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Preparation, Characterization and In Vitro Evaluation of Aceclofenac Solid Dispersions

Kamal Dua*[1], Kavita Pabreja[2], Ramana MV[2]

[1]Department of Pharmaceutical Technology, Faculty of Medicine & Health Sciences, International Medical University, Bukit Jalil, Kuala Lumpur, Malaysia-57000
[2]Vellore Institute of Technology, Vellore, Tamilnadu, India
kamalpharmacist@gmail.com, kamal_dua@imu.edu.my

ABSTRACS

The objective of the present investigation was to study the effect of various water soluble carriers like urea, mannitol, PVP and PVP/VA-64 on in vitro dissolution of aceclofenac from solid dispersions. Aceclofenac binary solid dispersions (SD) with different drug loadings were prepared using the melting or fusion method. In vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. Solid dispersion of aceclofenac with all four carriers (urea, mannitol, PVP and PVP/VA-64) showed considerable increase in the dissolution rate in comparison with physical mixture and pure drug in 0.1 N HCl, pH1.2 and phosphate buffer, pH, 7.4. Solid dispersions containing PVP showed maximum dissolution rate in comparison to formulation containing urea, mannitol and PVP/VA-64. Amorphous nature of the drug in solid dispersion was confirmed by scanning electron microscopy and a decrease in enthalpy of drug melting in solid dispersion compared to the pure drug. FT-IR spectroscopy and differential scanning calorimetry studies indicated no interaction between aceclofenac and carriers in solid dispersions in solid state. Dissolution enhancement was attributed to decreased crystallinity of the drug and to the wetting, eutectic formation and solubilizing effect of the carrier from the solid dispersions of aceclofenac. In conclusion, dissolution of aceclofenac can be enhanced by the use of various hydrophilic carriers like urea, mannitol, PVP and PVP/VA-64.

KEYWORDS: aceclofenac, urea, mannitol, PVP, PVP/VA-64.

INTRODUCCIÓN

Up to 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs ([1]). Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract ([2–4]). The dissolution characteristics of poorly soluble drugs can be enhanced by several methods ([5–7]). Solid dispersion is one of the effective and widely used techniques for dissolution enhancement ([8]). The two basic procedures used to prepare solid dispersions are the melting or fusion ([9]) and solvent evaporation ([10]) techniques. The increase in dissolution rate for solid dispersions can be attributed to a number of factors ([11]), which include reduction in particle size, absence of aggregation or agglomeration of fine crystallites of the drug, possible solubilization effect of the polymer, excellent wettability and dispersibility of the drug from solid dispersion and partial conversion of the drug into amorphous form.

Aceclofenac (AF), 2-[(2,6-dichlorophenyl) amino] benzene acetic acid carboxymethyl

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ester is a new generational non-steroidal anti-inflammatory drug showing effective anti-inflammatory and analgesic properties and a good tolerability profile in a variety of painful conditions like ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Aceclofenac is very slightly soluble in water ([12]) and therefore an attempt has been made to prepare solid dispersions of aceclofenac using various hydrophillic carriers like urea, mannitol, polyvinylpyrrolidone (PVP) and polyvinyl pyrrolidone vinyl acetate-64 (PVP/VA-64) with an aim to improve its extent and rate of dissolution. Urea, mannitol, PVP and PVP/VA-64 are used for the preparation of solid dispersions. A particular advantage of such carriers for the formation of solid dispersions is having good solubility in many organic solvents. Additional attractive features of such carriers include improved compound wettability ([13, 14, 15]. Therefore, in the present study, urea, mannitol, PVP and PVP/VA-64 was chosen as suitable polymers for the preparation of solid dispersions.

EXPERIMENTAL

Materials

Aceclofenac was obtained as a gift sample from Ipca Laboratories, Mumbai, India. PVP/VA-64 were purchased from BASF, Ludwigshafen, Germany. Polyvinylpyrrolidone (PVP), mannitol, urea were obtained from Merck (Germany).

Preparation of Solid Dispersions of Aceclofenac

Solid dispersions of AF were prepared with urea, mannitol, PVP and PVP/VA-64 in different ratios such as 1:0.5, 1:1 and 1:2 by weight basis using melting or fusion method. Weighed quantities of carrier (urea, mannitol, PVP and PVP/VA-64) and AF were thoroughly mixed and melted on hot plate with constant stirring to obtain a uniform melt. The melt was shock cooled on an ice cooled stainless steel plate. The solid mass was removed from the stainless steel plate, powdered and kept in a desiccator for two days. The powder was passed through sieve #100 and stored in closed airtight container ([16]).

Preparation of Physical mixtures:

The physical mixtures were prepared by mixing pre-weighed amounts of mesh. No 100-sieve fractions of aceclofenac and carriers in the same proportions as used in solid dispersions ([16]).

Characterisation

Percent Yield

The percent yield of SDs was calculated on the basis of dry weight (drug and carriers) and the final weight of SDs obtained ([17, 18]).

Average Particle Size

The SDs were dispersed in liquid paraffin and mounted on slides. Particle size of 200 particles was measured using calibrated stage micrometer and ocular micrometer. From the data the average particle size was calculated ([19]).

Wettability Study

Powdered mixture of SDs (300 mg) was placed in a sintered glass funnel with 33 mm internal diameter. The funnel was plunged into beaker containing water such that the surface of water in the beaker was at the same level as the powder or granules in the funnel. Methylene blue powder (10 mg) was layered uniformly on the surface of the powder or granules in the funnel. The time required for wetting of methylene blue powder was measured. The mean of three observations was used for drawing the conclusions ([20]).

Hygroscopic Studies

One hundred mg each of SDs (w_1) was placed on a watch glass and exposed to ambient atmospheric conditions (70±5% RH, 30±2°C) and saturation humidity conditions (99±1% RH, 30±2°C) for 2 days. The substance was weighed again (w_2). The gain in the weight was determined and the percentage moisture gained was calculated. ([21]).

Drug Content

The SDs (100mg) were accurately weighed and dissolved separately in 100ml of 20%v/v acetic acid. The solution was suitably diluted and the absorbance was measured at 275 nm . Drug content was calculated using the regression equation ([17]).

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was carried out for 1:1 SDs. The surface morphology of the selected binary systems was studied using a Phillips 1500, scanning electron microscope. The powders were previously fixed on a brass stub using double sided adhesive tape and then were made electrically conductive by coating in vaccum, with a thin layer of gold (approximately 300 Å), for 30s and at 30 W. The micrographs were taken at an excitation voltage of 15 KV and a magnification of 750 or 5000 X ([22, 23]).

Fourier Transformed Infrared Spectroscopic Studies

FTIR spectral studies were carried out for pure drug, freshly prepared and six months old 1:1 SDs and individual substances to check the compatibility between drug and carriers using Shimadzu FTIR-8400S Fourier transform infrared spectrophotometer.

Interaction between the components, if any, was indicated by either producing additional peaks or absence of the characteristic peaks corresponding to the drug and carrier ([24]).

Differential Scanning Calorimetric Studies

DSC studies were carried out for pure drug, freshly prepared and six months old 1:1 SDs, CPs and molecular inclusion complexes. All dynamic DSC studies were carried out on a calibrated Shimadzu DSC-50 Thermal Analyzer. Calorimetric measurements were made with empty cell (high purity alpha alumina discs as reference). The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/minute. Interaction between the drug and polymer, if any, was indicated either by a shift in the peak or presence of additional peaks at temperatures other than those corresponding to the drug and carrier ([22, 25]).

***In Vitro* Release Studies**

In vitro release studies were carried out using basket type USP XXII dissolution test apparatus ([26]). Release studies were carried separately for pure drug, physical mixtures, SDs for 2h in 900 ml of 0.1 N hydrochloric acid solution, pH 1.2 and phosphate buffer, pH 7.4 separately, with a stirring speed of 50 rpm at a temperature of 37±0.5 °C. Five ml aliquots of dissolution medium were withdrawn at an interval of 5 minutes for first 15 minutes and then 15 minutes intervals, for rest of the two-hour study Absorbance of the suitably diluted solutions was measured at 275 nm The drug content was calculated using regression equation. The dissolution experiments were conducted in triplicate ([27, 28]).

Kinetic Analysis of Drug Release

The dissolution profiles of all the solid dispersions were subjected to the kinetic analysis to establish the drug-release mechanism. The release data were fitted to zero order, first order, matrix (Higuchi model), and Hixson-Crowell equations to ascertain the kinetic modeling of drug release ([29]).

