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ORIGINAL ARTICLE

Development, characterization and performance evaluation of oro-dispersible tablet containing aceclofenac hydroxypropyl-β-cyclodextrin binary system

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Abstract The purpose of this research was to mask the intensely bitter taste of aceclofenac (ACF) and to formulate oro dispersible tablet (ODT) of the taste-masked drug. Taste masking was done by complexing aceclofenac with Hydroxypropyl-β-Cyclodextrin (HPβCD) by different methods. Phase solubility studies indicated complex with possible stoichiometry of 1:1 and a stability constant of 221.11 M^{-1}. The complexes were characterized by Fourier transform infrared spectroscopy, X-ray diffraction, and differential scanning calorimetry studies. The characterization studies confirmed inclusion of the ACF within the nonpolar cavity of HPβCD in the neutralization method (NM). Remarkable improvement in the in vitro drug release profiles in pH 6.8 phosphate buffer was observed with all complexes, especially the neutralization. The complexes of ACF–HPβCD (1:1) was compressed into tablet and properties of tablets such as tensile strength, wetting time, in vitro disintegration time, and disintegration in the oral cavity were investigated to elucidate the wetting and disintegration characteristics of tablets. Polyplasdone XL-10 7% wt/wt gave the minimum disintegration time. Tablets of batch F4 containing Avicel 200 and 7% wt/wt Polyplasdone XL-10 showed faster disintegration, within 12 s, than the marketed tablet (128 s). Good correlation between in vitro disintegration with in-house developed method and in the oral cavity was recognized. Taste evaluation of ODT in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

Keywords Aceclofenac · Hydroxypropyl-β-cyclodextrin · Taste masking · Oro dispersible tablet

Introduction

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which results into poor patient compliance [1]. This weakness leads to the development of innovative drug delivery systems such as "Oro-dispersible tablet" (ODT). In the European Pharmacopoeia, ODTs were defined as Orodisperse that can be placed in the mouth where it disperses rapidly before swallowing. The increasing popularity of orally disintegrating dosage form is in part owing to various factors such as patient preference and life cycle management. Some reasons for patient preference include fast disintegration, good mouth feel, easy to handle, easy to swallow, and effective taste masking [2–6]. Numerous approaches have been reported for masking the bitter taste of the drugs such as (1) use of flavors and sweeteners, (2) use of polymeric carriers, (3) drug resin complexes, (4) formation of inclusion complexes with cyclodextrins (CD), etc. [7–9]. Among the possibilities, the cyclodextrin approach is of particular interest.

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Cyclodextrins are 'bucketlike' molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule [10]. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex. During the past two decades, cyclodextrins and their derivatives especially Hydroxypropyl-β-Cyclodextrin (HPβCD) have aroused considerable interest in the pharmaceutical field because of their potential to form complexes with many varieties of drug molecules. Numerous scientific articles describe the advantages of drugs complexed with cyclodextrins in this way: increased solubility; enhanced bioavailability; improved stability; the masking of bad taste or odor; reduced volatility; transformation of liquid or gas into solid form; reduced side effects; and the possibility of a drug release system [10–12].

Aceclofenac (ACF) is chemically [[[2-[(2,6-dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. It is a potent nonsteroidal anti-inflammatory drug (NSAID), therapeutically used in inflammatory and painful conditions of rheumatic and nonrheumatic origin. It is an acid compound (pKa 4.30 at 25 °C) with a very low aqueous solubility (0.03 mM at 25 °C) in the unionized form [13, 14]. Another problem associated with this active principle aceclofenac lies in its very great bitterness. In general, aceclofenac required in acute painful conditions where prompt, quick action and relief required. However, aceclofenac results in poor bioavailability when administered in the form of conventional tablets because of its high hydrophobicity and poor aqueous solubility [15]. In this work, it was investigated whether the low water solubility problem and bitterness could be overcome by the formation of ACF–HPβCD binary systems.

In this study, investigations were performed on the possibility of complexation of aceclofenac with HPβCD for improving the bitterness, solubility and dissolution rate, thereby increasing the bioavailability and therapeutic efficacy of this NSAID. The complexes of ACF with HPβCD were prepared by using different methods: kneading, and neutralization at stoichiometric ratios. Selective physicochemical determinations based on Fourier transform infrared spectra (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffractometry (PXRD) were used to characterize the complexes. This ACF–HPβCD binary system was formulated into orodispersible tablets by direct compression method. The ODT formulations were evaluated for their physical, disintegration and dissolution properties. An accelerated stability study on selected ODT formulation was also conducted to assess the formulation shelf life and determine any possible degradation.

