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Improvement of dissolution rate of aceclofenac by solid dispersion technique

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ABSTRACT

The present study was carried out with a view to enhance dissolution rate of poorly water-soluble drug aceclofenac (BCS-class II) using Avicel 200 and Sylysia 350 as polymers. Surface solid dispersion (SSD) was prepared by kneading method using different ratios of aceclofenac and polymers. Phase solubility study was conducted to evaluate the effect of polymer on aqueous solubility of aceclofenac. Solid state characterization was evaluated by Scanning electron microscopy (SEM), Fourier transformation infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction study (XRD). *In vitro* dissolution study was performed in phosphate buffer at pH 6.8. Solid state study showed partial interaction between aceclofenac and polymer. *In vitro* dissolution rate of aceclofenac from solid dispersion (SD) was significantly higher compared to pure aceclofenac. The dissolution rate of the drug was affected by nature and amount of polymer used. The dissolution rate of aceclofenac/Avicel 200 solid dispersion (1:5) was higher than that of aceclofenac/Sylysia 350 solid dispersion (1:3). Thus, solid dispersion technique can be successfully used for the improvement of the dissolution profile of aceclofenac.

1. Introduction

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti-inflammatory drug (NSAID) of phenyl acetic acid group, which possesses remarkable anti-inflammatory, analgesic and antipyretic properties [1,2]. Aceclofenac appears to be particularly well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects [3]. Unfortunately, aceclofenac suffers from low aqueous solubility (0.058 μg/ml), leading to poor dissolution and insufficient oral bioavailability. The biopharmaceutical classification system (BSC) divides all drug candidates into four different groups, according to their solubility and permeability [4]. Aceclofenac is an example of BSC class II compound, its oral bioavailability is determined by dissolution rate in the gastrointestinal tract [5,6]. Therefore, the improvement of aceclofenac dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy.

Several techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as size reduction, use of surfactants, salt formation, pH adjustment, complexation, prodrug, nanomization, preparation of liposome and formation of solid dispersion (SD) [7–9]. The latter are defined as the dispersion of one or more active ingredients in an inert carrier in solid state [10,11]. Mechanisms involved include increased wettability, solubilization of drug by carrier at diffusion layer and reduction or absence of aggregation and agglomeration. Moreover, transformation of crystalline drug to amorphous state upon solid dispersion formulation increases the dissolution rate, since no lattice structure has to be broken down for dissolution to take place [12]. Solid dispersion techniques have been extensively used to increase the solubility of a poorly water-soluble drug [13]. Solid dispersion (SD) is a viable and economic method to enhance bioavailability of poorly water-soluble drugs and also it overcomes the limitations of previous approaches [14].

The rationale behind the selected kneading method is that, it is economic, environmentally friendly and avoids thermal degradation of drug, usage of organic solvent and sophisticated equipments [15]. Also solid dispersion powders which are obtained by this method and selected polymers are physico-chemically stable and can be easily formulated in tablet dosage form by direct compression method. Literature survey showed that the surface solid dispersion (SSD) using kneading method and selected polymers (Avicel 200 and Sylysia 350) has not been utilized for the augmentation of aceclofenac dissolution rate and bioavailability [16].

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2. Materials and methods

2.1. Materials

Aceclofenac was obtained as a gift sample from Aarti Pharmaceuticals Ltd, Gujarat, India. Sylysia 350 FCP was a kind gift from Fuji Silysia Chemical Ltd., Mumbai, India. Avicel 200 was purchased from S. D. Fine Chemicals Ltd., Ahmedabad, India. All other ingredients were of analytical or pharmaceutical grade. Deionized double-distilled water was used throughout the study.

2.2. Method

2.2.1. Solubility study

An excess quantity of aceclofenac was placed in 25 ml capacity glass flasks containing 20 ml of different solutions (distilled water, 0.1 N HCl and phosphate buffer at pH 6.8). The samples were sonicated for 10 min at room temperature and capped conical flasks were shaken for 24 h at 37 ± 0.1 °C using orbital shaking incubator. The sealed flask where equilibrated for 24 h at 37 °C in the incubator. The supernatant solution was then passed through a Whatmann Filter Paper (Grade 1) and the amount of the drug dissolved was analyzed spectrophotometrically (UV-1601PC, Shimadzu, Japan) at 276 nm after suitable dilution. This study was also carried out to select a suitable dissolution medium for the *in vitro* drug release studies. All solubility measurements were performed six times.

2.2.2. Phase solubility study

Phase solubility study was performed according to the method described by Higuchi and Connors [17]. An excess amount of aceclofenac was placed in a 25 ml glass flask containing different concentrations of polymers in 20 ml distilled water. Avicel 200 (0.5%, 1%, 1.5%, 2%, 2.5%, 3% and 4% w/v) and Sylysia 350 (0.5%, 1%, 1.5%, 2% and 2.5% w/v) were used as hydrophilic polymers. Flasks were covered with cellophane membrane to avoid solvent loss and then shaken (100 agitations/min) in orbital shaking incubator for 24 h at 37 °C. The sealed flask where equilibrium for 24 h at 37 °C in incubator, 5 ml of supernant was withdrawn and filtered through Whatmann Filter Paper (Grade 1). The filtrates were analyzed using a UV–visible spectrophotometer at 276 nm after suitable dilution. All solubility measurements were performed six times [18].

The ΔG°_{tr} value provides information about whether the treatment is favourable or unfavourable for drug solubilization in an aqueous medium. Negative Gibbs-free energy values indicate improved dissolution [19]. The ΔG°_{tr} values of aceclofenac were calculated using the following equation:

$$\Delta G^{\circ}tr = -2.303RTLog\frac{S_0}{S_S} \quad (1)$$

Where S_0/S_s, is the ratio of the molar solubility of aceclofenac before and after treatment. The value of gas constant (R) is 8.31 J K^{-1} mol^{-1} and T is temperature in degree kelvin.