RESULTS AND DISCUSSION

All the SDs prepared were found to be fine and free flowing powders. Percentage yield ranged from 84.2 to 96.5% (Table 1). Low coefficient of variance (CV) values (< 1.0 %) in percentage yield indicates the reproducibility of the technique employed for the preparation of SDs. Average particle size was found to be within the range of 51.11µm to 73.2µm (Table 1). This narrow range of particle size was satisfactory from the point of improving the aqueous solubility.

Table 1: Physical characteristics of solid dispersions of aceclofenac.

Carrier	*Product*	*Drug : carrier*	*Percent yield*	*Particle size range (μm)*	*Average particle size (μm)*	*Drug content (mg/100 mg)*	*Percent drug content*	*Wetting Time (sec)*
Urea	***AF-U-SD3***	***1 : 2***	87.3 (0.76)	6.1-154.3	73.2 (0.94)	31.5 (33)*	95.4 (0.96)	17.11 (0.21)
	AF -U-SD2	***1 : 1***	84.2 (0.96)	5.5-152.1	56.68 (0.91)	48.5 (50)*	97.0 (0.85)	19.23 (0.17)
	AF -U-SD1	***1 : 0.5***	96.5 (0.91)	6.3-151.5	64.15 (0.93)	63.6 (66.7)*	95.3 (0.81)	21.41 (0.19)
Mannitol	***AF -M-SD3***	***1 : 2***	89.4 (0.81)	7.2-134.2	59.15 (0.77)	30.0 (33)*	90.9 (0.96)	14.13 (0.23)
	AF -M-SD2	***1 : 1***	90.5 (0.94)	6.9-152.3	65.16 (0.81)	44.8 (50.0)*	89.6 (0.93)	17.32 (0.27)
	AF -M-SD1	***1 : 0.5***	86.5 (0.74)	7.1-142.8	62.13 (0.82)	65.2 (66.7)*	97.7 (0.95)	18.64 (0.23)
PVP	***AF-PVP-SD3***	***1 : 2***	89.4 (0.82)	7.5-153.2	61.12 (0.85)	31.6 (33)*	95.7 (0.76)	23.12 (0.15)
	AF-PVP-SD2	***1 : 1***	90.5 (0.96)	6.9-143.2	60.54 (0.98)	48.4 (50)*	96.8 (0.85)	22.16 (0.18)
	AF-PVP-SD1	***1 : 0.5***	94.3 (0.93)	7.1-143.6	53.21 (0.99)	65.9 (66.7)*	98.8 (0.87)	24.21 (0.28)
PVP/VA-64	***AF-PVP/VA-SD3***	***1 : 2***	94.1 (0.87)	6.9-150.2	67.43 (0.79)	31.9 (33)*	96.6 (0.95)	20.13 (0.21)
	AF-PVP/VA-SD2	***1 : 1***	89.5 (0.81)	7.0-148.4	63.21 (0.83)	49.3 (50)*	98.6 (0.91)	19.11 (0.15)
	AF-PVP/VA-SD1	***1 : 0.5***	92.1 (0.91)	6.3-155.7	51.11 (0.94)	63.5 (66.7)*	95.2 (0.88)	18.32 (0.12)

AF: aceclofenac; M: mannitol; PVP: polyvinyl pyrrolidone; PVP/VA-64: polyvinyl pyrrolidone vinyl acetate; SD: solid dispersion; U: urea. Values in parenthesis indicates the standard deviation

(n=3) and values given in the parenthesis marked with * indicates theoretical values of drug content.

Table 2: Determination of hygroscopicity of solid dispersions of aceclofenac.

Formulation code	*Drug: Carrier*	*Initial weight (mg)*	*Ambient conditions (70 ± 5% RH, 30 ± 2 ℃)*		*Saturation humidity conditions (99± 2% RH, 30 ± 2 ℃)*	
			Final weight (mg)	***Percent weight gained (mg)***	***Final weight (mg)***	***Percent weight gained (mg)***
AF	***Pure drug***	100	100.7	0.7 (0.11)	101.3	1.3 (0.34)
AF -U-SD3	***1 : 2***	100	119.3	19.3 (0.07)	163.6	63.6 (0.32)
AF -U-SD2	***1 : 1***	100	108.3	8.3 (0.13)	140.0	40.0 (0.29)
AF -U-SD1	***1 : 0.5***	100	107.5	7.5 (0.09)	120.5	20.5 (0.33)
AF -M-SD3	***1 : 2***	100	107.3	7.3 (0.11)	112.4	12.4 (0.31)
AF -M-SD2	***1 : 1***	100	102.1	2.1 (0.12)	109.1	9.1 (0.29)
AF -M-SD1	***1 : 0.5***	100	100.5	0.5 (0.05)	102.0	2.0 (0.31)
AF-PVP-SD3	***1 : 2***	100	112.2	12.2 (0.07)	145.4	45.4 (0.34)
AF-PVP-SD 2	***1 : 1***	100	109.6	9.6 (0.08)	139.7	39.7 (0.30)
AF-PVP-SD1	***1 : 0.5***	100	107.5	7.5 (0.13)	132.3	32.3 (0.28)
AF-PVP/VA-SD3	***1 : 2***	100	107.3	7.3 (0.13)	133.2	33.2 (0.32)
AF-PVP/VA-SD2	***1 : 1***	100	105.2	5.2 (0.17)	127.1	27.1 (0.29)
AF-PVP/VA-SD1	***1 : 0.5***	100	103.7	3.7 (0.05)	121.2	21.2 (0.31)

AF: aceclofenac; M: mannitol; PVP: polyvinyl pyrrolidone; PVP/VA-64: polyvinyl pyrrolidone vinyl acetate; SD: solid dispersion; U: urea. Values in parenthesis indicates the standard deviation (n=3)

The wetting time ranged from 14.13 to 24.21 sec .The maximum wetting time was observed with AF-PVP-SD1 (24.21 sec). The percentage entrapment of the drug in SDs was found to be approximately nearer to the theoretical values. Low value for CV (<1.0) indicates uniformity of drug content in the product. The obtained results implied that the drug remained

stable during preparation.

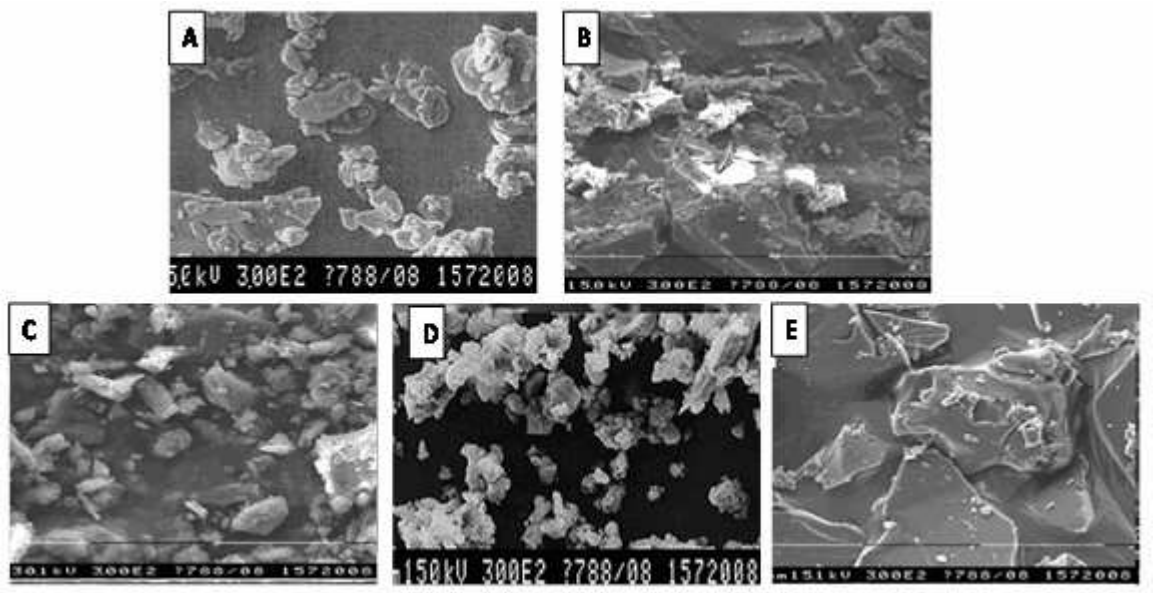
Hygroscopic Studies

The hygroscopicity of binary system containing AF-PVP was found to be more in comparison with other carriers under ambient as well as saturation humidity conditions. Similar results were reported by Sethia and Squilante ([30]) with carbamazepine and Martinez-ohariz *et al.* ([31]) with diflunisal. At saturation humidity conditions the weight gain was higher, compared to ambient conditions. SDs containing urea and PVP absorbed more moisture compared to SDs containing mannitol and PVP/VA-64.

