Effect of water soluble carriers on dissolution enhancement of aceclofenac

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The solid binary systems of aceclofenac (AC) with β-cyclodextrin (βCD) were prepared by co-grinding, kneading, and co-evaporation, and with PEG 6000 were prepared by the melt-solvent method in 1:1 and 1:2 molar and weight ratios, respectively. The phase solubility study with βCD suggested B_s type of curve with a possibility of 1:1 inclusion complex. The solid systems were characterized by *in vitro* release studies, DSC, and SEM. The results of solid state studies revealed that AC was completely dissolved in the carrier matrix in case of the melt-solvent method, which suggested the possible formation of solid solution with AC to be existed in an amorphous state. All the binary systems exhibited improved dissolution as compared to pure drug. However, the best dissolution enhancement was achieved with the binary system AC: PEG 6000 in 1:2 weight ratio using the melt-solvent method which was subjected to tablet preparation by direct compression. The tablets so compressed complied with in-house and compendial specifications. The *in vitro* dissolution test was carried out for the formulated tablets and three popular marketed brands of conventional AC tablets. None of the commercial brands showed complete drug release but the formulated tablets exhibited almost complete drug release within 50 min. The dissolution data were further characterized using model-independent parameters DP_{30}, DE_{50}, $t_{50\%}$, similarity factor f_2 and difference factor f_1. The tablets formulated incorporating the AC: PEG 6000 (1:2) binary system displayed significantly improved dissolution profile as compared to existing immediate release commercial tablets.

Key words: *Aceclofenac, BCS class II, dissolution enhancement, poorly water soluble drug, solid dispersion, water soluble carrier*

INTRODUCTION

Aceclofenac (AC), 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 gastro-intestinal events that are frequently experienced with NSAID therapy.[1] AC is practically insoluble in water with good permeability (calculated log P=2.170) and belongs to the biopharmaceutic classification system (BCS) class II (low solubility, high permeability). Therefore, AC shows dissolution rate limited absorption that gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability. This fact motivated the development of drug delivery technologies to overcome the obstacle to its solubilization. Besides enhancement of solubility or micronization of drug substances in order to increase the surface area and replacement of crystalline drugs by amorphous material, the solid dispersions with water soluble carriers is the promising and widely used approach to enhance the dissolution properties of water insoluble drugs.[2-5] The present work reports potential of water soluble carriers βCD and PEG 6000 in enhancing the dissolution properties of the AC. The selected solid binary systems were further subjected to direct compression in order to determine their suitability in developing better oral dosage form with improved dissolution and bioavailability.

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MATERIALS AND METHODS

AC was obtained as a generous gift from Kairav Chemicals (Ahmedabad, India). βCD was purchased from SD fine chemicals (India), PEG 6000, spray-dried lactose, sodium starch glycolate were from Merck (India) Ltd. Double distilled water was used throughout the studies.

Phase solubility studies

The phase solubility study was performed according to method reported by Higuchi and Connors.[6] Excess

amount of AC (50 mg) was added to 10 mL of purified water and 10 mL of βCD aqueous solutions (0.01-0.05 mol/L) taken in a series of 25 mL stoppered conical flasks. The suspensions were shaken for 48 h at 37°C on a rotary shaker. 2 mL aliquots were withdrawn at 12 h interval and filtered immediately (Whatmann® filter paper no.1). The filtered samples were suitably diluted and analyzed for AC at 275 nm. Shaking was continued until three consecutive estimations were reproducible. The solubility experiments were conducted in triplicate (coefficient of variation, CV<2%) and the control studies were performed on the same concentration of βCD in purified water so as to cancel any absorbances that may be exhibited by the βCD molecules. The apparent stability constant was calculated from the phase solubility diagram. For PEG 6000, excess amount of AC was added to 25 mL conical flasks containing different percentage of weighed amount of PEG 6000. Add 10 mL of distilled water to each flask, and then placed in a rotary mechanical shaker at 37°±0.5°C for 48 h. At the end of 48 h, samples were filtered, 5 mL of filtered samples were suitably diluted and analyzed at 275 nm.