2.2.3. Preparation of solid dispersions

Solid dispersion was prepared with aceclofenac: polymer in 1:1, 1:2, 1:3, 1:4 and 1:5 weight ratios by kneading method. Accurately weighed quantity of polymer was mixed with sufficient quantity water to obtain a smooth and homogeneous paste, after that weighed quantity of aceclofenac was mixed and kneaded for 30 min [20]. Finally the paste was dried in an oven at 60 °C for 6 h and then passed through sieve #100. Physical mixtures (PM) were prepared by mixing the ingredients in geometric proportion followed by passing the mixture through sieve #100 with minimum abrasion. The samples were stored in a screw-capped glass vial until use.

2.2.4. Solid state characterization

Solid state study was performed for aceclofenac, polymers, selected batch of solid dispersions and their physical mixtures.

2.2.4.1. Infrared (IR) spectroscopy. IR spectroscopy was conducted using an FTIR Spectrophotometer (Spectrum GX-FT-IR, Perkin Elmer, USA). The spectrum was recorded in the range of 4000–400 cm^{-1}. The procedure consisted of dispersing a sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 0.15 cm^{-1} and scan speed was 20 scan/s.

2.2.4.2. Differential scanning calorimetry (DSC). Differential Scanning calorimeter (DSC-PYRIS-1, Phillips, Netherlands) was used to study the thermal behavior of the samples. The experiments were performed in a dry nitrogen atmosphere. The samples were heated at a rate of 10 °C min^{-1} from ambient temperature to the melting point. The calorimeter measuring range was 1 μW to 750 mW with 11% accuracy. Empty aluminum pan was used as a reference.

2.2.4.3. X-ray diffraction (XRD). The X-ray diffraction study was carried out to characterize the physical form of aceclofenac in samples of selected batches. Vacuum grease was applied onto the glass slide to stick the sample. The sample was allowed to spread on the glass slide in approximately 0.5 mm thickness. The slide was then placed vertically at 0° angle in the X-ray diffractometer (X'Pert Model, Phillips, Netherlands) so that the X-ray beam fell on it properly. The results were recorded over a range of 0–90° (2θ) using the Cu-target X-ray tube and Xe-filled detector. The operating conditions were: voltage 40 kV; current 20 mA; scanning speed 1/min; temperature of acquisition: room temperature; detector: scintillation counter detector and sample holder: non-rotating holder.

2.2.4.4. Scanning electron microscopy (SEM). The surface characteristics of samples were studied by scanning electron microscopy (SEM). Double sided carbon tape was affixed on aluminum stubs. The powder sample was sprinkled onto the tape. The aluminum stubs were placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, acceleration voltage: 30.00 kV) XL 30, Philips (Eindhoven, The Netherlands). The particles were observed for surface characteristics.

2.2.5. Dissolution rate studies

Dissolution rate studies were performed in phosphate buffer (pH 6.8) at 37 ± 0.5 °C using USP II rotating paddle apparatus (ELECTROLAB, Mumbai, India) at 50 rpm. Pure aceclofenac, all the batches of SDs and physical mixtures each containing 100 mg of aceclofenac were subjected to dissolution. At predetermined time intervals for 1 h, 5 ml of dissolution medium was withdrawn, filtered through Whatmann Filter Paper (Grade 1) and spectrophotometrically assayed for drug content at 276 nm. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution medium. Each test was performed in triplicate. The dissolution profile was examined and percentage drug dissolved after 5 and 15 min (Q_5 and Q_{15}) was calculated out.

2.2.5.1. Model independent approach

2.2.5.1.1. Dissolution efficiency (DE%). DE% at 5 and 15 min were calculated out for all the batches for comparison according to Eq. (2). The dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time (t), expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad (2)$$

2.2.5.1.2. Mean dissolution time — MDT (min). In order to assess the comparative extent of the dissolution rate enhancement from SDs, mean dissolution time (MDT) was calculated. The dissolution data obtained of all the batches were treated according to Eq. (3), where i is dissolution sample number, n is number of dissolution sample times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of aceclofenac dissolved (mg) between times t_i and t_{i-1}.

$$MDT_{invitro} = \frac{\sum_{i=1}^{n} t_{mid}\Delta M}{\sum_{i=1}^{n} \Delta M} \quad (3)$$

2.2.5.1.3. Similarity factor (f_2) and dissimilarity factor (f_1). A model-independent, mathematical approach proposed by Moore and Flanner for calculating f_1 and f_2 was used for comparison among the dissolution profiles [21]. The f_2 and f_1 is a measure of similarity and dissimilarity factor respectively, between two dissolution profiles and is given by Eqs. (4) and (5) respectively.

$$f_2 = 50 \times log\left\{\left[1 + (1/n)\sum_{j=1}^{n}\left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\} \quad (4)$$

$$f_1 = \frac{\sum_{j=1}^{n}\left|R_j - T_j\right|}{\sum_{j=1}^{n} R_j} \times 100 \quad (5)$$

In which n is the number of withdrawal points, Rj is the percentage dissolved of reference at the time point t, and Tj is the percentage dissolved of test at the time point t.