Scanning Electron Microscopy

AF appeared as irregular shaped crystals and β-CD has shown a parallelogram shape. The original morphology of all other binary systems (SDs, CPs and molecular inclusion complexes) had disappeared and it was not possible to differentiate between the two components. All the binary systems appeared as agglomerates exhibiting the presence of a homogeneous solid phase of amorphous nature. Existence of a single phase is also responsible for the enhanced drug dissolution in comparison to pure AF (Figure 1).

Figure 1 : Scanning electron photomicrographs of aceclofenac (A); aceclofenac-urea (1:2) solid dispersion (B); aceclofenac-mannitol (1:2) solid dispersion (C); aceclofenac-PVP (1:2) solid dispersion (D); aceclofenac-PVP/VA-64 (1:2) solid dispersion (E)



Fourier Transformed Infrared Spectroscopic Studies

All the characteristic bands of AF were observed in the binary mixtures are shown in Table 3. Broadening of bands was observed to a large extent. The characteristic bands of urea (1150, 1455 and 1680 cm^{-1}), mannitol (3300, 1421, 1083 and 1019 cm^{-1}), PVP (2970, 1452, 1417,

1716 and 1270 cm^{-1}), PVP/VA-64 (2970, 1452, 1417, 1716 and 1270 cm^{-1}) and β-CD (3305, 1420, 1460 and 1083 cm^{-1}) were also observed. The FTIR spectra of physical mixtures, solid dispersions, coprecipitates and β-CD complexes indicate reduction in the intensity of several peaks like O-H (s) and C-H (s). The absence of any significant change in the IR spectral pattern in the formulations containing the drug and carriers indicated the absence of interaction between the drug and carriers employed for the solubility enhancement (Figure 2, 3, 4 and 5).

Table 3: FTIR characteristic bands of aceclofenac in solid dispersions.

Assignment of bands	*Absorption band for aceclofenac cm^{-1}*	*Absorption band for aceclofenac in urea, cm^{-1}*	*Absorption band for aceclofenac in mannitol, cm^{-1}*	*Absorption band for aceclofenac in PVP , cm^{-1}*	*Absorption band for aceclofenac in PVP/VA-64, cm^{-1}*
N-H (s)	3340	3330	3335	3319.26	3319.26
O-H (s)	3100	3120	3100	3070.46	3070.46
Ar C-H (s)	3050	3045	3060	3028.03	3028.03
C=O (s)	1730	1710	1722	1716.53	1716.53
Aromatic ring	1580	1530	1520	1580	1582
C-O-C (s)	1250	1262	1210	1255.57	1255.57
C-Cl (s)	750	730	760	750.26	750.26

Figure 2: FTIR spectra of aceclofenac, physical mixtures and different solid dispersion systems with urea. (A) AF; (B) AF-U (PM) 1:0.5; (C) AF-U (SD) 1:0.5; (D) AF-U (PM) 1:1; (E) AF-U (SD) 1:1; (F) AF-U (PM) 1:2; (G) AF-U (PM) 1:2 (SD). AF=aceclofenac; PM= physical mixture; SD= solid dispersion; U=urea.

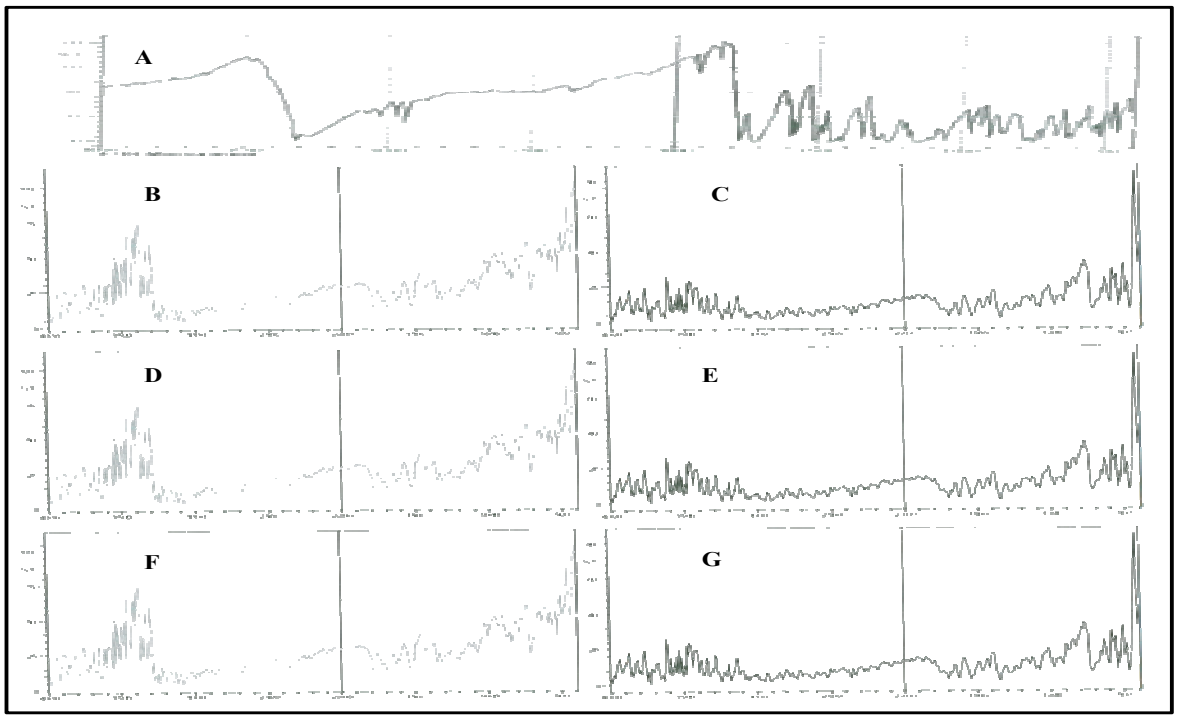


Figure 3: FTIR spectra of aceclofenac, physical mixtures and different solid dispersion systems with mannitol. (A) AF-M (PM) 1:0.5; (B) AF-M (SD) 1:0.5; (C) AF-M (PM) 1:1; (D) AF-M (SD) 1:1; (E) AF-M (PM) 1:2; (F)AF-M (PM) 1:2 (SD). AF=aceclofenac; M= mannitol; PM= physical mixture; SD= solid dispersion.

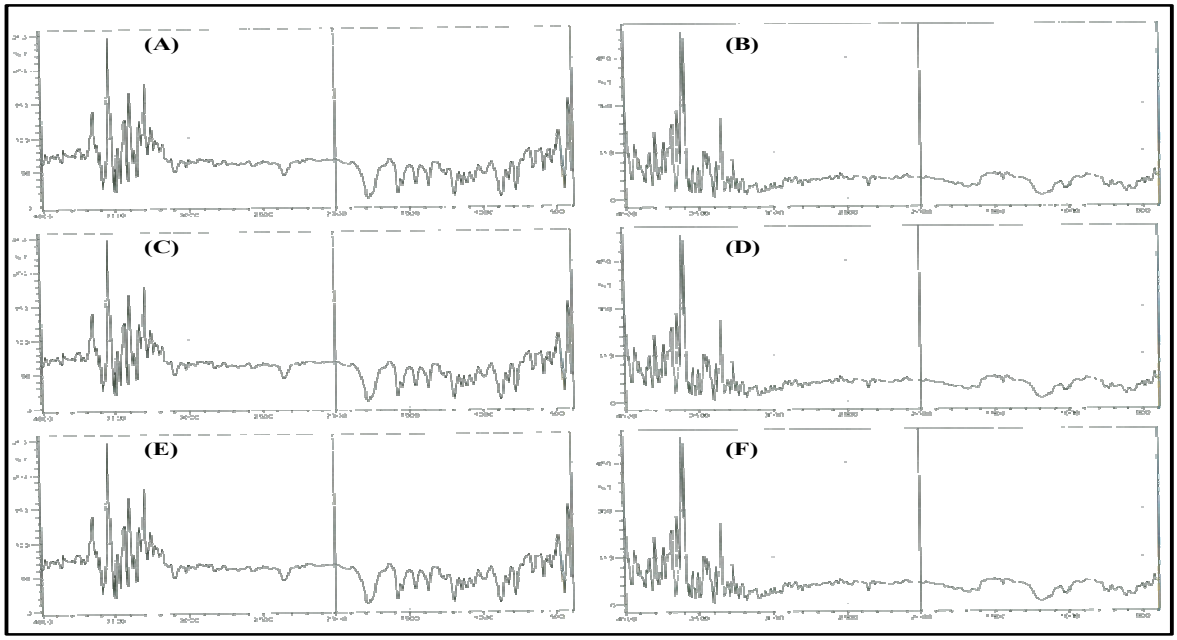


Figure 4: FTIR spectra of aceclofenac, physical mixtures and different solid dispersion systems with PVP. (A) AF-PVP (PM) 1:0.5; (B) AF-PVP (SD) 1:0.5; (C) AF-PVP (PM) 1:1; (D) AF-PVP (SD) 1:1; (E) AF-PVP (PM) 1:2; (F)AF-PVP (PM) 1:2 (SD). AF=aceclofenac; PM= physical mixture; PVP= polyvinyl pyrrolidone; SD= solid dispersion.