Preparation of AC-βCD binary systems

The solid binary systems of AC and βCD in 1:1 and 1:2 molar ratios were prepared using 0.3542 g AC with 1.135 g and 2.7 g βCD, respectively. The coground dispersions (CG) were prepared by geometric mixing and triturating AC and βCD powders (sieved through 85 mesh) for 20 min in the glass mortar pestle. To obtain kneaded product (KN), AC and βCD were triturated in mortar with 0.5 mL of water: ethanol (1:1 v/v) solution to obtain dough like mass. This was kneaded for 45 min and dried under vacuum at room temperature to constant weight. The dried mass was pulverized and screened through 85 mesh sieve. To obtain coevaporated product (CE), an aqueous solution of βCD was added to alcoholic solution of AC. The resulting mixtures were dried on magnetic stirrer (maintained at 45-50°C) by continuous stirring for 4 h. The nearly dried mass was pulverized and sieved through mesh 85.[7] The solid systems were coded as CG-1 and CG-2 (coground dispersion of AC: βCD in 1:1 and 1:2 ratio), KN-1 and KN-2 (kneaded product of AC: β-CD in 1:1 and 1:2 ratio), CE-1, and CE-2 (coevaporated product of AC: βCD in 1:1 ratio and 1:2).

Preparation of AC-PEG 6000 binary systems

The binary systems of AC with PEG 6000 were prepared using the melting solvent method in 1:1 and 1:2 weight ratios. PEG 6000 was melted at 50-60°C in preheated china dish on water bath. The ethanolic solution of AC was added into melted PEG 6000 with stirring. The mass obtained was cooled to room temperature and dried under vacuum to constant weight.[8] The prepared solid systems were pulverized using glass mortar pestle and sieved through mesh 85. The solid systems were coded as AP-1 and AP-2 (dispersion of AC: PEG 6000 in 1:1 and 1:2 ratio).

Preparation of physical mixtures

To obtain physical mixtures (PMs), the required amounts of drug and carriers were geometrically mixed (previously screened through 85 mesh) for 20 min in the glass mortar with the help of a stainless steel spatula. PMs were prepared for each drug: carrier ratios for characterization and coded as PM-1 and PM-2 (physical mixture of AC: βCD in 1:1 and 1:2 ratio), PMAP-1, and PMAP-2 (physical mixture of AC: PEG 6000 in 1:1 and 1:2 ratio).

Drug content analysis

Ten milligram of each of binary system was diluted to 10 mL with methanol. This solution was shaken for 1 min using vortex shaker (Hicon, Grover Enterprises, New Delhi). All the samples were filtered (Whatman® filter paper no.1). From this, 0.5 mL solution was withdrawn and again diluted to 10 mL with methanol. The concentration of AC in the filtrates was determined spectrophotometrically at 275 nm (Shimadzu-1700, Japan) with reference to suitably constructed calibration curve of AC in methanol. Drug content estimations were performed in triplicate.

***In vitro* dissolution studies**

In vitro dissolution tests for pure AC (100 mg) or its binary systems (equivalent to 100 mg of AC) were carried out with the *USP XXIII* dissolution test apparatus (Type II paddle) at 37°C and 100 rpm using 900 mL of simulated intestinal fluid (SIF) pH 7.5 without enzyme as dissolution medium (n=3).[9] Five milliliter of test samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh dissolution medium. The samples were filtered, suitably diluted, and assayed spectrophotometrically for AC content at 275 nm. The amount of AC in each sample was calculated with reference to regression equation generated from suitably constructed calibration curve of AC.

Differential scanning calorimetry studies

Thermograms were recorded on Perkin Elmer (Pyris Diamond) model differential scanning calorimeter. About 10 mg of samples were sealed in quartz pans and heated at a rate of 10°C/min at 50-350°C in nitrogen atmosphere at a flow rate of 400 mL/min.

Scanning electron microscopy studies

The surface morphology was examined by 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.