Experimental

Materials

All the materials used in the present study were commercial samples. Active agent: Aceclofenac (GlenMark Laboratory, Nasik, India); complexing agent: Hydroxypropyl-β-Cyclodextrin (GlenMark Laboratory, Nasik, India); diluent: Pearlitol 300 DC (spray dried mannitol, Signet Chemicals, Mumbai, India), Pharmatose DCL 11 (spray dried lactose, Signet Chemicals, Mumbai, India); Avicel PH 200 (microcrystalline cellulose, Signet Chemicals, Mumbai, India); de-aggregating agents: Polyplasdone XL 10 (crospovidone, BASF, Mumbai, India); Explotab (sodium starch glycolate, BASF, Mumbai, India); Ac-Di-Sol (croscarmellose sodium; BASF, Mumbai, India); sweetner: neotame (S.D. Fine chemicals, Mumbai, India); lubricant: calcium stearate (S.D. Fine chemicals, Mumbai, India) were of pharmaceutical grade, according to USP NF 23.

Methods

Phase solubility studies

Phase solubility measurements were performed according to the method reported by Higuchi and Connors [16]. An excess amount of drug was added to 10 mL HPβCD aqueous solutions (0.003–0.015 M) in volumetric flasks and shaken on rotary flask shaker at constant temperature of 37 ± 0.5 °C for 72 h in order to reach equilibrium. After equilibration the suspensions were filtered through 0.45 µm membrane filter and analyzed by HPLC. The Hewlett-Packard 1100 Series HPLC system (Agilent, USA) was consisted of a G 1311A quaternary pump, a G1314A UV detector. Experimental conditions: Column C18; mobile phase: methanol–acetonitrile–phosphate buffer (pH 7.4) phase (80:10:10 vol/vol); flow rate 1 mL/min; detection: UV detector; wavelength: 272 nm; injection volume: 10 µL. The linearity of this method was shown over a concentration range of 0.288–5.96 µg/mL ($y = 86{,}896x + 1{,}706.8$, $r^2 = 0.9999$). The limit of detection and limit of quantification was 0.148 and 0.296 µg/mL respectively. The coefficient of variation for precision was less than 1.0% and less than 0.7% for the accuracy. The recovery of the method was found to be 100.2–104.1%. Each experiment was carried out in triplicate. The apparent stability constant of the drug/HPβCD complex was calculated from the phase-solubility diagram using the following equation:

$$K_C = \frac{\text{Slope}}{\text{Intercept}\,(1 - \text{slope})}$$

Preparation of physical mixtures (PM)

The PM of molar ratio of 1:1 of drug and HPβCD i.e. (with weight 0.354/1.3) was prepared by simple mixing in mortar with spatula.

Preparation of inclusion complexes

Aceclofenac and HPβCD complexes were prepared in a molar ratio of 1:1 by kneading method and neutralization method.

Kneading method (KM) The solid drug and HPβCD complex of molar ratio of 1:1; i.e. (with weight 0.354/1.3) prepared using KM. The HPβCD of specific quantity according to molar ratio was dissolved in water and then drug was added to it and has been triturated with pestle for 2 h and then the complex prepared was placed in dessicator for 48 h to ensure proper drying.

Neutralization method (NM) The drug and HPβCD of molar ratio of 1:1 i.e. (with weight 0.354/1.3) was dissolved in 10 mL of 0.1 N sodium hydroxide solutions and mixed in beaker. The solution was stirred using a magnetic stirrer at 100 rpm for 15 min. Hydrochloric acid was added drop wise till the pH 7.50–7.55 was obtained (when the complex precipitated). Complete precipitation ensured with further gentle stirring for 15 min. The precipitate formed was filtered through Whatman filter paper of 0.45 µm washed with water until it was free from chloride ions. The residue was air dried at room temperature. The complex prepared was placed in dessicator for 48 h to ensure proper drying [17].

Characterizations of complexes

FTIR The spectra were recorded for pure drug, HPβCD, and for each inclusion complex using FTIR spectrophotometer (Jasco FTIR-410). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400–4,000 cm^{-1}.

DSC The DSC analysis of pure drug, HPβCD and for each inclusion complex was carried out using DSC (Mettler TC 11, TA Processor). The samples (6 mg each) were placed into a pierced aluminium sample container. The studies were performed under a static air atmosphere in the temperature range of 50–500 °C, at a heating rate of 10 °C/min. The peak temperatures were determined after calibration with standard.

PXRD X-ray diffractometry were carried out using a Philips PW 1050 scanner with filter Ni, CuKα radiation, voltage 40 kV and a current of 20 mA. The scanning rate employed was 1°/min over the 5°–50° diffraction angle (2θ) range. The XRD patterns of drug powder, HPβCD, and of complexes were recorded.

Selection of superdisintegrant

Before formulation of tablets, the best superdisintegrant among Polyplasdone XL-10, Ac-Di-Sol, and Explotab was screened out. Tablets were prepared in various batches containing a blend of Avicel PH 200 as a diluent and superdisintegrant in various concentrations (Table 1). The best superdisintegrant screened was used for the final formulation of tablets.

Physical properties of the tablet blend

Bulk density and tapped density The bulk density and tapped density were determined from the weight of 50 g resultant granules charged into 100 mL glass graduated cylinder, and the volume was recorded. The bulk density was 0.65 g/mL. Then the granules were tapped until a constant volume was obtained. And the tapped density of resultant granules was 0.70 g/mL.