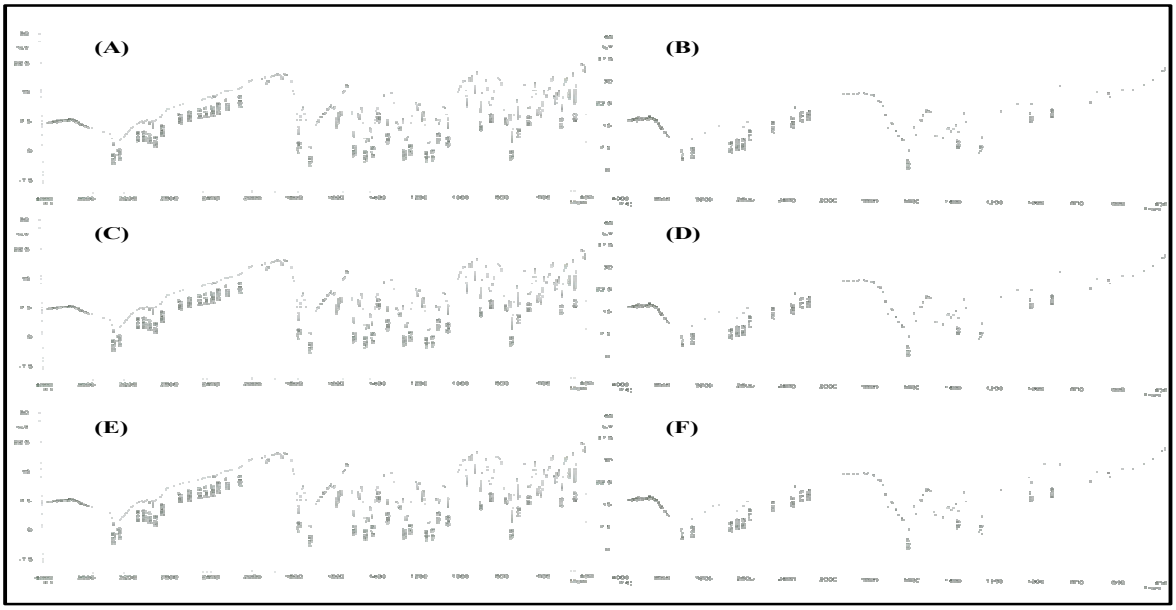
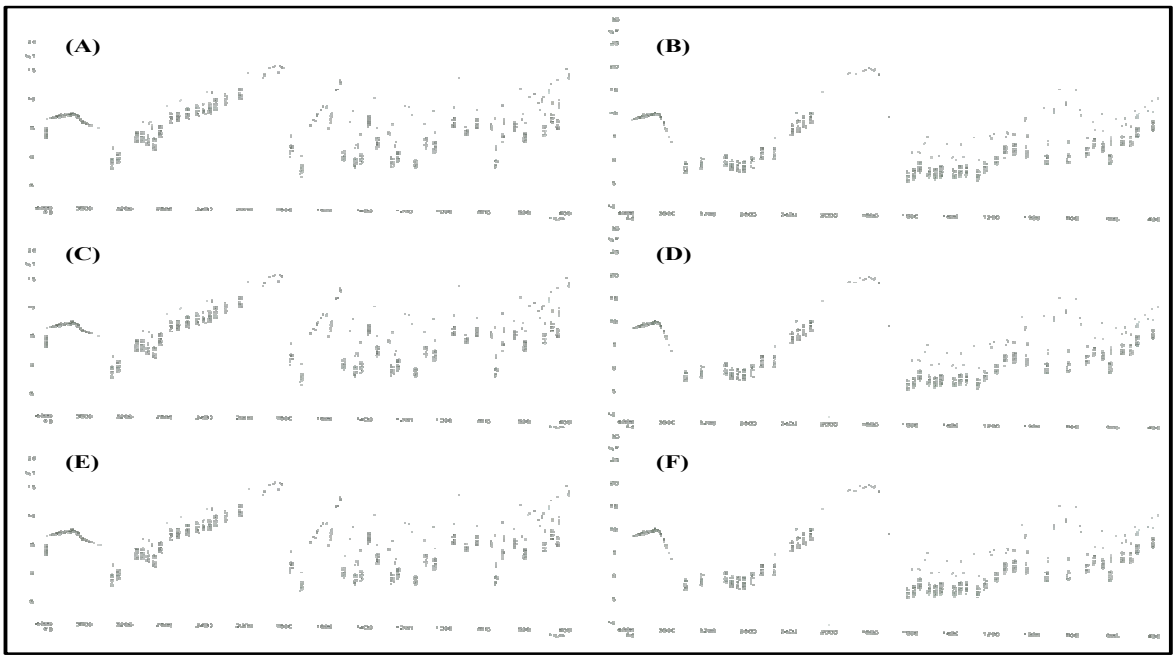


Figure 5: FTIR spectra of aceclofenac, physical mixtures and different solid dispersion systems with PVP/VA-64. (A) AF-PVP/VA-64 (PM) 1:0.5; (B) AF- PVP/VA-64 (SD) 1:0.5; (C) AF- PVP/VA-64 (PM) 1:1; (D) AF- PVP/VA-64 (SD) 1:1; (E) AF-PVP/VA-64 (PM) 1:2; (F)AF-PVP/VA-64 (PM) 1:2 (SD). AF=aceclofenac; PM= physical mixture; PVP/VA-64= polyvinyl pyrrolidone vinyl acetate; SD= solid dispersion.



Differential Scanning Calorimetric Studies

The DSC thermograms of AF, urea, mannitol, PVP, PVPVA, various physical mixtures and solid dispersion are given in Figure 6, 7, 8 and 9. The pure AF exhibited endothermic peaks at 152.48°C which represents melting of AF and in accordance with the literature value [(12)]. Urea, Mannitol, PVP and PVPVA depicted endotherms at 132.66 °C, 165.67 °C, 102 °C and 72.8 °C, respectively which corresponded to their respective melting points.

The DSC curve of AF with various carriers physical mixtures show peaks resulting from the superposition of their separated component DSC curves. The drug endothermic peak was suppressed in the thermograms of the solid dispersions and coprecipitates suggesting that the drug was able to dissolve partially in the carrier to form a solid-solid solution. The appearance of low intensity endothermic peak also indicated some of the drug still managed to crystallize out from the matrix of carrier. These phenomena could also be attributed to the amorphous form of the drug in prepared solid dispersions and coprecipitates.

DSC thermograms indicate the existence of the new solid phase and confirm FTIR spectral data concerning the presence of AF in an amorphous and homogenously dispersed state in carriers employed. The DSC further supported that AF was compatible with urea, mannitol, PVP and PVPVA under study. No additional or shift in endothermic peaks were observed which indicated the compatibility between the drug and carriers. The findings indicated that the drug was stable in SDs prepared freshly and after 6 months storage.

Figure 6: DSC thermogram of (A) AF; (B) Urea; (C) AF-U 1:0.5 (PM); (D) AF-U 1:0.5 (SD); (E) AF-U 1:1 (PM); (F) AF-U 1:1 (SD); (G) AF-U 1:2 (PM); (H) AF-U 1:2 (SD). AF= aceclofenac; PM= physical mixture; SD= solid dispersion; U= Urea.