A value of 100 for f_2 suggests that test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, whereas smaller values imply an increase in dissimilarity. The difference factor (dissimilarity factor f_1) measures the percent error between the two profiles over all time points. The value of f_1 is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

3. Results and discussions

3.1. Solubility study

The solubility of aceclofenac in water, 0.1 N HCl and phosphate buffer (pH 6.8) are shown in Table 1. The solubility of aceclofenac in water at 37 °C ± 1 °C was found to be 0.076 ± 0.0023 mg/ml, which is in agreement with the previous article [22]. The solubility values of aceclofenac in 0.01 N HCl and phosphate buffer (pH 6.8) were observed to be approximately 0.018 ± 0.0011 mg/ml and 6.79 ± 1.615 mg/ml respectively. The pH of solution had a significant effect on the solubility of aceclofenac. The reason for choosing phosphate buffer (pH 6.8) as the dissolution medium is that aceclofenac has a low solubility in water and in acidic media and hence the sink condition is hard to maintain, whereas the solubility of aceclofenac in phosphate buffer (pH 6.8) is 6.79 mg/ml, making it easier to maintain the sink condition.

Table 1
Solubility of aceclofenac in selected media at 37 °C ± 1 °C.

Vehicle	Solubility of aceclofenac (mg/ml)
Distilled water	0.076 ± 0.0023
0.01 N HCl	0.018 ± 0.0011
Phosphate buffer pH 6.8	6.79 ± 1.615

All values are expressed as mean ± SD, $n = 6$.

3.2. Phase solubility study

The influence of Avicel 200 and Sylysia 350 on solubility of aceclofenac in distilled water at 37 °C is presented in Fig. 1. The phase solubility diagram corresponds to A_L-type profiles. The stability constant for Avicel 200 and Sylysia 350 was found to be 51.73 and 92.91 mg ml^{-1} respectively, indicating a possible interaction between drug and polymer. At 4% and 2.5% w/v concentrations of Avicel 200 and Sylysia 350, the solubility of aceclofenac was increased by 3.1 and 4.39 fold respectively. The enhancement in solubility might be due to the hydrophilic nature of polymers and surface adsorption of drug on the polymer.

3.3. Gibbs-free energy (ΔG°_{tr}) study

The values of Gibbs-free energy (ΔG°_{tr}) associated with the aqueous solubility of aceclofenac in the presence of Avicel 200 and Sylysia 350 are presented in Table 2. The ΔG°_{tr} values were negative at the treated concentrations of the polymers, which reflect the spontaneous nature of the aceclofenac solubilization. Also, the values decreased with increasing concentrations of polymer, thereby demonstrating that reaction became more favourable as the concentration of polymer was increased.

3.4. Solid state characterization study

3.4.1. SEM

SEM micrographs of aceclofenac, physical mixtures and solid dispersions at different magnifications are shown in Fig. 2. The pure aceclofenac was characterized by crystals of bigger size and regular shape with an apparently smooth surface. In physical mixtures, aceclofenac crystals adhered on the surface of polymer. In contrast, the particles of solid dispersion of Avicel 200 and Sylysia 350 were fine, porous with rough surface, which might have resulted in the enhanced dissolution rate as compared to pure drug. The reduced crystallinity of aceclofenac in solid dispersion was further confirmed from the results of XRD and DSC studies.

3.4.2. FTIR

The FTIR spectrum of pure aceclofenac and that of the physical mixtures and optimum solid dispersions are shown in Figs. 3 and 4 respectively. The spectrum of aceclofenac showed characteristic bands at 3319.3 cm^{-1} (N–H stretching), 2970.2 and 2935.5 cm^{-1} (O–H stretching), 1716.5 cm^{-1} (C O stretching), 1589.2 cm^{-1} (skeleton vibration of aromatic C C stretching), 1506.3 cm^{-1} (in plane bending for N–H), 1380 cm^{-1} (O–H in plane bending), 1280.6 cm^{-1} (C–N aromatic amine), 944 cm^{-1} (O–H out plane bending) and 746 cm^{-1}(out plane bending for N–H). Avicel 200 showed major

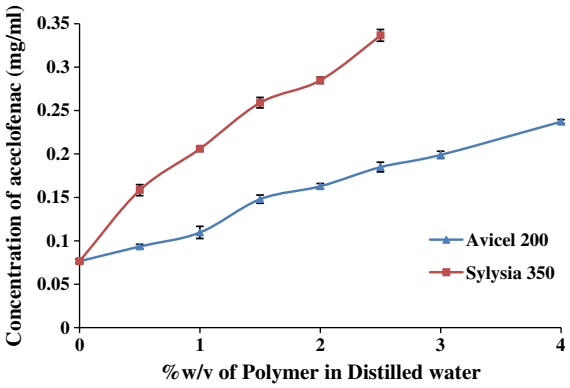

Fig. 1. Phase solubility diagrams for aceclofenac in the presence of Avicel 200 and Sylysia 350 in water at 37 ± 0.5 °C ($n = 6$).

Table 2
Phase solubility and ΔG°_{tr} of aceclofenac at different concentrations of Avicel 200 and Sylysia 350.

Concentration of polymer (% w/v)	Concentration of aceclofenac (mg/ml)	ΔG°_{tr} (J K^{-1} mol^{-1})	Concentration of aceclofenac (mg/ml)	ΔG°_{tr} (J K^{-1} mol^{-1})
	Avicel 200		Sylysia 350	
0.5	0.093 ± 0.002	−515.88	0.158 ± 0.006	−1872.73
1	0.109 ± 0.007	−925.87	0.206 ± 0.003	−2551.81
1.5	0.148 ± 0.004	−1698.41	0.259 ± 0.006	−3142.03
2	0.162 ± 0.003	−1945.32	0.284 ± 0.003	−3386.43
2.5	0.185 ± 0.005	−2273	0.336 ± 0.006	−3816.89
3	0.199 ± 0.004	−2462.44	–	–
4	0.237 ± 0.002	−2915.03	–	–
Stability constant K (ml^{-1} mg)	51.73		92.91	
R^2	0.989		0.977	
Type of curve	A_L		A_L	

All values are expressed as mean ± SEM, $n = 6$.

peaks at 3409 cm^{-1}(O–H stretching) and Sylysia 350 at 3409 cm^{-1} (O–H stretching).