Preparation of tablets

Tablets were prepared from the selected binary systems by the direct compression method using 10 mm punches on a hand operated single punch tablet machine (Hicon, India). Each tablet consisted of the binary system amount ≅ 100 mg of AC [Table 1]. Superdisintegrant sodium starch glycolate was incorporated in the tablet formulation as it is a modified low substituted carboxymethyl starch with excellent water

Table 1: Composition for directly compressible tablets of AC incorporating selected binary systems

Ingredients (mg)	Formulations*				
	TAC	TPM-AP-2	TAP-2	TPM-1	TKN-1
Aceclofenac	100.00	326.19	313.65	496.30	469.92
Maize starch (5.0% w/w)	30.0	30.0	30.0	30.0	30.0
Sodium starch glycolate (2.0% w/w)	12.0	12.0	12.0	12.0	12.0
Magnesium stearate (0.2% w/w)	1.20	1.20	1.20	1.20	1.20
Talc (1% w/w)	6.0	6.0	6.0	6.0	6.0
Spray-dried lactose q.s.	600	600	600	600	600

*TAC is tablet formulated with pure AC; TPM-AP-2 and TAP-2 are tablets formulated incorporating physical mixture and solid dispersion of the AC:PEG 6000 1:2 binary system; TPM-1 and TKN-1 are tablets formulated incorporating AC:βCD 1:1 physical mixture and kneaded product

absorbing and swelling property. One additional advantage of using this modified starch is that disintegration time may be independent of compression force.[10]

Evaluation of tablets

Thickness, diameter and hardness

Both diameter and thickness of the tablets were determined using Vernier calipers. Hardness of tablets was measured using Monsanto hardness tester. The values were reported as average of three determinations.

Friability test

The percent weight loss was determined after rotating 20 preweighed tablets for 4 min at 100 rotations per min using digital friabilator (HICON, India).

Uniformity of weight

Twenty tablets were randomly chosen and weighed (Shimadzu Electronic Balance AY 120) individually and the average weight and standard deviation was determined.

Disintegration test

The disintegration test was carried out using distilled water as disintegration medium (Disintegration test apparatus USP, Hicon, India). One tablet was introduced into each tube and a disc was added to each tube. Assembly was suspended in the beaker containing 900 mL distilled water. Time for disintegration of all six tablets was noted down.

Assay

Twenty tablets were selected at random from each batch of formulated tablets and powdered. Ten milligram powder from each tablet batch was diluted to 10 mL using methanol, and the resultant solution was shaken for 1 min using the vortex mixer. All the samples were filtered using Whatman® No.1 filter paper. From this, 0.5 mL solution was withdrawn and diluted to 10 mL with methanol. The concentration of AC in the filtrates was determined spectrophotometrically at 275 nm with reference to suitably constructed calibration curve of AC in methanol.

In vitro dissolution test

In vitro dissolution test for the formulated tablets of AC (100 mg) and/or its binary system (equivalent to 100 mg of AC) was carried out using *USP XXIII* type II paddle dissolution apparatus at a temperature of 37°C and a stirring rate of 100 rpm, using 900 mL simulated intestinal fluid (SIF) pH 7.5 without enzyme as dissolution medium (n=3). Samples were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were suitably diluted and analyzed at 275 nm.

Analysis of dissolution data

The best formulated tablet was selected based on its evaluation parameters and compared with three commercial brands using similarity factor f_2 and difference factor f_1:[11]

$$f_1 = 100\left[\frac{\sum_{i=1}^{n}|R_i - T_i|}{\sum_{i=1}^{n} R_i}\right]$$

$$f_2 = 50\log\left[100\left(1\Big/\sqrt{1+\frac{1}{n}\sum_{i=1}^{n}(R_i - T_i)^2}\right)\right]$$

where R_i and T_i are the percentage dissolved of the reference and test profile respectively, at *i*th time point.

Stability study

Stability study was carried out as per ICH Q_1A stability testing guidelines for zone III. The best formulated tablets of AC were subjected to storage condition of 30°C/70% RH for 3 months at the sampling intervals 0, 1, 2 and 3 months.[12] The test parameters were appearance, disintegration time, hardness, and assay.