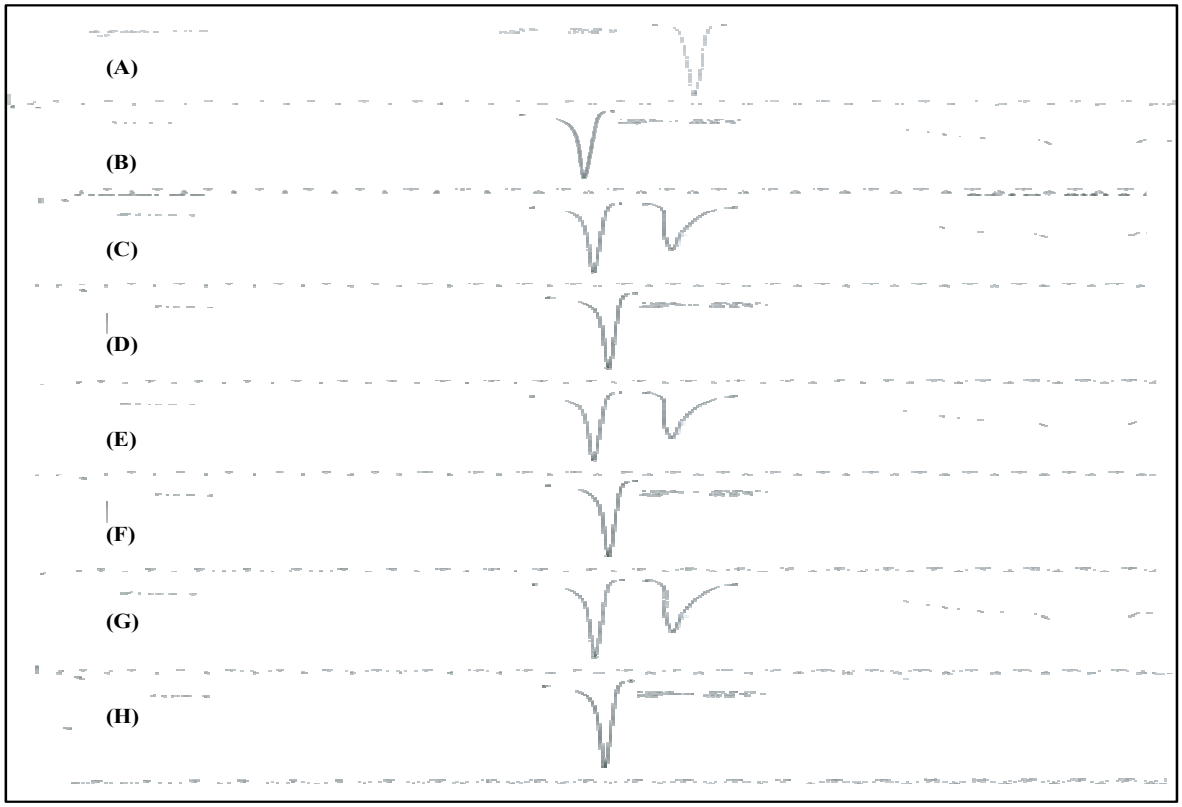


Figure 7: DSC thermogram of (A) AF; (B) Mannitol; (C) AF-M 1:0.5 (PM); (D) AF-M 1:0.5 (SD); (E) AF-M 1:1 (PM); (F) AF-M 1:1 (SD); (G) AF-M 1:2 (PM); (H) AF-M 1:2 (SD). AF=

aceclofenac; M= mannitol; PM= physical mixture; SD= solid dispersion.

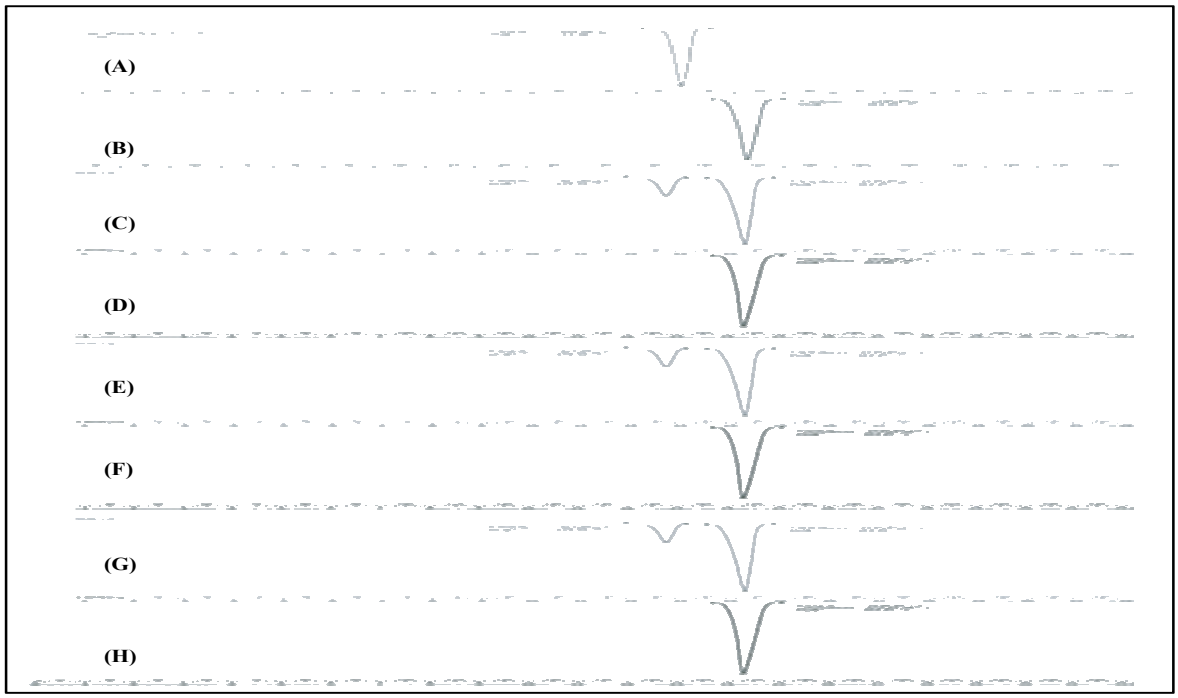


Figure 8: DSC thermogram of (A) AF; (B) PVP; (C) AF-PVP 1:0.5 (PM); (D) AF-PVP 1:0.5 (SD); (E) AF-PVP 1:1 (PM); (F) AF-PVP 1:1 (SD); (G) AF-PVP 1:2 (PM); (H) AF-PVP 1:2 (SD). AF= aceclofenac; PM= physical mixture; PVP= polyvinylpyrrolidone; SD= solid dispersion.