In aceclofenac/Avicel 200 physical mixture, characteristic peaks of aceclofenac showed O–H stretching at 2929 cm^{-1} and N–H stretching at 3425.49 cm^{-1}. While with the same ratio in solid dispersions, N–H stretching peak of aceclofenac shifted towards lower frequency 3424 cm^{-1} and O–H stretching at 2929 cm^{-1} disappeared. These results suggest hydrogen bonding interaction between aceclofenac and Avicel 200. The FTIR spectra of the physical mixture of aceclofenac/Sylysia 350 showed a distinct peak of aceclofenac at 2925 cm^{-1} for O–H stretching, which is shifted to lower frequencies 2922 cm^{-1} in its kneaded particles with the same ratio. The reason for this observation might be interpreted as a consequence of hydrogen bonding between –OH of –COOH of aceclofenac and oxygen molecule of SiO_2.

3.4.3. Interpretation of DSC

The DSC curves obtained for pure aceclofenac, solid dispersions and their corresponding physical mixtures were displayed in Fig. 5. Aceclofenac showed a sharp endotherm at 153.7 °C corresponding to its melting point. There was a noticeable reduction in endothermic peak height and heat of fusion, in physical mixtures and in solid dispersions as compared to pure aceclofenac (Table 3). These suggest that the physical state of aceclofenac changed from crystalline to amorphous. It has been known that transforming the physical state of the drug to amorphous or partially amorphous state leads to a high-energy state and high disorder, resulting in enhanced solubility and faster dissolution.

3.4.4. XRD

The XRD pattern of pure aceclofenac and that of polymers, solid dispersions and their physical mixtures are shown in Figs. 6 and 7 respectively. The XRD scan of pure aceclofenac showed intense peaks of crystallinity; whereas the XRD pattern of prepared solid dispersions exhibited a reduction in both number and intensity of peaks compared to the plain aceclofenac indicating the decrease in crystallinity or partial amorphization of the drug in its kneaded form [23].

The relative degree of crystallinity (RDC) was determined by comparing the representative peak height at 25.9 Pos. [°2Th.] in the diffraction patterns of aceclofenac with those of solid dispersion. The relationship used for the calculation of crystallinity was (RDC) = I_{SD}/I_{drug} where I_{SD} is the peak height of SD under investigation and I_{drug} is the peak height at the same angle for the aceclofenac with the highest intensity. The RDC for all samples are shown in Table 4. The order of

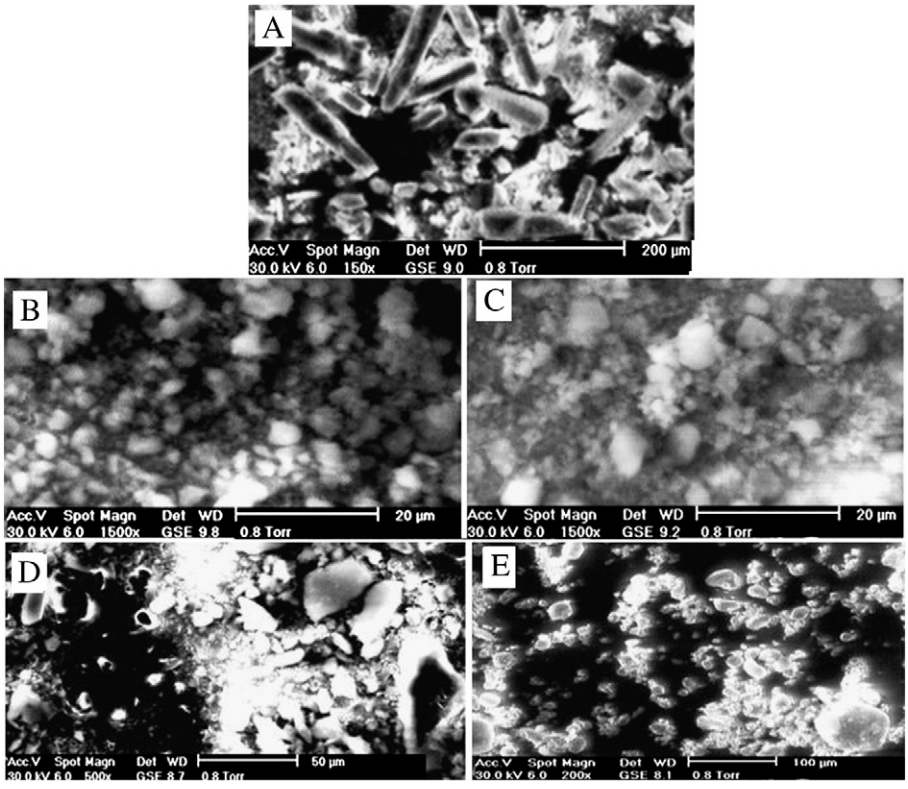

Fig. 2. SEM photomicrographs. A = pure aceclofenac, B = Sylysia 350 PM (1:3), C = Sylysia 350 SD (1:3), D = Avicel 200 PM (1:5), and E = Avicel 200 SD (1:5).