RESULTS AND DISCUSSION

Phase solubility studies

The phase solubility diagram [Figure 1] can be classified as B_S type according to Higuchi and Connors. Considering this B_S type curve, it can be seen that, from S_0, the apparent solubility of AC increases due to the formation of a soluble complex between AC and βCD. When the solubility limit of this complex is reached (at 0.03 mol/L conc. of βCD), the ascending linear portion starts leveling off, and further addition of βCD resulted in precipitation of a microcrystalline complex. The concentration of uncomplexed drug is maintained constant by dissolution of solid AC as long as the drug reservoir is present. The complex formation continues in the plateau region and it precipitates from saturated solution as the

concentration of βCD increases. The stoichiometric ratio of complex determined from the plateau region of the diagram was found to be 1:1 (AC-βCD). $K_{1:1}$ was calculated according to equation 1 and was found to be 30.47 M^{-1}:

$$K_s = S_t - \frac{S_0}{S_0}(L_t - S_t + S_0) \quad (1)$$

where S_0 is the solubility of AC in the absence of βCD, S_t is the total concentration of dissolved drug, and L_t is the total concentration of βCD.[13] The solubility study of AC with water-soluble PEG 6000 was performed by taking weighed amount the drug and polymer. The solubility of AC was found to be 0.552, 1.215, 1.620, 2.443 mg/mL for 0.25. 0.5. 0.75 and 1.0% w/w of PEG 6000, respectively. The results showed that as the amount of carrier increased the solubility of AC also increased.

Drug content analysis

The actual drug content of binary systems ranged between 10.728 and 50.970% and exhibited good agreement with theoretical drug content [Table 2].

***In vitro* dissolution studies of binary systems**

The results of dissolution studies revealed that about 64% of AC was released from its pure powder form in 2 h which was due to its poor aqueous solubility. All the PMs showed marginal improvement in dissolution which may be attributed to hydrophilic nature of the carriers. However, both the type and amount of carrier influenced the release behavior as evidenced by comparison of dissolution performance of binary systems prepared in 1:1 ratio with that of 1:2 ratio [Figures 2, 3]. When 1:1 molar ratio was used with βCD, 86.746% drug was released at 30 min in kneaded product as compared to only 67.267% drug release when PEG 6000 was used in 1:1 weight ratio by using the melt-solvent method. However, when 1:2 molar ratio was used with βCD, 78.686% drug was released at 30 min by the kneading method as compared to 90.441% drug release when PEG 6000 was used in 1:2 weight ratio by the melt-solvent method. This fact suggested that the systems prepared with βCD showed marked improvement in dissolution even in equimolar ratio but increment of molar ratio from 1:1 to 1:2 did not

Table 2: Percentage drug content of binary systems*

Binary system	% Drug content
PM-AP-1	50.970±0.808
AP-1	50.565±0.076
PM-AP-2	32.313±1.697
AP-2	31.882±1.312
PM-1	20.149±0.008
CG-1	18.666±0.897
KN-1	21.280±3.085
CE-1	19.364±0.909
PM-2	10.554±0.785
CG-2	12.647±2.489
KN-2	10.728±0.835
CE-2	11.339±0.658