The angle of repose of granules Fifty gram of resultant granules were filled into a funnel with a 6 mm internal stem diameter fixed on a clamp. The angle of repose was 20 °C, which demonstrated that the flow property of resultant granules was fairly good.

Preparation of tablet

The composition of aceclofenac ODT is shown in Table 2 and all excipients used for aceclofenac ODT were within limits as per CDER IIG guideline. The batch size was taken of 2,000 tablets. Aceclofenac–HPβCD complex and the excipients except lubricants were sieved through #24 ASTM mesh and #40 ASTM mesh respectively. Neotame, orange flavor and peppermint flavor were passed through sieve #100 ASTM. Aceclofenac–HPβCD complex granules containing amount equivalent to 100 mg of aceclofenac, were mixed with the other excipients, sweetner, flavor, and the whole mixture was blended with the Turbula shaker mixer T2F (Glen Mills Inc. USA) for 15 min. Then lubricant calcium stearate was passed through #60 ASTM mesh and added to the above blend and mixed for 2 min. The above blend was compressed into tablet weight of 600 mg using 12.5 mm flat beveled edge tooling on a 16 station single rotary compression machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India) keeping the

Table 1 Disintegration time of different superdisintegrants

Batch	Disintegrant	Disintegrant (% wt/wt)	Diluent (Avicel PH 200) (% wt/wt)	Disintegration time (s)
A1	–	–	100	90
A2	Polyplasdone XL-10	6	94	11
A3	Polyplasdone XL-10	7	93	9
A4	Polyplasdone XL-10	8	92	10
A5	Polyplasdone XL-10	10	90	12
A6	Polyplasdone XL-10	12	88	13
A7	Ac-Di-Sol	8	92	24
A8	Ac-Di-Sol	10	90	20
A9	Ac-Di-Sol	12	88	18
A10	Explotab	8	92	38
A11	Explotab	10	90	37
A12	Explotab	12	88	43

Table 2 Composition of aceclofenac ODT (mean ± SD, n = 3)

Components	F1	F2	F3	F4	F5	F6
Aceclofenac	100	–	–	–	–	–
Aceclofenac–HPβCD (PM)	–	452.82	–	–	–	–
Aceclofenac–HPβCD (KM)	–	–	452.82	–	–	–
Aceclofenac–HPβCD (NM)	–	–	–	452.82	452.82	452.82
Avicel 200	397.4	44.58	44.58	44.58	–	–
Pharmatose DCL 15	–	–	–	–	44.58	–
Pearlitol 300 DC	–	–	–	–	–	44.58
Polyplasdone XL-10	38.5	38.5	38.5	38.5	38.5	38.5
Neotame	1.1	1.1	1.1	1.1	1.1	1.1
Orange flavor	5.5	5.5	5.5	5.5	5.5	5.5
Peppermint flavor	5.5	5.5	5.5	5.5	5.5	5.5
Calcium stearate	2.0	2.0	2.0	2.0	2.0	2.0
Total	550	550	550	550	550	550

tabletting speed of 20 rpm and the compression pressure at such a level so as to achieve hardness of 60–70 N.

Evaluation of tablet properties

The tablet geometry was determined by a means of a micrometer (Baty Co Ltd, Sussex, England).

Hardness The crushing strength of ten tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India).

Friability The friability of a sample of 20 tablets was measured using a Roche friabilator (Electrolab, Chennai, India). Twenty pre-weighed tablets were rotated with speed of 25 rpm for 4 min. The tablets were then dedusted and reweighed, and the percentage of weight loss was calculated.

Drug content estimation Ten intact tablets (each equivalent to 100 mg of aceclofenac) were transferred individually into clean and dry 100 mL volumetric flasks. 50 mL of 6.8 phosphate buffer was added and sonicated in ultrasonic water bath for 30 min while swirling occasionally. Then it was allowed to cool to room temperature and volume was made up to the mark with 6.8 phosphate buffer. After suitable dilutions samples were analyzed by HPLC.

Disintegration time (DT) In vitro DT for ODT was determined using USP method and a relatively simple method with rigorous conditions was developed to evaluate the DT of rapidly disintegrating tablets. Each individual tablet was dropped into 10 mL glass test tube (1.5-cm diameter) containing 4 mL distilled water, and the time required for complete tablet disintegration was observed visually and recorded using a stopwatch. The visual inspection was enhanced by gently rotating the test tube at

a 45-angle, without agitation, to distribute any tablet particles that might mask any remaining undisintegrated portion of the tablets.