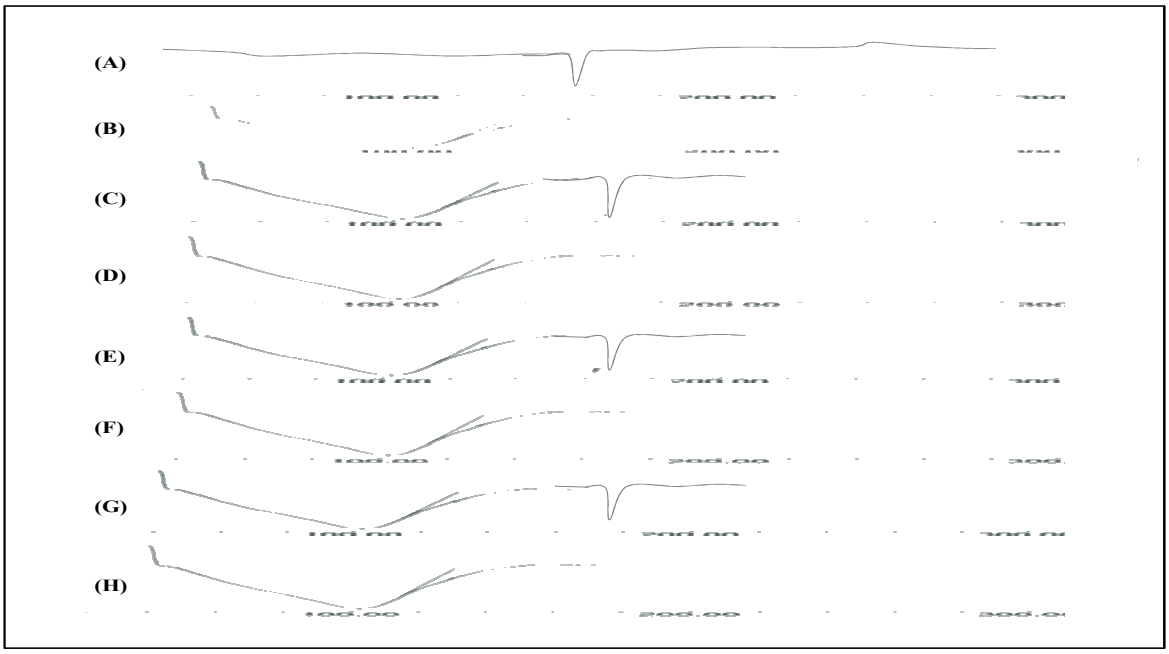
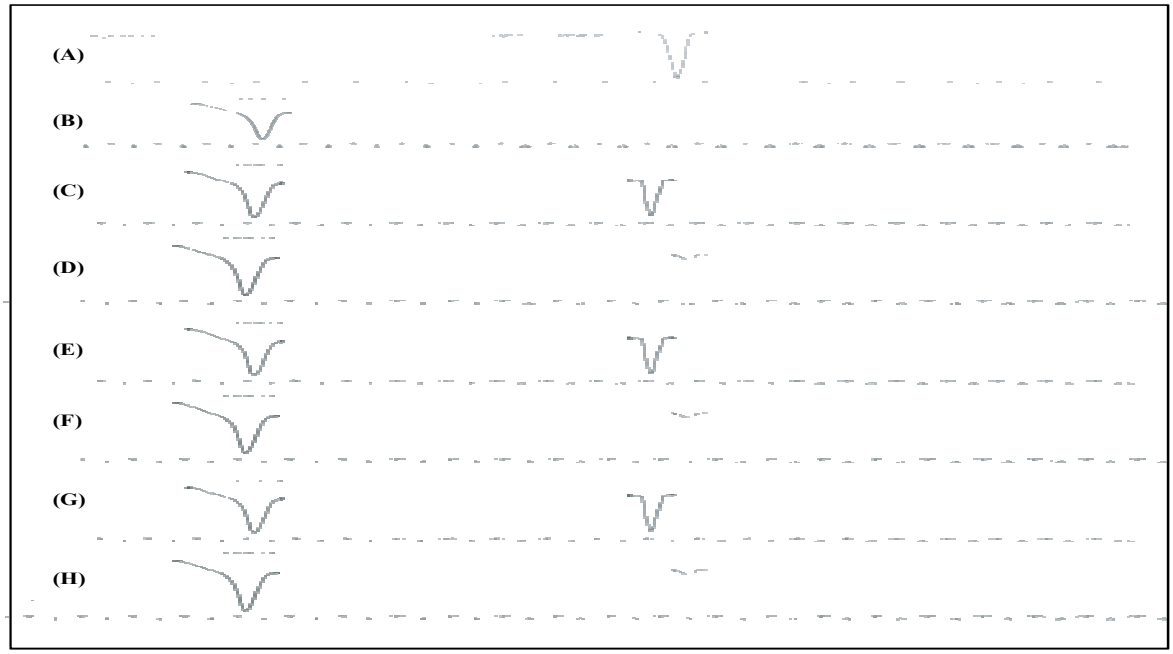


Figure 9: DSC thermogram of (A) AF; (B) PVP/VA; (C) AF-PVP/VA 1:0.5 (PM); (D) AF-PVP/VA 1:0.5 (SD); (E) AF-PVP/VA 1:1 (PM); (F) AF-PVP/VA 1:1 (SD); (G) AF-PVP/VA 1:2 (PM); (H) AF-PVP/VA 1:2 (SD). AF= aceclofenac; PM= physical mixture; PVP/VA= polyvinylpyrrolidone vinyl

acetate 64; SD= solid dispersion.



In Vitro Release Studies

In both, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4), the physical mixtures and SDs with all drug: carrier ratios exhibited faster dissolution rates than that of pure AF at all time points. The dissolution rate of SDs was faster as compared to their corresponding physical mixtures at all the time intervals (Table 4). With the increase in the proportion of carrier, rate of dissolution of SDs also increases. The SDs with 1:2 drug carrier ratio exhibited higher dissolution rate than others with lower carrier content (1:0.5 and 1:1). The order of dissolution shown by the SDs was found to be 1:2 > 1:1 > 1:0.5. Figure 10 and 11 depicts the comparative release from the selected solid dispersions in 0.1 N HCl, pH1.2 and phosphate buffer, pH, 7.4.

Figure 10: *In vitro* dissolution profile of selected aceclofenac solid dispersions in 0.1N HCl, pH 1.2.

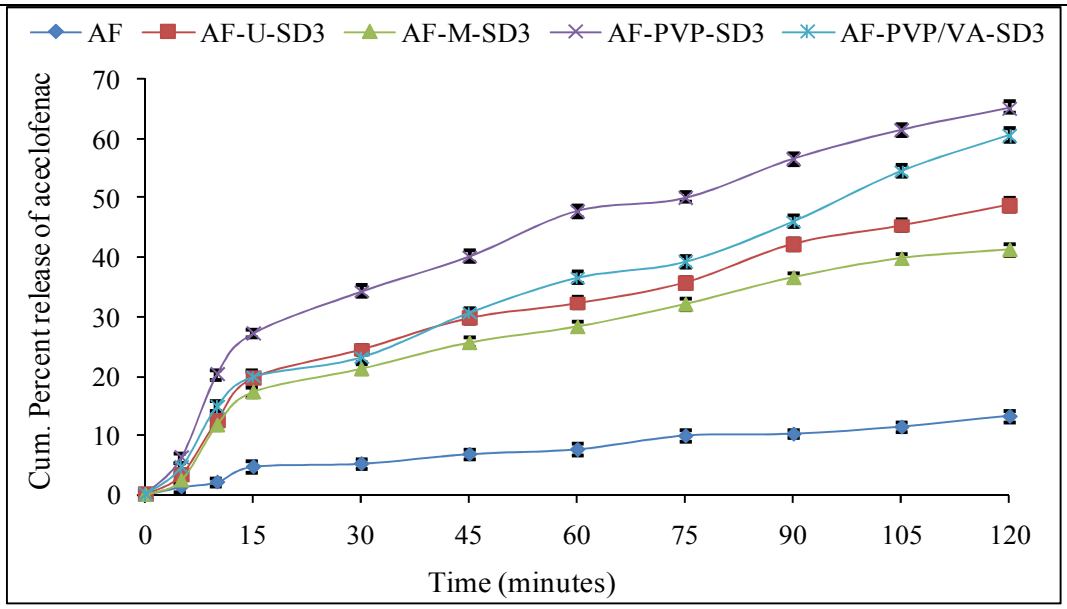
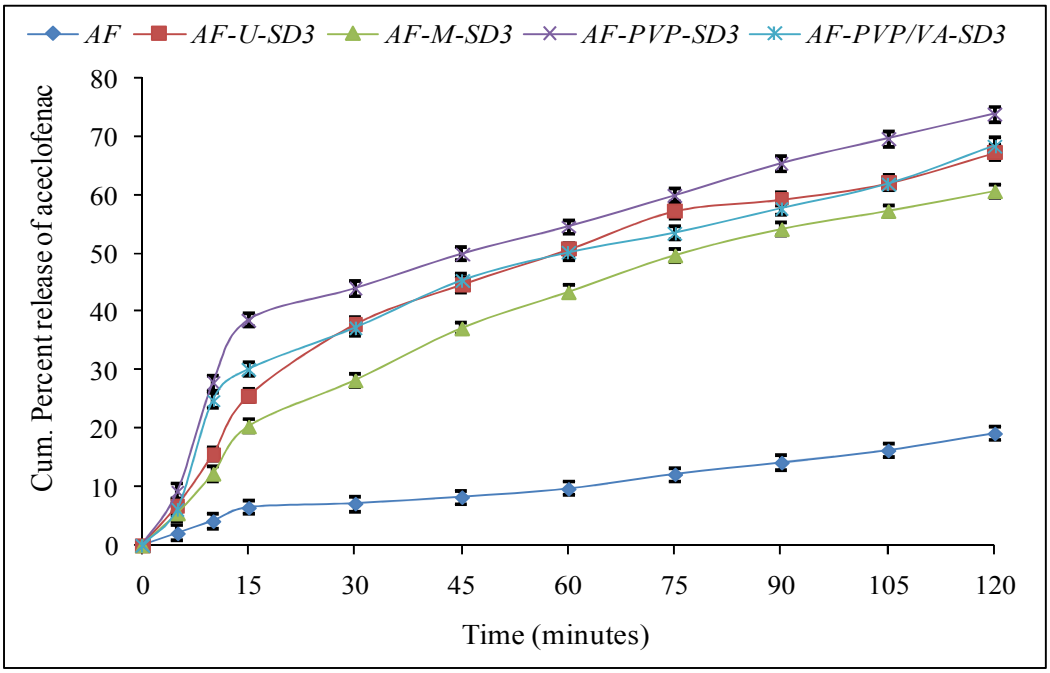


Figure 11: *In vitro* dissolution profile of selected aceclofenac solid dispersions in phosphate buffer, pH 7.4.