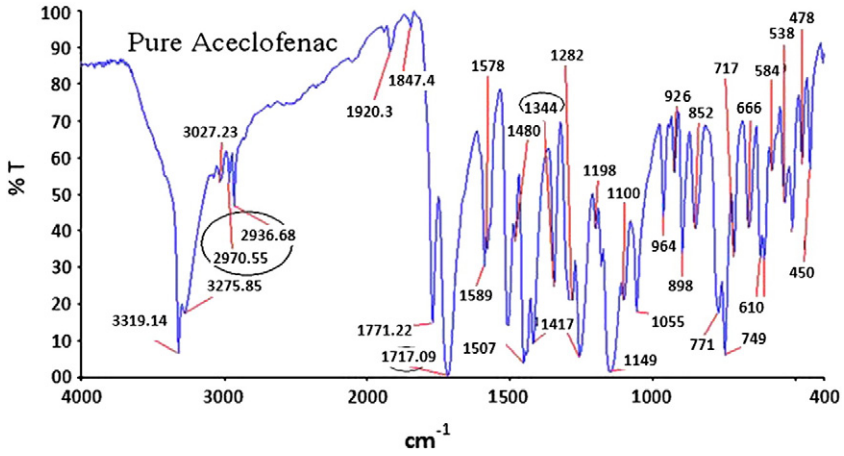

Fig. 3. FTIR spectra of pure aceclofenac.

reduction in the crystallinity is as follows: Avicel SD Kneading>Avicel PM (1:5)>Sylysia 350 Kneading (1:3) > Sylysia 350 PM (1:3).

3.5. In vitro dissolution study

3.5.1. In vitro dissolution study of binary solid dispersion prepared using Avicel 200

The results of *in vitro* drug release studies in phosphate buffer at pH 6.8 for 1 h are depicted in Fig. 8. The pure drug showed a release of 66.37% at the end of 1 h, while SD showed 95–99% drug release in 1 h. The percent drug dissolution increased with an increase in the ratio. Physical mixtures (PM) also showed an improved dissolution rate to a significant extent as compared with pure aceclofenac.

Table 5 summarizes the percentage drug dissolved in 5 min (Q_5) and 15 min (Q_{15}), dissolution efficiency at 5 min (DE_{15}) and 15 min (DE_{15}), MDT (mean dissolution time), f_1 and f_2 for aceclofenac/Avicel 200 SD. The pure drug showed 26% (Q_5) and 49% (Q_{15}) drug releases. In SD, Q_5, Q_{15} and DE% increases with an increase in ratio. The highest dissolution rate was exhibited by aceclofenac/Avicel 200 SD (1:5), i.e. $Q_5 = 96\%$ $Q_{15} = 98\%$ drug release. The dissolution rate was 3.64 times higher than the untreated drug at 1:5 ratio. Similarity (f_2) and dissimilarity factor (f_1) were calculated to compare the dissolution profiles between untreated aceclofenac and SD batches. For the dissolution profile to be dissimilar, f_2 should be between 0 and 50. Table 4 reveals that the f_2 values were smaller (18.14–15.72) and is ratio dependent. This finding shows that there was a significant variation between the dissolution of SDs and aceclofenac in phosphate

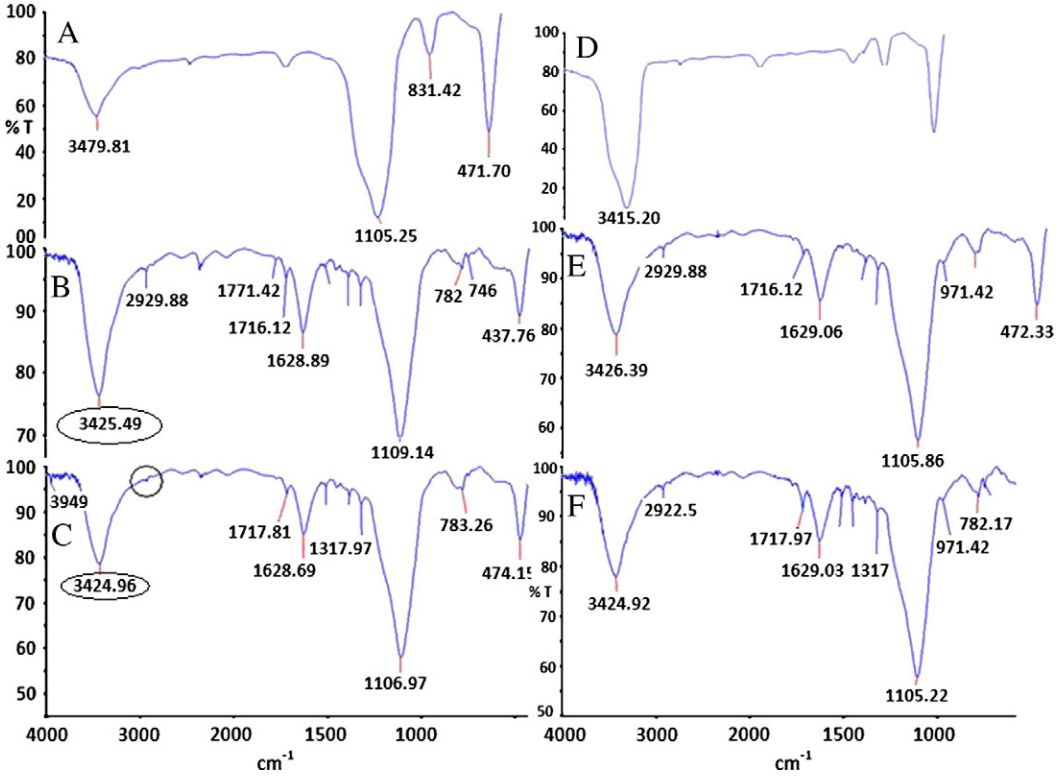

Fig. 4. FTIR spectra. A = Avicel 200, B = Avicel 200 PM (1:5), C = Avicel 200 SD (1:5), D = Sylysia 350, E = Sylysia 350 PM (1:3), and F = Sylysia 350 SD (1:3).