Wetting time Circular tissue papers (10 cm diameter) were placed in artificial saliva (pH—6.8) to simulate the tongue conditions in a Petri dish. Methylene blue, a water-soluble dye, was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

In vitro dissolution In vitro dissolution studies of aceclofenac–HPβCD ODT formulation and of marketed tablet were studied using USP dissolution Apparatus II. The dissolution medium was phosphate buffer (pH 6.8), the volume being 900 mL. The temperature was maintained at 37 ± 0.5 °C. The rotation speed was 100 rpm. Five milliliters of aliquot were withdrawn at predetermined time intervals. The medium was replenished with 5 mL of fresh buffer each time. Sample was analyzed by using HPLC as described earlier. The study was performed in triplicate.

In vivo disintegration time, sensory evaluation of roughness and taste evaluation

In vivo disintegration was performed on 6 healthy human volunteers, from whom informed consent was first obtained. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded. The disintegrated material was held in the mouth for another 60 s, and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and, finally, the roughness levels were recorded on a numerical scale ranging from 0 to 3 where 0, 1, 2, and 3 indicate no, slight, moderate, and high roughness, respectively. Taste evaluation was done using the time intensity method on 9 healthy human volunteers from whom informed consent was first obtained. The aceclofenac–HPβCD equivalent of 100 mg of aceclofenac was held in the mouth for 10 s and then spat out, and 1 ODT (containing 100 mg aceclofenac) was held in the mouth until complete disintegration. Bitterness was recorded immediately and at several intervals for 5 min according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness [18].

Stability study

Selected batch of aceclofenac ODT (F6) was packed in 30 cc HDPE bottle, sealed and kept at 40 °C and 75% relative humidity in stability chamber (Narang Scientific Works Pvt. Ltd., New Delhi, India) for a period of 6 months as per ICH guidelines. Samples withdrawn at 1, 2, 3 and 6 months were analyzed for drug content, hardness, and disintegration time.

Statistical analysis

All data were statistically analyzed by analysis of covariance (ANOVA); results were quoted as significant where $p < 0.05$.

Results and discussion

The phase solubility diagram for aceclofenac–HPβCD system in water is shown in Fig. 1. A linear increase in solubility of aceclofenac was observed with increasing concentration of HPβCD, giving rise to the A_L type solubility diagram. This linear aceclofenac–HPβCD correlation with slope less than 1, the complex stoichiometry was assumed to be 1:1. The value of the stability constant was found to be 221.11 M^{-1}, indicating that complex of aceclofenac–HPβCD is sufficiently stable. In fact, values of stability constants should be always within the range of 100–1,000 M^{-1}, which is believed to indicate an ideal value [19]. Actually, smaller values of Kc indicate a too weak interaction between drug and carrier, while larger values are symptomatic of an incomplete drug release from the inclusion complex. So value we got is considered as ideal and is expected to be stable.

FTIR

ACF showed a very strong absorption bands between 1,720 and 1,460 cm^{-1} for carbonyl stretching band, which split into triplet (the absorption peak showed in 1650, 1631 and

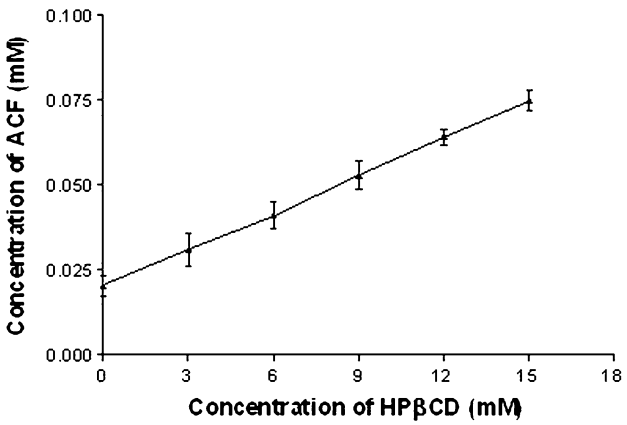

Fig. 1 Phase solubility plot for aceclofenac/HP-β-CD system (mean ± SD, n = 3)

1593 cm^{-1}, respectively), −OH stretching of carbonyl group shows sharp peak around 3,400 cm^{-1}; 1,527 cm^{-1} was denoted for stretching vibration of C≡C in the aromatic ring (Fig. 2). All the binary systems of aceclofenac–HPβCD did not show any new peaks, indicating no chemical bonds created in the formed complexes. The main characteristic -OH stretching of carboxyl group; appeared also at the same position in the PM. Further, the characteristic CO stretching band of ACF was slightly shifted to a higher frequency in the PM and the KM product. However, the spectra of binary system of ACF–HPβCD obtained by and inclusion complexes prepared by KM and NM, shows no sharp peak in 3,400 cm^{-1}, suggested that the hydroxyl group of aceclofenac was entrapped into the host cavities, during inclusion complexation as shown in Fig. 2. Furthermore, the characteristic CO stretching band of ACF disappeared in the spectrum of the complex prepared by NM. These results support the conclusion that formation of the inclusion compound was obtained when the NM was used.