All the AF formulations showed a better dissolution profile in phosphate buffer, pH 7.4 in comparison to 0.1N HCl, pH 1.2. Similar results were reported by Soni *et al.* ([32]) in their saturation solubility studies of AF carried out in different dissolution media. Furthermore, this may be due to the weakly acidic nature of AF. With reference to pH-solubility profile, the dissolution rate of AF has been shown to increase on increasing pH of the medium ([33]). This supports higher drug release in phosphate buffer, pH 7.4 in the present study.

Table 4: *In vitro* dissolution profile of aceclofenac solid dispersions in 0.1 N HCl, pH 1.2 and phosphate buffer, pH 7.4.

Composition	Ratio	Percent drug released after 2 hr	
		0.1 N HCl, pH 1.2	**Phosphate buffer, pH 7.4**
AF (Pure Drug)	1:0	13.2 (0.91)	19.2 (1.02)
AF-U	1:0.5	29.3 (0.99)	46.3 (1.09)
	1:1	37.6 (1.09)	58.3 (1.17)
	1:2	48.9 (1.04)	67.3 (1.24)
AF-M	1:0.5	24.1 (0.99)	40.2 (1.15)
	1:1	31.2 (0.92)	51.2 (1.17)
	1:2	41.3 (0.93)	60.7 (1.16)
AF-PVP	1:0.5	50.6 (0.97)	52.3 (1.31)
	1:1	61.3 (0.99)	63.1 (1.27)
	1:2	65.3 (0.99)	73.9 (1.27)
AF-PVP/VA	1:0.5	39.3 (1.22)	48.5 (1.21)
	1:1	52.4 (0.99)	60.3 (1.25)
	1:2	60.7 (1.11)	68.5 (1.31)

AF: aceclofenac; M: mannitol; PVP: polyvinyl pyrrolidone; PVP/VA-64: polyvinyl pyrrolidone vinyl acetate; SD: solid dispersion; U: urea. Values in parenthesis indicates the standard deviation (n=3)

Formulations containing PVP showed maximum dissolution rate in comparison to formulation containing urea, mannitol and PVP/VA-64 which is in agreement with previous study on pizotifen malate with PVP as carrier ([34]). The present study revealed that 1:2 ratio of AF-PVP showed maximum drug release. Among all the solid dispersions, AF-PVP-SD3 showed the maximum dissolution in 0.1N HCl, pH 1.2 (65.3±0.99%) and phosphate buffer pH 7.4 (73.9±1.27%) respectively. Due to the hydrophilic nature, PVP enhances the wetting of hydrophobic drugs in SDs. Since, wetting is prerequisite for dissolution, this effect contributed to the faster drug release as reported by Simonelli *et al.* ([35]) and Leuner and Dressman, ([36]). Solubility could be enhanced further in presence of hydrogen bonding. Nevertheless, no hydrogen bonding interaction between PVP and AF could be detected in FTIR analysis.

Another mechanism for this preferential enhancement of dissolution rate from SDs may be due to the formation of a eutectic mixture, or a solid solution [(8).] Such a solid solution cannot result from just physically mixing the two components and hence, physical mixture fails to increase the dissolution rate ([37]).Enhancement of dissolution rate from SDs can also be attributed to the amorphization of drug and the particle size reduction. The particle size reduction results in increased surface area available and thus, acceleration of dissolution ([38]). In SDs , the presence of the water soluble carrier results in improvement of wetting

characteristics of poorly soluble drug like AF ([39]).

Kinetic Analysis of Drug Release

The kinetics of *in vitro* release of the best formulations of AF (AF-U-SD3, AF-M-SD3, AF-PVP-SD3 and AF-PVP/VA-SD3) was carried out. The release of drug from all formulations was observed to follow the first order release kinetics, since the correlation coefficient (R^2) for first order was higher in comparison to zero order release. The results were in agreement with the previous investigations performed by Goracinova *et al.* ([40]), Shivkumar *et al.* ([41]) and El-Maradny *et al.* ([42]).

Table 5: Comparison of Orders of *In Vitro* dissolution profile of selected formulations of aceclofenac in 0.1N HCl, pH 1.2 and Phosphate buffer, pH 7.4

Dissolution media	Formulation	Regression equations			
		Zero order	First order	Higuchi	Hixson Crowell
0.1N HCl pH 1.2	AF-U-SD3 (1:2)	y = -0.3728t + 92.037 R² = 0.9191	y = -0.0023t + 1.9685 R² = 0.9594	y = 4.5731√t - 1.7262 R² = 0.9805	y = 0.0072x + 0.1172 R² = 0.9479
	AF-M-SD3 (1:2)	y = -0.3207t + 92.88 R² = 0.9105	y = -0.0018t + 1.9706 R² = 0.9476	y = 3.9489√t - 1.3091 R² = 0.9790	y = 0.0059x + 0.1074 R² = 0.9364
	AF-PVP-SD3 (1:2)	y = -0.4906t + 87.499 R² = 0.9049	y = -0.0036t + 1.9526 R² = 0.9692	y = 6.0758√t - 0.6094 R² = 0.9841	y = 0.0106x + 0.1821 R² = 0.9525
	AF-PVP/VA-SD3 (1:2)	y = -0.4537t + 92.838 R² = 0.9615	y = -0.003t + 1.9801 R² = 0.9761	y = 5.4214√t - 3.7315 R² = 0.9734	y = 0.0093x + 0.0884 R² = 0.9659
Phosphate Buffer pH 7.4	AF-U-SD3 (1:2)	y = -0.5233t + 87.55 R² = 0.8925	y = -0.0039t + 1.952 R² = 0.961	y = 6.5177√t - 1.7632 R² = 0.9816	y = 0.0114x + 0.1832 R² = 0.9416
	AF-M-SD3 (1:2)	y = -0.4923t + 91.291 R² = 0.9365	y = -0.0034t + 1.9705 R² = 0.9812	y = 6.0099√t - 3.9081 R² = 0.9898	y = 0.0102x + 0.1189 R² = 0.9690
	AF-PVP-SD3 (1:2)	y = -0.5231t + 81.554 R² = 0.8453	y = -0.0043t + 1.9232 R² = 0.9503	y = 6.6242√t + 3.5547 R² = 0.9613	y = 0.0123x + 0.2856 R² = 0.9224
	AF-PVP/VA-SD3 (1:2)	y = -0.4911t + 85.124 R² = 0.8699	y = -0.0037t + 1.9394 R² = 0.9515	y = 6.1611√t + 1.2593 R² = 0.9708	y = 0.0108x + 0.2259 R² = 0.9297

AF: aceclofenac; CP: coprecipitates; M: mannitol; PVP: polyvinyl pyrrolidone; PVP/VA-64: polyvinyl pyrrolidone vinyl acetate; SD: solid dispersion; U: urea.

The data was further subjected to Higuchi equation and Hixson-Crowell cube root law. A higher correlation, as indicated by R^2 was observed for the Higuchi matrix release kinetics in all the selected formulations suggesting the diffusion as a probable prominent mechanism of drug release ([40, 41]). In diffusion, the rate of dissolution of drug particles within the matrix must be much faster than that of the diffusion rate of drug leaving the matrix. The selection criteria (R^2) and the equations best describing the kinetics of *in vitro* drug release is given in Table 5.

CONCLUSION

This study clearly shows that addition of various hydrophillic carriers like urea, mannitol, PVP and PVP/VA-64 to aceclofenac improves its dissolution rate. Further, all the solid dispersions performed better than the corresponding physical mixtures. The present study also showed that urea, mannitol and PVP/VA-64 yielded solid dispersions with a less improved dissolution rate than PVP as carrier. DSC thermograms of physical mixture and solid dispersion indicated complete miscibility of the drug in melted carrier. Amorphous nature of the drug in solid dispersion was confirmed by scanning electron microscopy and a decrease in enthalpy of drug melting in solid dispersion compared to the pure drug. Results from FT-IR spectroscopy concluded that there was no well-defined interaction between aceclofenac and carriers employed in the preparation of solid dispersions. The solid dispersion of aceclofenac with PVP lends an ample credence for better therapeutic efficacy.