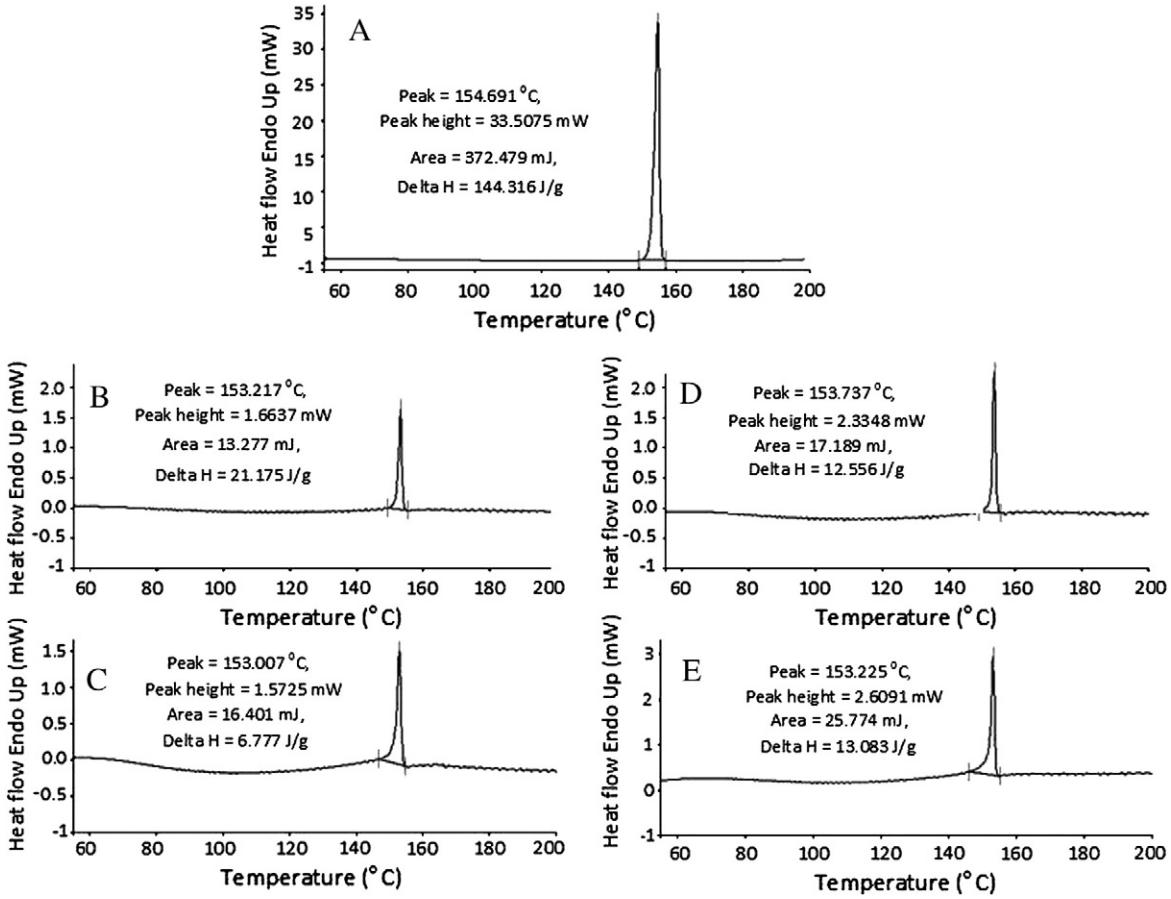

Fig. 5. DSC thermogram. A = pure aceclofenac, B = Avicel 200 PM (1:5), C = Avicel 200 SD (1:5), D = Sylysia 350 PM (1:3), and E = Sylysia 350 SD (1:3).

buffer with pH 6.8. The dissimilarity is also confirmed by high f_1 value, i.e. >15.

The results for MDT are shown in Table 5. The MDT for aceclofenac profile was 12.96, while minimum MDT was seen in the case of aceclofenac/Avicel 200 SD (1:5). This result endorses the fulfillment of the objective of the dissolution enhancement of aceclofenac. The ANOVA (Tukey) was performed on the dissolution data parameter (Q_5 and Q_{15}). The P values were less than 0.01, indicating a high significant difference between the dissolution profiles of pure aceclofenac and aceclofenac/Avicel 200 SD (1:5).

The enhancement in the dissolution of aceclofenac from solid dispersion can be ascribed due to several factors, like lack of crystallinity, particle size reduction, reduction in interfacial tension between hydrophobic drug and dissolution medium, increased wettability and effective surface adsorption of drug on hydrophilic carrier (i.e. surface solid dispersion is formed). Avicel 200 (size of particle-180 um) has a large surface area and can adsorb a large amount of drug. During dissolution studies, the immediate sinking of the particles was noted, whereas the untreated drug floated on the surface of the dissolution medium for a longer time.

Table 3
Interpretation of DSC showing peak height, peak area and heat of fusion.