DSC

DSC can be used for the recognition of inclusion complexes. When guest molecules were embedded in CD cavities or in the crystal lattice, their melting, boiling or sublimation points generally shifted to a different temperature or disappeared [20]. The thermograms of aceclofenac, HPβCD and the binary systems are shown in Fig. 3. The DSC diagram of ACF exhibited a sharp endothermic peak at 152.9 °C, indicating the melting point of ACF. The thermogram of HPβCD exhibited a very broad endothermic peak between 60 and 100 °C (maximum at 90 °C), corresponding to release of water molecules.

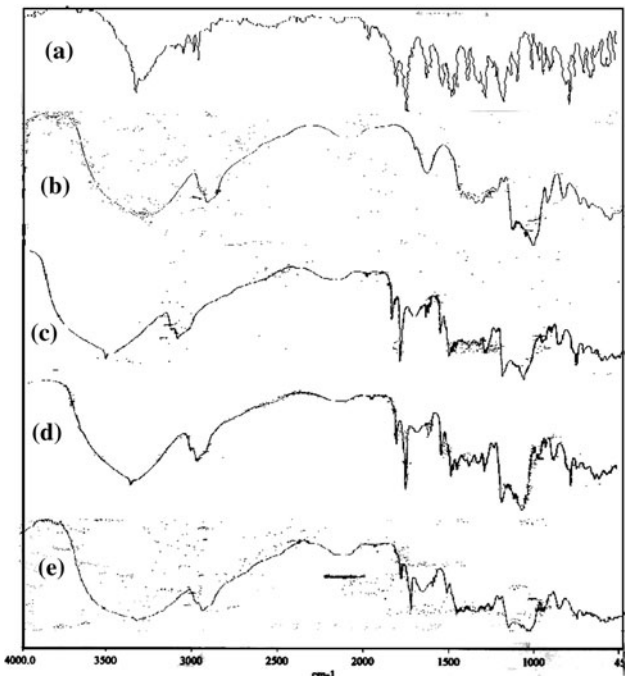

Fig. 2 FTIR spectra of (*a*) aceclofenac; (*b*) HP-β-CD; (*c*) PM (1:1) of ACF and HP-β-CD; (*d*) KM complexation (1:1); (*e*) NM complexation (1:1)

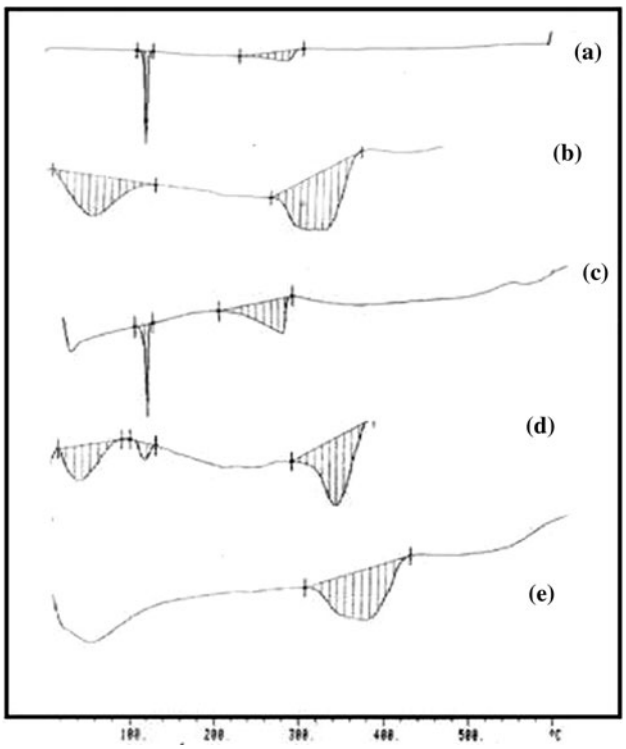

Fig. 3 DSC curve of (*a*) aceclofenac; (*b*) HP-β-CD; (*c*) PM (1:1) of aceclofenac and HP-β-CD; (*d*) KM complexation (1:1); (*e*) NM complexation (1:1)

The trace of physical mixture showed the sharp drug melting endotherm, which shifted to lower temperature. Concerning the thermal curves of inclusion complexes of aceclofenac with HP-β-CD prepared by two different methods, the endothermic peak of aceclofenac at 152.9 °C disappeared but showed only peak corresponding to HP-β-CD with reduced in intensity as a consequence of interaction between the components. This phenomenon is generally considered as indicative of complex formation/drug amorphization and/or stronger interaction in the solid state between aceclofenac and HPβCD.