*n=3

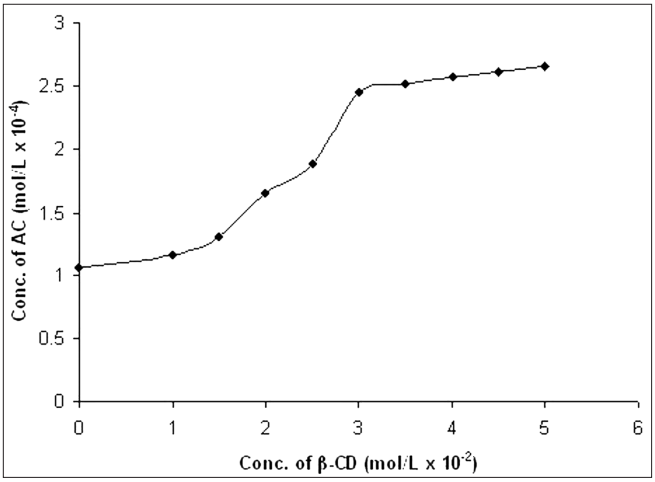

Figure 1: Phase solubility diagram of AC-βCD suspensions

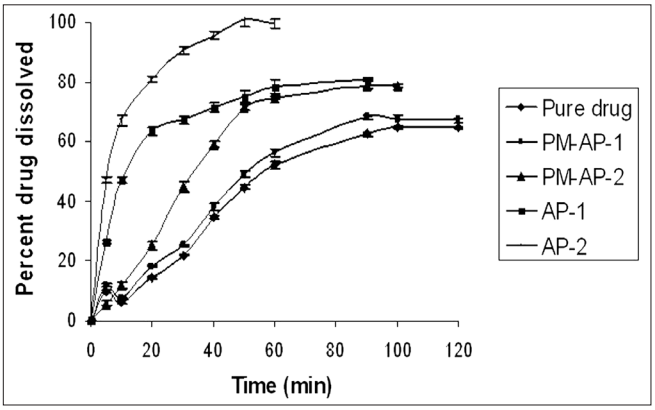

Figure 2: Comparative dissolution profiles of pure drug and AC-βCD binary systems

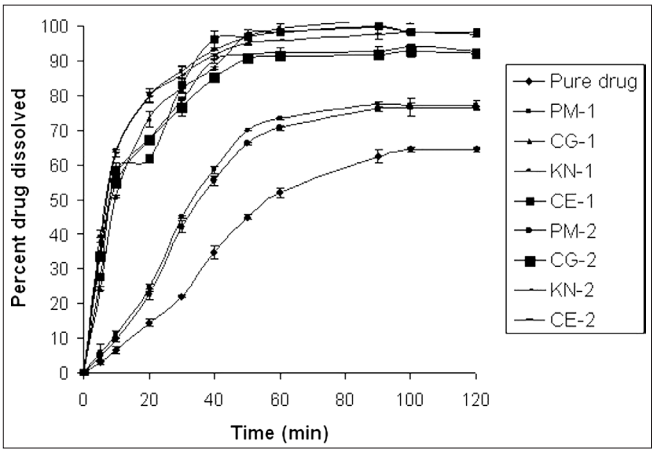

Figure 3: Comparative dissolution profiles of pure drug and AC-PEG 6000 binary systems

result in proportionate enhancement of AC release. It was also evidenced that cogrinding and coevaporation was less effective compared to the kneading method as kneading allowed better interaction of drug and carrier. Percent drug dissolved at 10 min (DP_{10}), dissolution efficiency at 10 min (DE_{10}), and time for 50% drug release ($t_{50\%}$) were found to be 67.28%, 40.41%, 5.6 min for AC: PEG 6000 (1:2) prepared by the melt-solvent method (AP-2) and 64.25%, 35.79%, 6.4 min for AC: βCD (1:1) prepared by the kneading method (KN-1) [Table 3]. However, the AP-2 and KN-1 formulations showed 90.441% and 86.746% drug released at the end of 30 min compared to that of 21.93% by pure AC. This fact revealed that both the solid systems fulfilled the criteria of at least 85% drug release within 30 min which is set by FDA for immediate release dosage forms of class I drugs.[14] Hence, these two binary systems were further characterized by DSC and SEM and selected for tablet preparation by direct compression.

