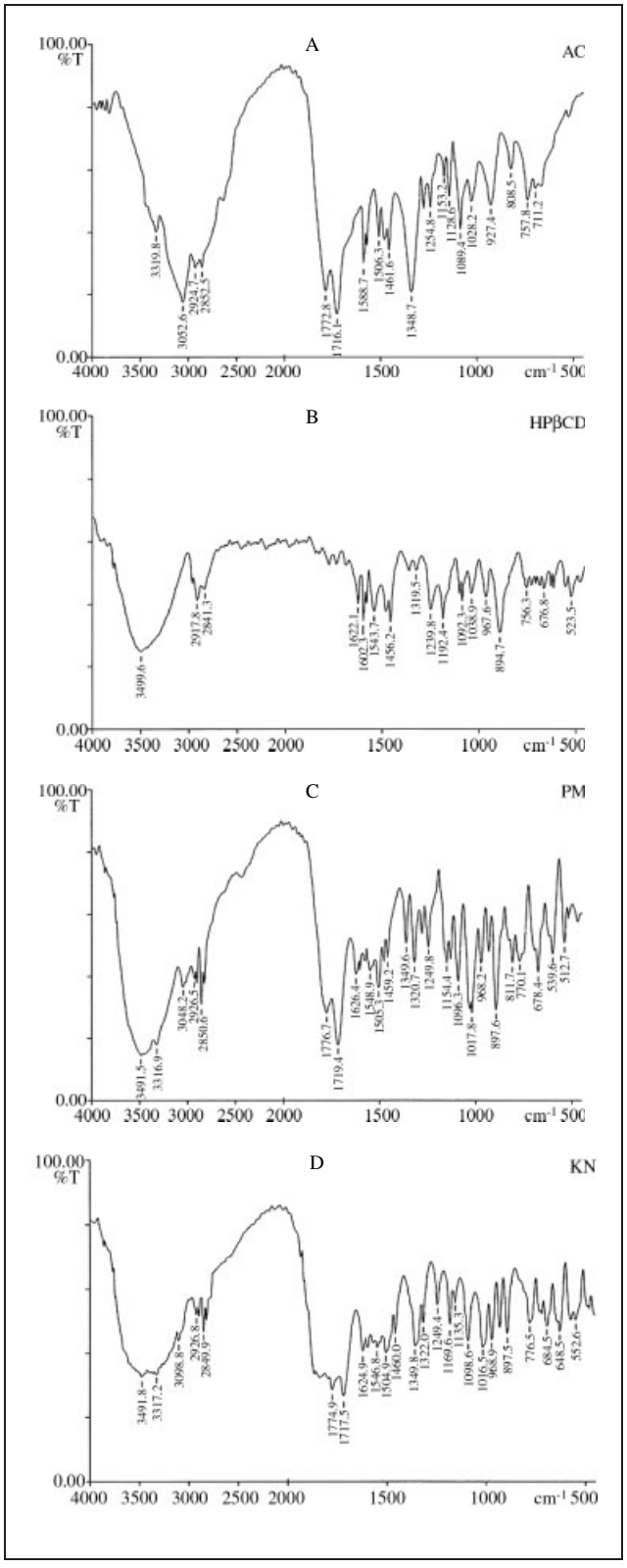

Fig. 4: FT-IR spectra of pure AC, HPβCD, PM and KN

^{1}H NMR spectroscopy would be necessary (Gladys et al. 2003; Jug and Becirevik-Lacan 2004). FT-IR spectra of pure compounds, PM and KN are shown in Fig. 4.

2.5. SEM studies

From scanning electron photomicrographs, pure AC was evidenced as small plate-like crystals forming aggregates while pure HPβCD was seen as spherical particles. SEM images of the physical mixture showed the presence of particles of both components without any modification in shape and size. In particular, with KN, it was not possible to differentiate crystals of both components indicating the better interactions of drug particles with HPβCD. The particles were all irregular in shape and the obtained micrographs supported the idea of the consecution of a new single component, thus confirming the inclusion process of AC with HPβCD (Naidu et al. 2004). SEM images of pure compounds, PM and KN are shown in Fig. 4.