SD system	Peak point °C	Peak height (mW)	Peak area (mJ)	Heat of fusion ΔH_F (J/g)
Avicel SD (1:5)	153.00	1.572	16.40	6.77
Avicel PM (1:5)	153.21	1.663	13.27	21.15
Sylysia 350 PM (1:3)	153.73	2.334	17.18	12.55
Sylysia 350 SD (1:3)	153.22	2.609	25.77	13.08

3.5.2. In vitro dissolution study of solid dispersion prepared using Sylysia 350

The dissolution profiles of aceclofenac and aceclofenac/Sylysia 350 SD are shown in Fig. 9. SD showed an improved dissolution when compared with the pure drug. The reasons for the enhancement in drug dissolution could be the dispersion of drug in pores of Sylysia 350 and increased wettability. The dissolution rate of the drug increased up to the ratio of 1:2, but at higher ratios it decreased. This might be due to the firm adsorption of the drug on Sylysia 350, which hinders the dissolution of the drug. A very large surface area (3.5–4.3 um) of Sylysia 350 (SiO_2) can be responsible for the firm adsorption of the drug. Physical mixtures (PM) also showed an improved dissolution rate. As indicative from the dissolution data of physical mixtures, even

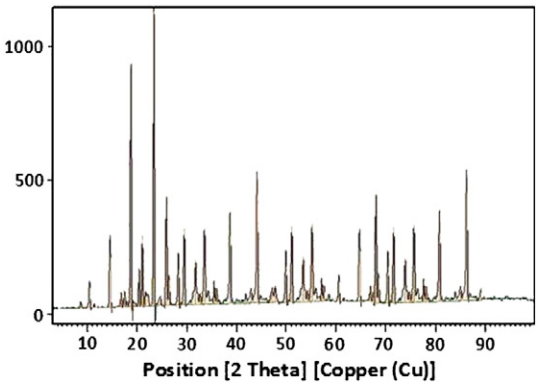

Fig. 6. X-ray diffraction pattern of aceclofenac.

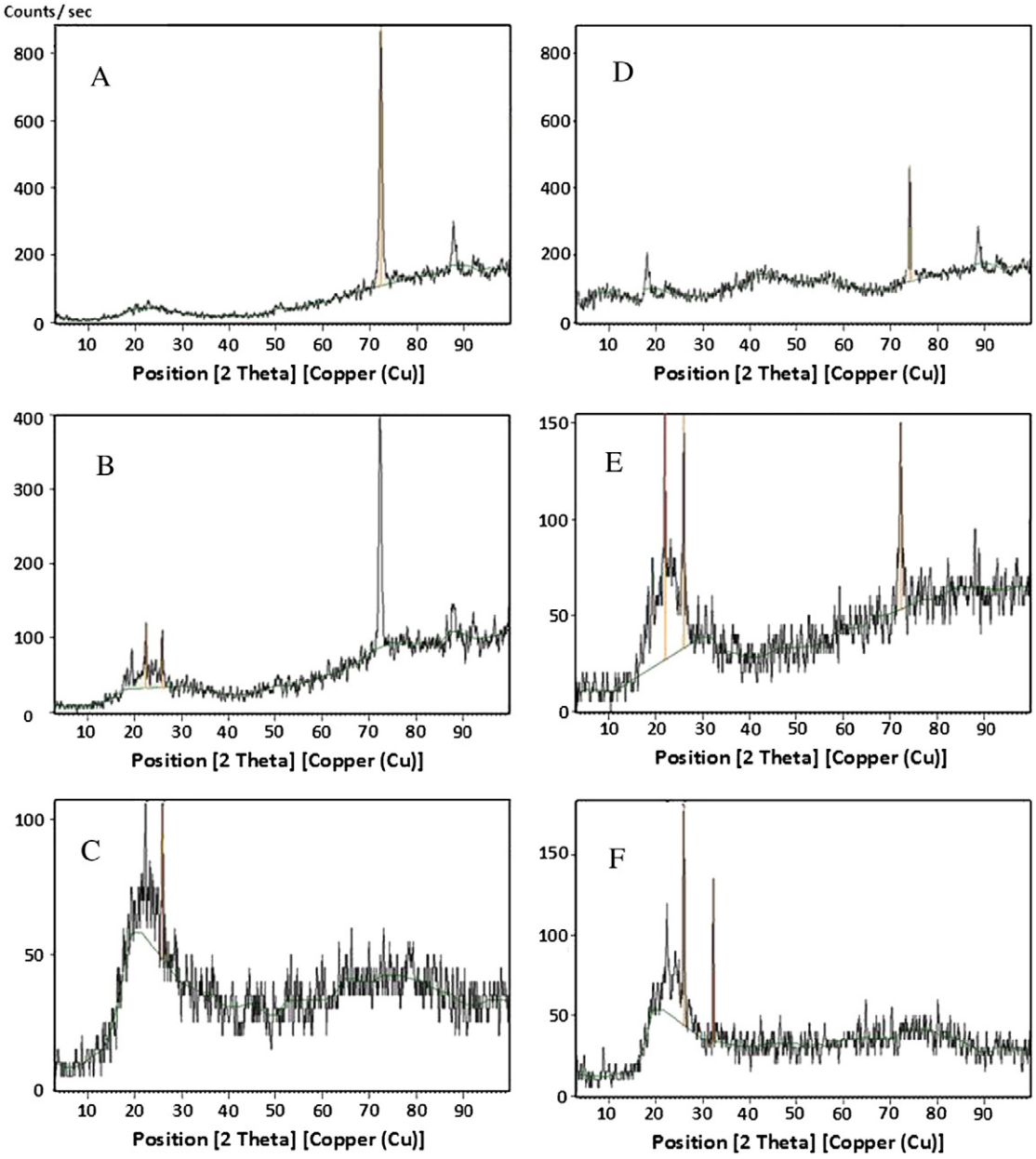

Fig. 7. X-ray diffraction pattern. A = Avicel 200, B = Avicel 200 PM (1:5), C = Avicel 200 SD (1:5), D = Sylysia 350, E = Sylysia 350 PM (1:3), and F = Sylysia 350 SD (1:3).

dry mixing of a drug with Sylysia 350 results in greater surface adsorption and wetting which result in the improvement in dissolution profile.