PXRD

The PXRD patterns for the aceclofenac, aceclofenac–HPβCD PM, and the corresponding aceclofenac–HPβCD complexes are presented in Fig. 4. The XRD pattern of aceclofenac showed peaks at a diffraction angle (2θ) of 18.05, 21.74, 25.41, 31.83, and 37.13 that were intense and

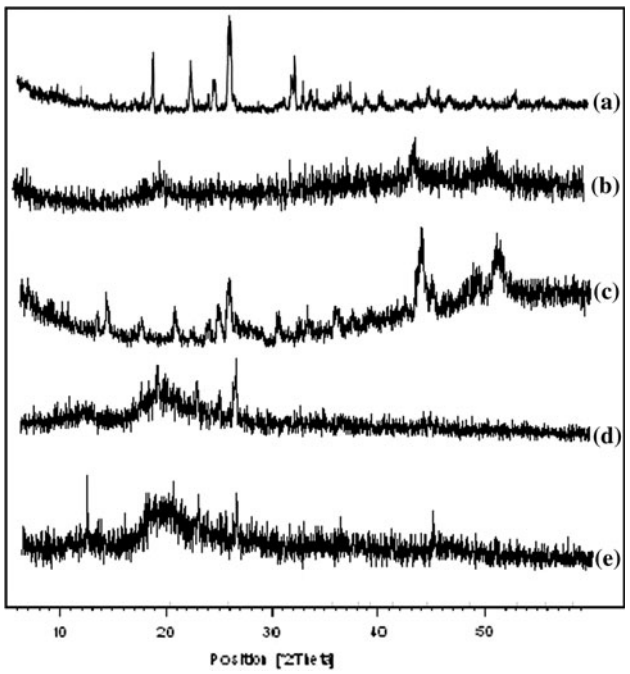

Fig. 4 XRD spectra of (*a*) aceclofenac; (*b*) HP-β-CD; (*c*) PM (1:1) of aceclofenac and HP-β-CD; (*d*) KM complexation (1:1); (*e*) NM complexation (1:1)

sharp, indicating its crystalline nature (Fig. 4). The diffraction patterns of the physical mixture and kneaded systems show simply the sum of each component, indicating the presence of aceclofenac in the crystalline state. In contrast, the complex prepared by NM exhibits considerable diminution of the diffraction peaks, suggesting that it is less crystalline than the PM, kneaded system. It may be concluded that as the heights of the diffraction peaks were reduced, the degree of crystallinity was reduced in the case of solid inclusion complexes [21].

Selection of superdisintegrant

We have studied comparison among different superdisintegrants like Polyplasdone XL-10; Explotab; and Ac-Di-Sol, in terms of their dispersion time. Tablets comprised of Polyplasdone XL-10, Explotab and Ac-Di-Sol was placed in petri dish containing a small amount of water, as shown in Fig. 5a. The ability of Polyplasdone XL-10 to wick water into the tablet is readily observed in Fig. 5b compared to Explotab and Ac-Di-Sol. In less than 1 min, the tablet with Polyplasdone XL-10 disintegrant was fully hydrated and began to flake and disintegrate. In contrast, tablet with Explotab and Ac-Di-Sol formed gels that block water penetration to the center of the tablet. This could be explained as Polyplasdone XL-10 quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressure necessary to provide rapid disintegration in the mouth. Unlike Explotab and Ac-Di-Sol which rely principally on swelling for disintegration, Polyplasdone XL-10 use a combination of swelling and wicking [22]. Further, due to its high crosslink density, Polyplasdone XL-10 swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in tablets formulations. After selection, the concentration of Polyplasdone XL-10 was further reduced to get the minimum optimal concentration. Polyplasdone XL-10 7% wt/wt was selected as the optimum concentration that showed minimal disintegration time of 8 s. It was observed that further increase in concentration led to the increase in disintegration time. Such delay in disintegration may be because of the higher water requirement by a larger amount of Polyplasdone XL-10, which consequently transformed into swelling force for rapid disintegration of the tablet.

Evaluation of tablet properties

Properties like hardness, friability, and drug content of tablets of all the batches were found to be within acceptable limits as shown in Table 3.

In the USP disintegration test for oro-dispersible tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time limit for tablet disintegration. The USP apparatus and specifications for the disintegration of ODT were not suitable for these formulations because the aceclofenac ODT disintegrate so rapidly that differences in DT cannot be measured using them. An alternative apparatus to detect the differences in oral tablet DT was designed by Bi et al. [2]. The speed of the apparatus paddle was 100 rpm and the volume of the immersion fluid was 900 mL. These conditions do not reflect the in vivo oral cavity conditions, where a very limited volume (2–3 mL/min) of saliva is available under normal conditions, with a maximum of 6–8 mL/min after stimulation. Also, the agitation in the immersion fluid created by the paddle rotation, which would not exist in the sublingual cavity, could enhance tablet disintegration, resulting in a shorter DT compared with what might be expected in the sublingual cavity.

A relatively simple method, as previously described, was therefore developed to evaluate the DT of these fast disintegrating tablets. In this method, the diameter (1.5 cm) of the test tube used is smaller than the diameter of oral cavity area in humans ($\sim$3–4 cm). The larger oral area in humans might actually enhance rather than reduce tablet disintegration. The 1.5 cm diameter of the 10 mL test tube does compare with the oral cavity in small laboratory animals such as rabbits, which have been used to date for in vivo studies and are being considered for future studies.