2.6. AC tablets

Tablet formulations containing pure AC (50 mg), PM (equivalent to 50 mg) and KN (equivalent to 50 mg) were prepared separately. All the tablet formulations showed acceptable physical properties as shown in Table 1.

2.7. In vitro dissolution studies

When an assumed drug-HPβCD binary system is dispersed in a dissolution medium, a very rapid dissolution is often observed. Rapid dissolution is a characteristic behavior of inclusion complexes. In the present investigation, the dispersed powder method was used to investigate various dissolution parameters of AC and AC−HPβCD binary systems before tableting. The dissolution characteristics of pure AC, PM and KN in a powder state were studied in simulated intestinal fluid (pH 7.5) without enzyme. The KN showed a significantly higher drug release than pure AC. Further, the release studies of AC from the prepared tablets showed that tablet containing KN had higher value of DE_{10} followed by PM and pure AC tablets.

The results in terms of dissolution efficiency (Khan 1975) at 10 min (DE_{10}) and percent of active ingredient dissolved at 30 min (DP_{30}) are presented in Table 2.

Dissolution efficiency (DE) is defined as the area under the dissolution curve up to the time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. The DE can have a range of values depending on the time interval chosen. In any case, constant time interval should be chosen for the comparison of profiles. In the present investigation, DE_{10} values were calculated from the dissolution data of each product and used for comparison.

The comparative dissolution profiles of pure AC, PM and KN by dispersed powder method is presented in Fig. 6 and the results of DE_{10} before and after tableting are summarized in Table 2 and Fig. 7.

One-way ANOVA was used to test the statistical significance of difference between pure and treated samples. Significance of differences in the means was tested using Fishers Least Significant Difference at 95% confidence. The DP_{30} and DE_{10} values of KN were significantly higher ($P < 0.05$) when compared to pure AC. The dissolution profiles of pure AC and PM before and after tableting were compared in a pairwise fashion using model independent parameters namely the difference factor (f_1) and similarity factor (f_2) taking KN as the reference batch (Costa and Lobo 2001; Yuksel et al. 2000). According to SUPAC FDA guidelines for immediate release dosage forms, for two dissolution profiles to be similar, the difference factor should be between 0 and 15 and the similarity factor should be in the range of 50 to 100. The values of

Table 1: Physical properties of tablets

Formulation	Tensile strength (Kg cm^{-2})	Uniformity of thickness (mm)	Uniformity of diameter (mm)	Friability (loss %)	Disintegration time (min)	Uniformity of weight (gm)
AC tablet	75.49	3.596 ± 0.0524[a] (1.457)	10.173 ± 0.1350 (1.33)	0.298 ± 0.0196 (6.577)	5.100 ± 0.0163 (0.319)	0.3036 ± 0.0151 (4.973)
PM tablet	69.92	3.716 ± 0.0169 (0.455)	10.186 ± 0.1543 (1.514)	0.447 ± 0.0069 (1.543)	3.120 ± 0.0163 (0.522)	0.3060 ± 0.0153 (5.0)
KN tablet	70.32	3.696 ± 0.0573 (1.550)	10.180 ± 0.1395 (1.370)	0.429 ± 0.0335 (7.808)	2.806 ± 0.1247 (4.44)	0.3055 ± 0.0152 (4.975)

[a] All values are presented as mean ± S.D. (n = 3). Values in parentheses are the coefficient of variation percent (CV %)