Table 6 summarizes the dissolution parameters for aceclofenac/Sylysia 350 SD. The highest dissolution rate was exhibited by aceclofenac/Sylysia 350 SD (1:3), i.e. $Q_5 = 83.1\%$ and $Q_{15} = 87.63\%$. Also we observed that, f_2 value is lower than 50 and as the ratio is increasing the value moves to the lower side from 41 to 22, suggesting that there is a significant variation between the dissolution rates of aceclofenac/Sylysia 350 SDs and pure aceclofenac. The same is confirmed from high dissimilarity value f_1 (from 74.25 to 63.88), i.e. >15. The maximum dissimilarity was found with 1:2 ratio. MDT results also confirm the fulfillment of the objective for dissolution

Table 4
Results of relative degree of crystallinity (RDC) at 25.9 Pos. [°2Th.]

Type of system	Height [cps]	RDC
Avicel SD (1:5)	57.52	0.052
Avicel PM (1:5)	77.59	0.070
Sylysia 350 SD (1:3)	122.41	0.111
Sylysia 350 PM (1:3)	135.01	0.122

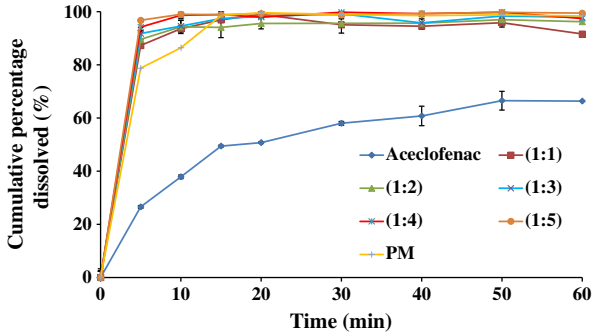

Fig. 8. The dissolution profiles of aceclofenac, physical mixture (PM of 1:5 ratio) and solid dispersion (SD) at different aceclofenac/Avicel ratios. Each point represents the mean ± S.D. ($n = 3$).

Table 5
Summary of dissolution parameters for solid dispersions prepared using Avicel 200.

Parameters	Q_5	Q_{15}	DE_5	DE_{15}	MDT	f_1	f_2
Drug	26.58	49.44	13.29	29.73	12.96	–	–
PM (1:5)	78.73	98.57	39.36	71.48	4.82	82.04	18.14[a]
1:1	87.27	96.91	43.63	76.44	6.9	81.01	17.9
1:2	89.59	94.13	44.79	76.99	3.99	82.07	17.73
1:3	91.79	97.41	45.89	78.35	5.58	85.64	16.85
1:4	94.22	98.96	47.11	80.78	4.82	88.79	16.07
1:5	96.77[b]	98.86[b]	48.38	81.74	3.29	89.99	15.72

All values are expressed as mean ± SEM, $n = 6$.
[a] Significant difference.
[b] High significant difference.

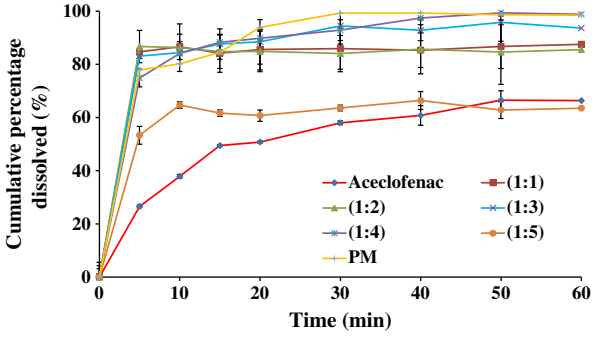

Fig. 9. The dissolution profiles of aceclofenac, physical mixture (PM of 1:3 ratio) and solid dispersion (SD) at different aceclofenac/Sylysia 350 ratios. Each point represents the mean ± S.D. ($n = 3$).

Table 6
Summary of dissolution parameters for solid dispersions prepared using Sylysia 350.

Parameters	Q_5	Q_{15}	DE_5	DE_{15}	MDT	f_1	f_2
Drug	26.58	49.44	13.29	29.73	12.96	–	–
PM (1:3)	77.86	84.53	38.93	66.77	6.02	75.85	19.92[a]
1:1	84.72	84.16	42.36	71.13	4.45	64.85	22.14
1:2	86.69	84.75	43.34	71.78	4.46	63.88	22.19
1:3	83.10[b]	87.63[b]	41.55	70.43	7.2	72.95	20.43
1:4	74.88	88.29	37.44	67.71	6.87	74.25	20.42
1:5	53.33	61.65	26.66	49.61	8.16	22.44	41.39

All values are expressed as mean ± SEM, $n = 6$.
[a] Significant difference.
[b] High significant difference.

enhancement of aceclofenac. The ANOVA (Tukey) was performed on dissolution data parameters (Q_5 and Q_{15}). The P values were less than 0.01, indicating a high significant difference between the dissolution rates of pure aceclofenac and aceclofenac/Sylysia 350 SD (1:3).

4. Conclusion

The present study demonstrated a successful and simple method to prepare aceclofenac solid dispersion to enhance its aqueous solubility and dissolution rate. Nature and the amount of the carrier used, played an important role in the enhancement of dissolution rate. The solid state studies showed partial interaction of aceclofenac with polymer and the decrease in crystallinity of aceclofenac. The increase in dissolution rate would provide rapid onset of action after the drug is taken orally. The dissolution rate of the SD prepared using Avicel 200 (1:5) was higher than that of SD prepared using Sylysia 350 (1:3).

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