DSC and SEM studies

The solid state DSC studies revealed that the drug peak was almost disappeared with no significant change in carrier peak when PEG 6000 was used at higher mixing ratio using the melt-solvent method [Figure 4]. The results of SEM studies were in agreement with DSC thermograms, as in the micrographs, it was not possible to distinguish pure components in case of binary systems prepared by the melt-solvent method with PEG 6000 with uniform distribution of drug in the polymer matrix. However, the corresponding physical mixture was seen merely as the combination of characteristics of pure drug and carrier [Figure 5]. The solid state characterization suggested possibility of forming of solid solution in case of AC: PEG 6000 binary systems at a 1:2 mixing ratio. The possible mechanism could be that the dispersed component which is the drug was molecularly dispersed in the carrier matrix possessing no crystal structure in the solid solution, and therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a limitation to the release of a drug from a solid solution.[15] However, more advanced analytical methods such as FTIR, Raman spectroscopy, and solid state NMR should be employed to study and confirm the nature of the interactions between the drug and the carrier and to define the solid state structure of the solid dispersions.[16]

Table 3: Model-independent dissolution parameters of pure drug and binary systems

Binary systems	DP_{10} (%)	DE_{10} (%)	DP_{30} (%)	$t_{50\%\ (min)}$
Pure drug AC	6.48	3.19	21.93	54.4
PM-AP-1	7.59	3.45	25.25	50.4
PM-AP-2	12.00	5.88	44.99	32.8
AP-1	47.12	24.95	67.27	11.2
AP-2	67.28	40.41	90.44	5.6
PM-1	11.18	5.71	44.76	36.0
CG-1	51.15	24.95	82.05	9.6
KN-1	64.25	35.79	86.75	6.4
CE-1	58.54	31.08	83.05	8.2
PM-2	9.50	4.79	42.08	38.2
CG-2	54.84	20.58	76.67	8.2
KN-2	63.57	34.11	85.74	7.0
CE-2	56.86	24.64	78.69	8.4

Evaluation of tablets

Physical parameters and official tests

The formulated tablets prepared incorporating pure AC, KN-1 and AP-2 (coded as TAC, TKN-1, and TAP-2, respectively) and their PMs (TPMKN-1 and TPMAP-2) were satisfactory with respect to physical parameters such as thickness, diameter, hardness, friability, and drug content [Table 4]. The tablets

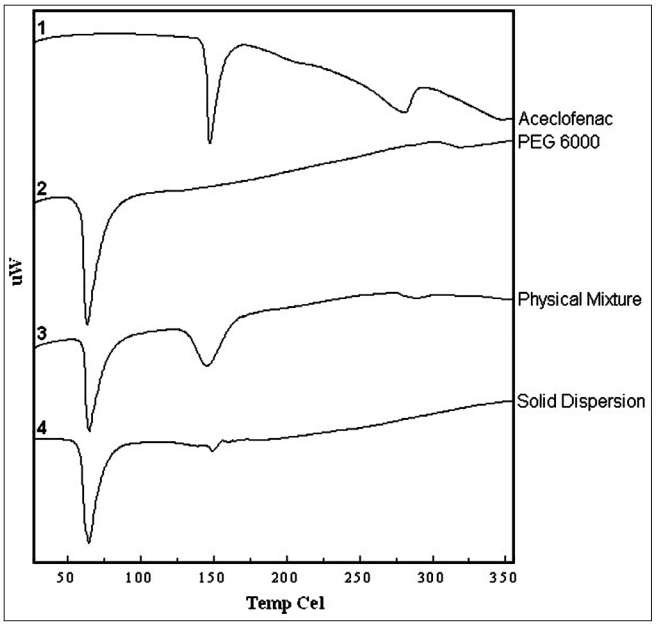

Figure 4: DSC thermograms of pure components and binary systems of AC:PEG 6000 (1:2)

Table 4: Physical parameters of formulated tablets

Formulation	Physical parameters			
	Diameter*	Thickness*	Hardness*	Friability**
TAC	10.412±0.123	7.632±0.045	5.008±0.235	0.003
TPM-AP-2	10.012±0.145	6.983±0.062	5.162±0.468	0.991
TAP-2	10.642±0.188	7.062±0.098	4.501±0.881	0.002
TPM-1	09.998±0.102	7.428±0.157	4.663±0.610	0.015
TKN-1	10.320±0.113	7.002±0.062	5.168±0.957	0.443

*Values are average of three determinations. **Test has been performed for 10 tablets