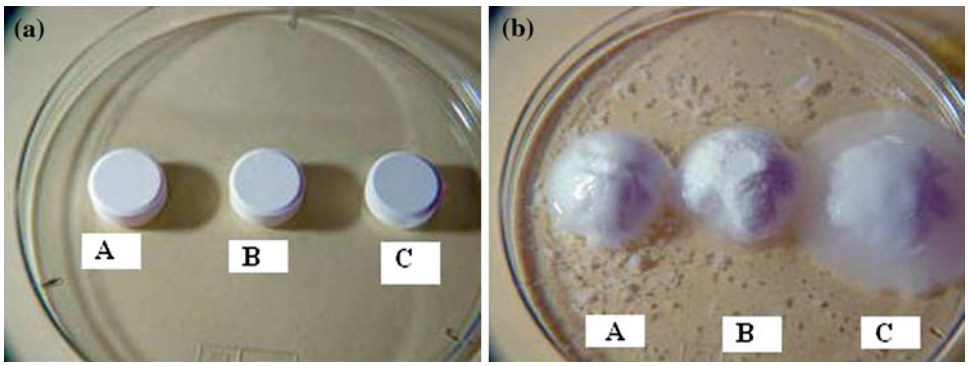

Fig. 5 **a** Tablets at initial time; (*A*) Polyplasdone XL 10; (*B*) Ac-Di-Sol; (*C*) Explotab. **b** Tablets after 1 min; (*A*) Polyplasdone XL 10; (*B*) Ac-Di-Sol; (*C*) Explotab

Table 3 Evaluation of aceclofenac ODT (mean ± SD, n = 3)

Parameter	F1	F2	F3	F4	F5	F6
Diameter (mm)	12.01 ± 0.02	12.02 ± 0.02	12.02 ± 0.04	12.03 ± 0.03	12.01 ± 0.03	12.00 ± 0.02
Thickness (mm)	4.30 ± 0.05	4.40 ± 0.07	4.30 ± 0.04	4.32 ± 0.06	4.33 ± 0.04	4.34 ± 0.05
Hardness (N)	90 ± 5	58 ± 5	52 ± 3	56 ± 4	52 ± 4	55 ± 3
Friability (% loss)	0.017	0.259	0.299	0.271	0.353	0.212
Drug content	100.2 ± 0.57	98.84 ± 0.78	99.73 ± 1.43	100.03 ± 1.56	99.16 ± 0.95	99.23 ± 1.07
Disintegration time (s)	96 ± 4	14 ± 3	12 ± 3	10 ± 2	74 ± 4	62 ± 3
Wetting time (s)	50 ± 4	16 ± 4	15 ± 5	13 ± 3	34 ± 2	29 ± 2

The small volume of water (4 mL) used for tablet disintegration evaluation approximates the volume of saliva secreted under normal conditions. This in vitro DT simulates the relatively small oral area, the small volume of saliva, and the relatively static environment in the human oral cavity.

Although a wetting test is not a USP standard test, it is useful for quality control and provides supportive evaluation of these ODT. Unlike the disintegration test, the wetting test uses minimal water, which may be more representative of the quantity of moisture available orally. Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release aceclofenac in the presence of minute volumes of saliva. The wetting test designed by Bi et al. compares favorably with the conditions in the oral cavity area of humans and animals. This test was modified with regard to the dimensions of the dish and the volume of water used, as previously described.

From Table 3 it is observed that tablets containing complex of aceclofenac–HPβCD (NM) shows lesser DT and wetting time compared to tablets containing complex of aceclofenac–HPβCD (kneading method) and aceclofenac–HPβCD (PM). Among the tablets containing complex of aceclofenac–HPβCD (NM); batch F1 containing Avicel 200, and 5% wt/wt Polyplasdone XL-10 showed faster disintegration, within 10 s, than the marketed tablet 128 s ($p < 0.005$). Batch F6 which contains (spray-dried mannitol), showed increased wetting and disintegration time. It may be due to the polyol quantity in the tablet formulation. As polyols are readily soluble in water, there exists a competition between spray-dried mannitol and Polyplasdone XL-10 for water penetrating into the tablet, consequently leading to poor swelling of Polyplasdone XL-10 with subsequent delay in disintegration [23]. Disintegration time of tablets of batch F5 containing spray-dried lactose was also slightly more than F4, probably because of the formation of a sticky layer due to the dissolution of lactose and subsequent hindrance in the further ingress of water into the tablet.

The dissolution profiles of aceclofenac alone, PM, and the aceclofenac–HPβCD complexes are reported in Fig. 6.