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REFERENCES

1. Hite M, Turner S, Federici C. Pharmaceutical Manufacturing and Packing Sourcer, Part 1. Oral Delivery of Poorly Soluble Drugs, Summer; 2003; www. scolr.com/lit/PMPS_2003_1.pdf.
2. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures – I – theoretical consideration and discussion of the literature. J Pharm Sci 1965; 54: 1145-1148. *DOI: 10.1002/jps.2600540810.*
3. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures – II – experimental evaluation of eutectic mixture: urea-acetaminophen system. J Pharm Sci 1966; 55: 482–487. *DOI: 10.1002/jps. 2600550507*.
4. Goldberg AH, Gibaldi M, Kanig JL, Mayersohn M. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures – IV – chloramphenicol- urea system. J Pharm Sci 1966; 55: 581–583. DOI: 10.1002/jps.2600550610.
5. Hoerter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Deliver Res 1997; 25: 3–14.
6. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical system. J Pharm Sci 1997; 86: 1–12. *DOI: 10.1021/js.9601896.*
7. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: Drug solubilization and stabilization. J Pharm Sci 1996; 85: 1017–1025. *DOI:*

10.1021/js.950534b.

8. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersions. J Pharm Sci 1971; 60: 1281–1302.
9. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures – I. A comparison of the behavior of eutectic mixture of sulphathiazole and that of ordinary sulphathiazole in man. Chem Pharm Bull 1961; 9: 866–872.
10. Tachibana T, Nakamura A. A method for preparing an aqueous colloidal dispersion of organic material by using water soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone. Kolloid-Z Polym 1965; 203: 130–133.
11. Swarbrick J, Boylon J, Encyclopedia of Pharmaceutical Technology, Vol. I. 2nd ed. Marcel Dekker, New York; 2002.
12. Moffat AC, Osselton MD, Widdop B, Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and postmortem materials, Vol. 2. 3rd ed: Pharmaceutical Press; 2004.
13. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture II. absorption of fused conglomerates of chloramphenicol and urea in rabbits. Chem Pharm Bull (Tokyo) 1964; 12: 134-144.
14. Shah J, Vasanti S, Anroop B, Vyas H. Enhancement of dissolution rate of valdecoxib by solid dispersions technique with PVP K 30 & PEG 4000: preparation and *in vitro* evaluation. J Inclusion Phenomena and Macrocyclic Chemistry 2009; 63(1-2): 69-75.
15. Janssens S, Nagels S, Novoa de Armas H, D'Autry W, Schepdael AV, Mooter GV. 'Formulation and characterization of ternary solid dispersions made up of Itraconazole and two excipients, TPGS 1000 and PVPVA 64, that were selected based on a supersaturation screening study. Eur J Pharm Biopharm 2008; 69: 158–166.
16. Patil MP, Gaikwad NJ. Preparation and characterization of gliclazide-polyethylene glycol 4000 solid dispersions. Acta Pharm 2009; 59: 57–65.
17. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech 2005; 6(3): E405-E412.
18. Barakat NS, Elanazi FK, Almurshedi AS. The influence of various amphiphilic excipients on the physicochemical properties of carbamazepine-loaded microparticles. J Microencapsulation 2009; 26(3): 251-262.
19. Papageorgiou GZ, Bikiaris D, Karavas E, Politis S, Docoslis A, Park Y, Stergiou A, Georgarakis E. Effect of physical state and particle size distribution on dissolution enhancement of nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation. AAPS Journal 2006; 8(4): E623-E631.
20. Gohel MC, Patel LD. Processing of nimesulide-PEG 400-PG-PVP solid dispersions: preparation, characterization and *in vitro* dissolution. Drug Dev Ind Pharm 2003; 29: 299-310.
21. Otsuka M, Onoe M, Matsuda Y. Hygroscopic stability and dissolution properties of spray-dried solid dispersions of furosemide with eudragit. J Pharmaceutical Sciences 2006; 82(1): 32–38.
22. Newa M, Bhandari KH, Li DX, Kwon TH, Kim JA, Yoo BK, Woo JS, Lyoo WS , Yong CS and Choi HG. Preparation, characterization and *in vivo* evaluation of

ibuprofen binary solid dispersion with poloxamer 188. Int J Pharm 2007; 343: 228-237.

23. Agrawal GP, Bhargava S. Preparation & Characterization of Solid Inclusion Complex of Cefpodoxime Proxetil with β-Cyclodextrin. Current Drug Delivery 2008; 5(1): 1-6.
24. Aigner Z, Hassan HB, Berkesi O, Kata M, Eros I. Thermoanalytical, FTIR and X-ray studies of gemfibrozil-cyclodextrin complexes. Journal of Thermal Analysis and Calorimetry 2005; 81(2): 267-272.
25. Balaji A, Pandey VP, Srinath MS, Manavalan R. Synthesis and characterization studies of cisplatin/hydroxypropyl-β-cyclodextrin complex. Pharmacologyonline 2009; 1: 1135-1143.
26. Babu MMGV, Prasad SD, Ramana Murthy KV. Development of new controlled release formulations of flurbiprofen: *in vitro-in vivo* correlation. Ind J Pharm Sci 2002; 64: 37-43.
27. Fernandes CM, Teresa Vieiraz M, Veiga FJ. Physicochemical characterization and *in vitro* dissolution behavior of nicardipine-cyclodextrin inclusion compounds. Eur J Pharm Sci 2002; 15(1): 79-88.
28. Azarmi S, Roa W, Lobenberg R. Current perspectives in dissolution testing of conventional and novel dosage forms. Int J Pharmaceutics 2007; 328(1): 12-21.
29. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13: 123-133.
30. Sethia S, Squilante E. Solid dispersions of carbamazepine in PVP-K30 by conventional solvent evaporation and super critical methods. Int J Pharm 2004; 272(1-2): 1-10.
31. Martinez-ohariz MC, Rodriguez-Espinosa C, Martin C, Goni MM, Tros-lladuya, Sanchez M. Solid dispersions of diflunisal-PVP: Polymorphic and amorphous states of drug. Drug Dev Ind Pharm 2002; 28(6): 717-725.
32. Soni T, Nagda C, Gandhi T, Chotal NP. Development of discriminating method for dissolution of aceclofenac marketed formulations. Dissolution Technol 2008; 5: 31-35.
33. Mutalik S, Naha A, Usha AN, Ranjit AK. Musmade PM, Manoj K, Anju P, Prasanna S. Preparation, *in vitro*, pre-clinical and clinical evaluations of once daily sustained release tablets of aceclofenac. Arch Pharm Res 2007; 30(2): 222-234.
34. Margarit MV, Marin MT, Contreras MD. Solubility of solid dispersions of pizitifen malate and povidone. Drug Dev and Indus Pharm 2001; 27(6): 517-522.
35. Simonelli AP, Mehta SC, Higuchi WI. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J Pharm Sci 1969; 58(5): 538-549.
36. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50(1): 47-60.
37. Shah JC, Chen JR, Chow D. Preformulation study of etoposide:II. Increased solubility and dissolution rate by solid-solid dispersions. Int J Pharm 1995; 113: 103-111.
38. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in the pharmaceutical systems. J Pharm Sci 1997; 86: 1-12.
39. Dehghan MHG, Jafar M. Improving dissolution of meloxicam using solid dispersions.

Iranian J Pharm Res 2006; 4: 231-238.

40. Goracinova K, Klisarova L, Simov A, Fredro-Kumbaradzi E, Petrusevska-Tozi L. Preparation, physical characterisation, mechanisms of drug/polymer interactions and stability studies of controlled release of solid dispersion granules containing weak base as active substance. Drug Dev Ind Pharm 1996; 22(3): 255-262.
41. Shivkumar HN, Desai BG, Deshmukh G. Design and optimization of diclofenac sodium controlled release solid dispersions by response surface methodology. Ind J Pharm Sci 2008; 70: 22-30.
42. El-Maradny HA, Mortada SA, Kamel OA, Hikal AH. Characterisation of ternary complexes of meloxicam-HPβCD and PVP or L-arginine prepared by the spray drying technique. Acta Pharm 2008; 58: 455-466.