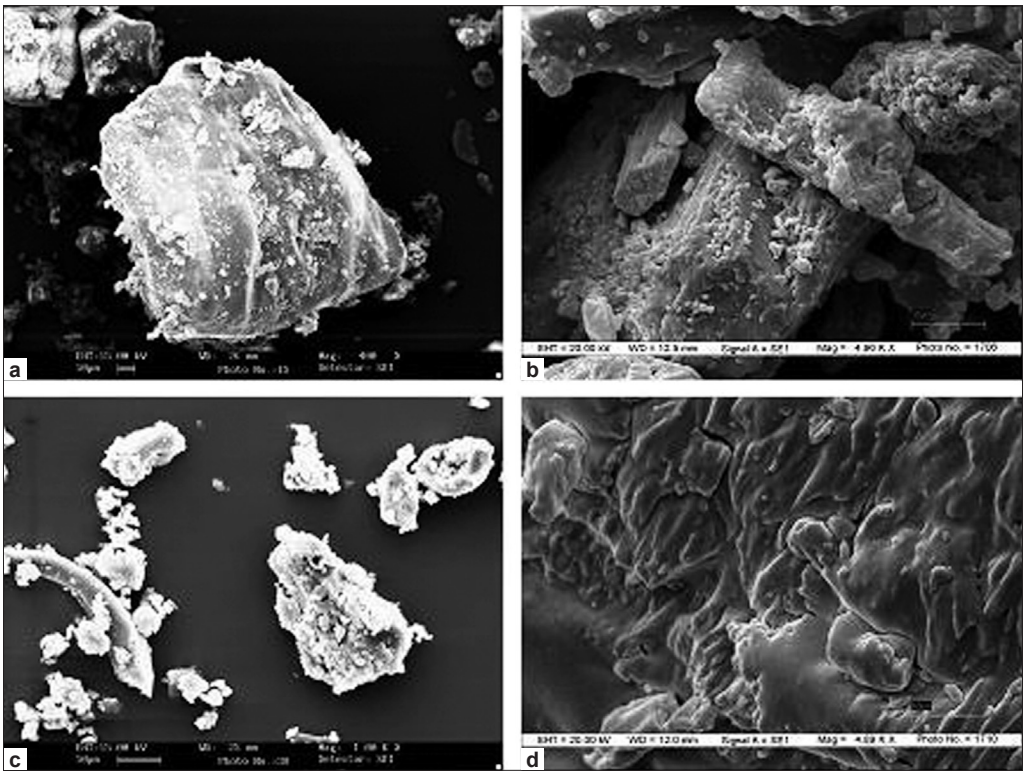

Figure 5: SEM images of (a) aceclofenac (b) PEG 6000 (c) physical mixture of AC:PEG 6000 (1:2) and (d) solid dispersion of AC:PEG 6000 (1:2)

Table 5: Results for official tests of tablets

Formulation	Average weight* (g)	Disintegration** time (min)	Assay (%)
TAC	0.5868±0.00218	5.50±0.254	100.258±1.587
TPM-AP-2	0.5910±0.00245	5.34±0.253	99.326±2.567
TAP-2	0.6100±0.00302	3.50±0.178	98.472±1.679
TPM-1	0.5822±0.00296	4.98±0.242	100.568±1.773
TKN-1	0.5510±0.00300	3.32±0.263	99.489±3.421

*Values are average of 20 tablets. **Values are average of six tablets

Table 6: Results of model independent parameters of best formulated tablet and marketed brands

Formulation*	DP_{30}	DP_{50} (%)	DE_{50} (%)	$t_{50\%}$ (min)	f_1	f_2
TAP-2	91.14	100.79	80.33	33.80	27.02	54.39
Brand A	74.99	78.69	65.30	47.60	0.85	99.34
Brand B	73.31	77.35	62.39	47.70	2.54	95.05
Brand C	75.66	79.36	66.01	46.90	0.00	100.00

*TAP-2 is formulated tablets incorporating the AC: PEG 6000 1:2 binary system, A, B and C are marketed brands of AC tablets

also complied with test for uniformity of weight and disintegration time [Table 5].