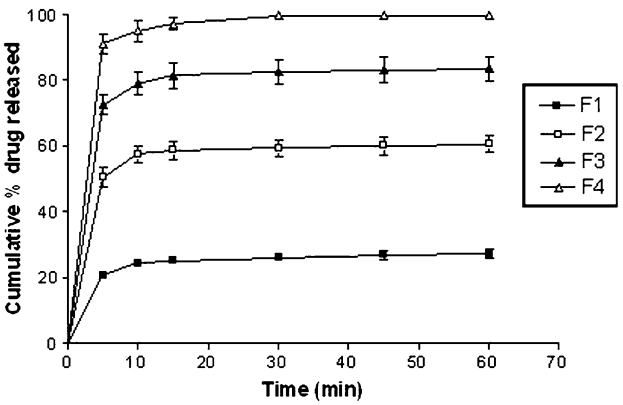

Fig. 6 In vitro release profile of aceclofenac ODT (mean ± SD, n = 3)

Table 4 Comparison of disintegration time by different methods (mean ± SD, n = 3)

Formulation	Disintegration time (s)		
	USP method	Modified method	In vivo disintegration
F1	96 ± 4	120 ± 6	129 ± 6
F2	14 ± 3	21 ± 3	23 ± 2
F3	12 ± 3	21 ± 5	22 ± 3
F4	10 ± 2	16 ± 4	18 ± 1
F5	74 ± 4	94 ± 7	97 ± 5
F6	62 ± 3	88 ± 5	90 ± 4

According to these results, the inclusion complexes released up to 80% of the drug in 10 min, whereas aceclofenac pure drug exhibited the release of ~25% after 10 min and not more than 30% after 60 min. These quantities contrast with the markedly 4–5 fold increase in the release of aceclofenac–HPβCD (NM). It is also evident that the neutralization and kneaded systems exhibit higher dissolution rates than the PM and the pure drug. The extent of the enhancement of the dissolution rate was found to be dependent on the preparation method, since the neutralization products exhibited the highest dissolution rates. This enhancement has been attributed in all these cases both to the formation of an inclusion complex in the solid state and to the reduction of the crystallinity of the product, as confirmed by PXRD and DSC studies. The dissolution rate increase reached for the physical and kneaded mixtures is only due to the wetting effect of the HPβCD; in fact, this effect is more evident for the kneaded product, where the mixing process between the 2 components is more intensive. The effect of complexation with HPβCD on the solubility of aceclofenac can be explained in terms of the reduction in the crystallinity of the drug caused by the neutralization process and the inclusion into the hydrophobic cavity of the HPβCD.

Further, the complexes prepared by neutralization technique offer a dissolution rate of approximately 90% in 10 min, which may be of particular interest for industrial scale preparations because of the low cost, the simple process, and easy scale up, as it involves less energy, time, and equipment.

Between the two used disintegration test methods, newer developed method was found to provide more comparable results with the in vivo test than USP disintegration method. Disintegration times of tablets from all the batches with newer method were found nearly same as in vivo disintegration time (Table 4).

Taste masking evaluation by volunteers indicated that the complex formation was an efficient method of taste masking of this drug (Table 5). The ODT prepared using HPβCD complex showed better acceptability than ODT without HPβCD complex. The combination of pleasant tasting flavors for better mouth feel and taste masked complex attributed to better palatability.

From Table 6 it is clear evident that formulation F4 was stable and no significant ($p > 0.005$) variation was observed in drug content, hardness, disintegration time, and dissolution time over the period of 6 M at 40 °C/75% RH.

Table 5 Bitterness evaluation by taste panel

Samples	Volunteers					
	I	II	III	IV	V	VI
Aceclofenac	3	3	3+	3	3+	3+
ACF–HPβCD (NM) complex	0.5	0.5	0	1.0	0	0
ODT (taste mask flavor)	1.5	2.0	2.0	1.5	2.5	1.5
ODT (HPβCD complex)	0	0	0	0.5	0	0

0 = Tasteless, 0.5 = aftertaste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3.0 = strong, 3+ = very strong

Conclusion

Phase solubility studies showed a higher solubility of aceclofenac when HPβCD was used in combination, with stability constant ($K = 221.11\ M^{-1}$). FTIR, DSC and XRD studies suggest the conversion of aceclofenac from crystalline to amorphous form. Analysis of dissolution data showed a significant enhancement in dissolution rate with complexation using HPβCD. Complex compressed into tablet showed acceptable hardness, disintegration time and dissolution behavior. The formulations were subjected to stability studies as per ICH guidelines and were found to be stable after 6 months study. The study conclusively

Table 6 Stability study data of selected batch (F4) of aceclofenac ODT at 40 °C/75% RH (mean ± SD, n = 3)

Parameters	Initial	1 M	2 M	3 M	6 M
Drug content	100.03 ± 1.56	99.76 ± 0.60	99.30 ± 0.41	99.10 ± 0.46	98.80 ± 0.51
Hardness (N)	56 ± 4	57 ± 3	56 ± 4	54 ± 5	53 ± 4
DT (s)	18 ± 1	19 ± 2	19 ± 2	20 ± 1	19 ± 3
Dissolution profile (15 min)	99.8 ± 1.06	99.5 ± 1.40	99.22 ± 0.56	98.8 ± 0.61	98.82 ± 0.36

demonstrated complete taste masking of ACF and rapid disintegration and dissolution of ODT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of ACF in a more palatable form without water. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non-cooperative patients, can be successfully formulated using this technology.

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