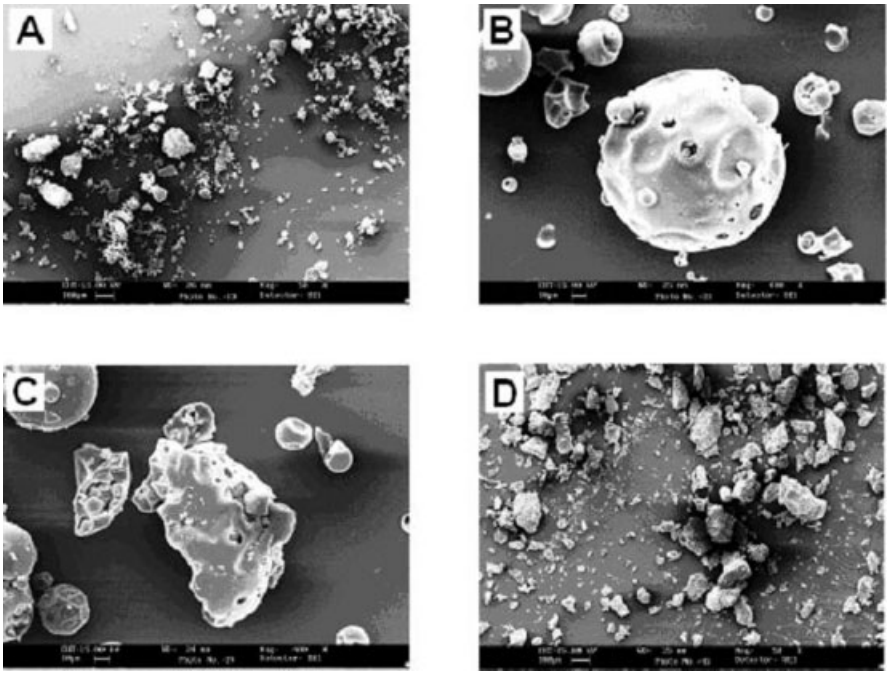

Fig. 5:
Scanning electron micrographs of AC (A), HPβCD (B), PM (C) and KN (D)

f_1 and f_2 suggested that the dissolution curves of pure AC and PM were quite different from that of the KN as shown in Table 2. Overall, the rank order of DP_{30} and DE_{10} values was KN > PM > AC before and after tableting.

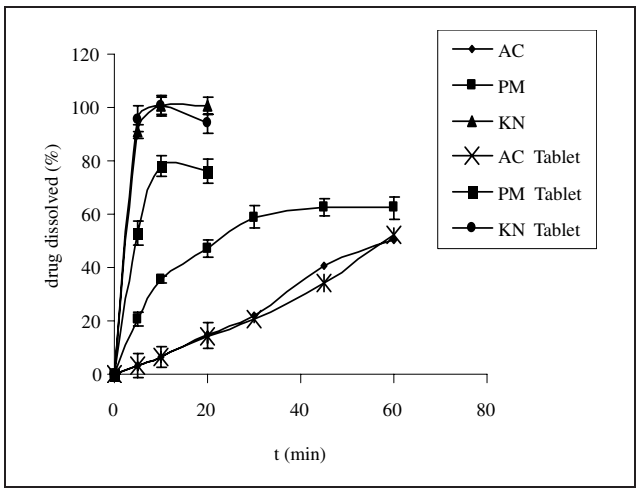

Fig. 6: Comparative *in vitro* dissolution profile of pure AC and its formulations

Table 2: Dissolution parameters of formulations

Sample	DP_{30}	DE_{10}	f_1	f_2
AC	1.93 ± 2.41[a]	3.19 ± 1.996	96.9	12.9
PM	59 ± 1.98	34.71 ± 3.058	22.39	44.24
KN	100.52 ± 1.57[b]	74.12 ± 1.784	0	100
AC Tablet	20.964 ± 1.76	3.104 ± 1.02	93.65	13.19
PM Tablet	75.989 ± 4.55	47.10 ± 2.43	22.67	43.94
KN Tablet	0.692 ± 3.89[b]	72.89 ± 0.78	0	100

[a] Values are presented as mean ± S.D. (n = 3)
[b] Dissolution was completed within 10 min.

3. Discussion

The increase in dissolution rate and efficiency values recorded for the physical mixtures may be explained on the basis of the solubility of the drug in aqueous HPβCD solutions. As the HPβCD dissolved more rapidly in the dissolution medium than the pure drug, it can be assumed that, in early stages of the dissolution process, the HPβCD molecules operate locally on the hydrodynamic layer surrounding the particles of the drug (Uekama et al. 1983).