***In vitro* dissolution study and analysis of dissolution data**

The formulated tablets exhibited almost similar dissolution properties as compared to their respective binary system, with best dissolution enhancement by TAP-2. Further, it was interesting to note that none of the commercial brands provided complete drug release even at 2 h, whereas TAP-2 showed 100% drug release within 50 min [Figure 6]. The TAP-2 provided markedly improved results of DP_{30}, $t_{50\%}$, and DE_{50}[17] as compared to three commercial brands A, B and C. The similarity factor f_2 and difference factor f_1 are the important model-independent parameters for the mathematical comparison of the dissolution data of different formulations.[18] The values of f_2 between 50 and 100 and f_1 between 0 and 15 show similarity of the dissolution profiles as per the SUPAC FDA guidance. The values of f_2 and f_1 were 54.39 and 27.02

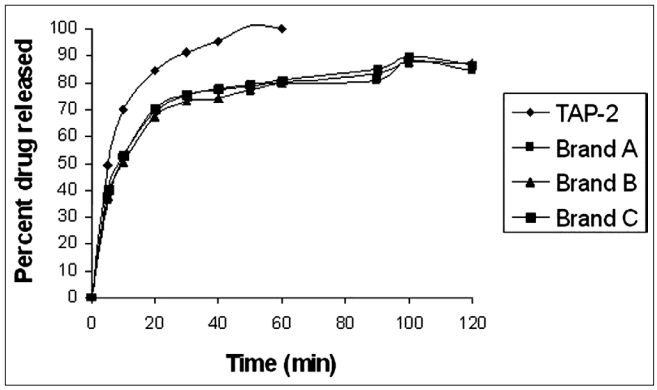

Figure 6: Comparative dissolution profiles of best formulated and marketed tablets

respectively for the formulated tablet, when brand C was taken as reference, indicated that the dissolution profile of formulated tablet was not significantly similar to that of the marketed brands [Table 6].

Table 7: Results for stability studies of best formulation TAP-2

Study parameter	Time interval (months)			
	0	1	2	3
Appearance	Smooth texture, white	No change	No change	No change
Disintegration time (min)	3.50±0.178	3.34±0.114	3.26±0.266	3.02±0.158
Hardness (kg/sq. cm)	4.50±0.881	4.26±0.235	4.12±0.455	3.91±0.148
Assay	98.47±1.679	98.23±0.987	98.14±1.579	97.95±1.589

Further, the amount of the AC: PEG 6000 (1:2) binary system which was equivalent to 100 mg of AC was found to be 313.65 mg based on drug content analysis, which was practically feasible to be formulated as tablet dosage form for oral administration.

Stability study

The proceeding condition that is temperature and humidity is one of the most important factors from the view point of manufacturing of tablets at production scale. The stability study of best developed formulation was carried out as per I.C.H. Q_1 A guideline for a period of 3 months to investigate the influence of humidity and temperature on appearance, disintegration time, hardness, and assay of tablets (Table 7). The results revealed that the tablets exhibited non-significant changes for the investigated parameters for 3 months indicating stability of the developed formulation.

CONCLUSIONS

The dissolution enhancement from binary systems depended on nature of carrier, mixing ratio, and method of preparation. PEG 6000 was found more effective carrier as compared to βCD for improving the dissolution properties of AC at higher ratio and the melt-solvent method was effective to achieve the AC: PEG 6000 binary system with good flow properties and compressibility. The physicochemical characterization at solid and solution state indicated that the enhancing effect of binary systems on dissolution was mainly attributed to the transformation of AC into the amorphous state as well as improvement of solubility of binary systems in the presence of water soluble carriers. The studies revealed that βCD and PEG 6000 can be successfully used to improve the dissolution and possibly bioavailability of poorly water-soluble AC by a solid dispersion approach in a simple and economic manner. The studies also offered development of promising oral solid dosage forms after scaling up the formulation in order to be potential commercial oral dosage form of AC over conventional marketed formulation.

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