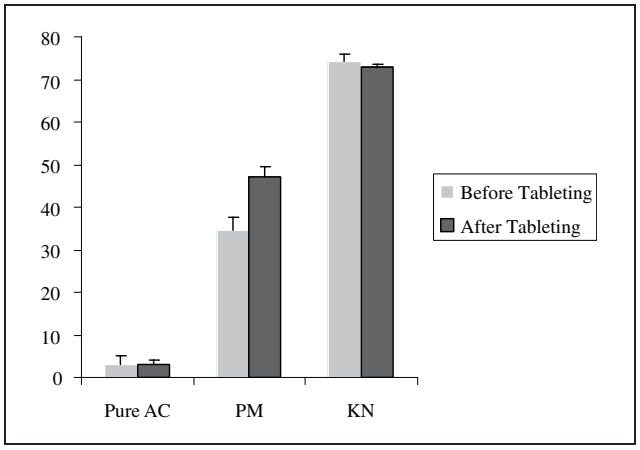

Fig. 7: Dissolution efficiency of pure AC, PM and KN at 10 min (DE_{10}) before and after tableting

The superior dissolution properties observed with the kneaded system may be due to a better interaction of AC with HPβCD during the kneading process. Various authors have suggested that dissolution rates from drug-HPβCD binary systems are also dependent on other factors such as diffusion and dissociation of the complex in the dissolution medium and decrease in crystallinity and enhanced wettability of the drug by the inclusion complexation (Gandhi and Karuru 1988; Donbrow and Tomitou 1978). Further, for a immediate release oral dosage forms $\geq 85\%$ of the labeled amount should be dissolved within 30 min. In the present study, complete drug release was obtained within 10 min with the kneaded formulation.

AC−HPβCD equimolar complex was formulated using the kneading method and was characterized by phase solubility studies, DSC, XRD, FT-IR, SEM and *in vitro* dissolution studies. The stoichiometry for complex formation was found to be 1 : 1. FT-IR studies revealed the possibility of the terminal phenyl moiety to be involved in the inclusion complexation. The AC−HPβCD solid complex prepared by the kneading method showed good compressibility and excellent dissolution enhancement and was employed for the preparation of directly compressible tablets. The tablets were uniform in all physical parameters and showed complete drug release within 10 min. Thus, inclusion complexation of AC with HPβCD in equimolar ratio by the kneading method offers significant improvement in the solid pharmaceutical formulation rendering it sufficiently soluble for its clinical applications with added advantages of simple, effective and economic technique which if scaled-up, can prove promising for formulation development of aceclofenac from the standpoint of industry.

4. Experimental

4.1. Materials and methods

Aceclofenac was generously donated by Kairav Chemicals, Ahmedabad, India. HPβCD with an average molecular weight of 1371.6 purchased from HiMedia, India. All other chemicals used were of analytical reagent grade. Double distilled water was used throughout the studies.

For the kneaded product, the physical mixture was mixed with sufficient volume of water : ethanol (1 : 1) for 20 min to produce dough, and the mixture was further kneaded in a mortar for 1 h to produce a paste of suitable consistency. The obtained semi-wet mass was dried in vacuum desiccator at room temperature for 72 h using anhydrous calcium chloride as a desiccant and passed through a 85 mesh.

The physical mixture of AC and HPβCD in a molar ratio 1 : 1 (0.354 g drug and 1.3716 g HPβCD) was prepared by mixing the compounds manually with a stainless steel spatula for 20 min and sifted through mesh 85 BS. It was used as a reference in characterization.

4.2. Phase solubility studies

Excess amount of AC (50 mg) was added to 10 ml of purified water or HPβCD aqueous solutions (0–3.5 M) taken in a series of 25 ml stoppered conical flasks and the mixtures were shaken for 48 h at 37 °C on a rotary flask shaker. After 48 h of shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 12 h interval and filtered immediately using a 0.45 μm nylon disc filter. The filtered samples were diluted suitably and assayed for AC at 275 nm. Shaking was continued until three consecutive estimations were the same (96 h). The solubility experiments were conducted in triplicate (coefficient of variation, CV $< 5\%$). The blanks were performed on the same concentration of HPβCD in purified water so as to cancel any absorbances that may be exhibited by the HPβCD molecules. The pH of the phase-solubility media was 4.2−4.9. The stoichiometry of the inclusion complexation was determined from the slope of the phase solubility diagram (Higuchi and Connors 1965).

4.3. Differential Scanning Calorimetry (DSC)

Thermograms of pure materials, PM and KN were recorded on a Perkin Elmer (Pyris Diamond) model differential scanning calorimeter. About 10 mg of samples were sealed in aluminium pans and heated at a rate of 10 °C/min from 50–350 °C under nitrogen atmosphere of flow rate 400 ml/min.

4.4. X-ray Diffractometry (XRD)

Powder X-ray diffraction patterns were recorded using a Rigaku 2002 B, Japan, X-ray diffractometer, with a copper target, voltage 50 kV, current 150 mA, at a scanning speed of 5 °C/min.

4.5. FT-IR studies

The FT-IR spectra of the free drug, cyclodextrin, physical mixture and kneaded product were recorded with the Perkin-Elmer FTIR Spectrophotometer. The samples were prepared by the potassium bromide disc method and scanned for absorbance 4000–500 cm^{-1}.

4.6. Scanning Electron Microscopy (SEM)

The surface morphology of pure materials and all binary systems were examined by a scanning electron microscope (Joel, JSM-840 A, Tokyo, Japan). The samples were fixed on a brass stub using double sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 15 KV.

4.7. In vitro dissolution studies

In vitro dissolution studies of pure drug, PM and KN were carried out in 900 ml of simulated intestinal fluid without enzyme (pH 7.5 ± 0.05) of USP 23 using an USP type 2 dissolution rate test apparatus (Nalluri et al. 2003) by a powder dispersed amount method. Samples equivalent to 100 mg of AC at a speed of 50 rpm and a temperature of 37 ± 1 °C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered using a 0.45 μm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for AC by measuring absorbances at 275 nm. The dissolution experiments were conducted in triplicate.

4.8. Tablet preparation

The ingredients of each formula were sufficiently mixed in a double cone blender (HICON, India) for 10 min. The solid mixtures were compressed into 300 mg (10 mm punch) tablets using a single punch semi-automatic tablet machine (HICON, India) (Nagarsenkar and Shenai 1996). The tablet composition is shown in Table 3.

Table 3: Composition of tablet formulations

Ingredients (mg)	AC Tablet	PM Tablet	KN Tablet
Aceclofenac	50	252.52 (Equivalent to 50 mg AC)	225.68 (Equivalent to 50 mg AC)
Maize starch	15	15	15
Sodium starch glycolate	6	6	6
Magnesium stearate	0.75	0.75	0.75
Talc	3	3	3
Spray-dried lactose	q.s 300	q.s 300	q.s 300

4.9. Evaluation of prepared tablets

4.9.1. Weight uniformity

Twenty tablets were randomly chosen and weighed (Shimadzu Electronic Balance AY 120) individually, and the average weight, standard deviation and the coefficient of variation percent (CV %) were calculated.

4.9.2. Tensile strength

The tensile strength (T_S) was calculated using the equation $T_S = 2\,H \div \pi TD$ (Aly et al. 2003) in which H is the tablet hardness, T is tablet thickness, D is tablet diameter. The hardness, thickness and diameter of ten tablets randomly selected from each batch were determined using a hardness tester (Monsanto) and vernier calipers (Mitutoyo, Japan).

4.9.3. Friability

The percent weight loss was determined after rotating 20 preweighed tablets for 4 minutes at 25 rotations per minute using digital friabilator (HICON, India).

4.9.4. Disintegration time

The disintegration time of six tablets for each tablet formulation was determined in distilled water using a disintegration test apparatus, USP (HICON, India)

4.9.5. Dissolution studies

A USP/NF dissolution rate test apparatus II with six units was used for dissolution studies. One tablet was placed in each unit and rotated at 50 rpm in 900 ml of dissolution medium simulated intestinal fluid without enzyme (pH 7.5 ± 0.05) at 37 ± 0.5 °C (USP 23 1995). The experiment was performed for 2 h during which the samples were withdrawn at suitable time intervals and replaced by an equal volume of fresh dissolution medium, which was kept heated at 37 °C. Samples were assayed spectrophotometrically at 275 nm for AC. Each determination was performed in triplicate.

4.10. Data analysis

The student t-test was applied as the statistical method of analysis in which $p < 0.05$ was considered as the least significant level.

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