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Solubility Enhancement of Aceclofenac by Solid Dispersion

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ABSTRACT

The aim of the study was to improve the solubility of aceclofenac, which is poorly water soluble drug belongs to BCS class-II. Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. To improve the solubility of drug by solid dispersions were prepared with different methods like physical mixture, kneading method and solvent evaporation method with various carriers like poloxamer188, poloxamer407 and PEG 6000 in different ratios from 1:1 to 1:5. The prepared formulations were evaluated for physicochemical characteristics, characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), *in-vitro* dissolution studies and saturation solubility. Based on the evaluation parameters poloxamer407 in ratio of 1:5 through solvent evaporation method was optimized and formulated into tablets by direct compression method. These tablets showed a higher *in-vitro* dissolution drug release which is 99.62% in 30 minutes when compared with pure drug which showed 26.62% in 60 minutes, whereas marketed tablet (Hifenac) shows 99.64±0.10% in 40 minutes. Hence it was concluded that solid dispersion of aceclofenac drug by using polaxamer 407 with solvent evaporation method enhances solubility, absorption rate and increase bioavailability of the aceclofenac drug.

Keywords: NSAIDs, Poloxamer188, Polaxamer 407, PEG 6000, Solid dispersion.

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INTRODUCTION

A major challenge to drug development today is poor solubility. Several ways in which solubility of the drug can be enhanced by decreasing crystallinity or increasing the surface area of the drugs which includes micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation and complexation with cyclodextrins etc.,. The development of solid dispersions as a practically feasible method to enhance solubility and bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilisation by co-solvents and particle size reduction.

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic/ water insoluble drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous (clusters) or in crystalline particles. Solid dispersion when exposed to aqueous media, the carrier dissolved the drug was released as very fine, colloidal particles. Because of enhanced surface area, the dissolution rate and the bioavailability of poorly water-soluble drugs are increased.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties. It has higher anti-inflammatory action or at least comparable effects than conventional NSAIDs. Aceclofenac belongs to BCS Class II as it possesses poor aqueous solubility and displays high permeability. In order to improve the solubility, dissolution rate and bioavailability of the drug, it was attempted to prepare aceclofenac solid dispersion.

Aceclofenac is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration. The main objective of this work was to investigate the viability of improving the solubility and dissolution rate of aceclofenac by preparing solid dispersions with various carriers such as polyethylene glycol6000, poloxamer188, polaxamer 407. The prepared solid dispersions were evaluated and optimized by its evaluation parameters. The optimized solid dispersion converted to tablets by direct compression method by various excipients and evaluated[1-5].

MATERIALS AND METHOD

Materials

Aceclofenac, poloxamer188, polaxamer 407 from Hetero drugs Pvt. Ltd., Hyderabad. PEG 6000, PVC, MCC, magnesium stearate from SD fine chemicals Ltd., Mumbai and Talcum powder from Accord labs Ltd.

Methods

Analytical Studies:

Aceclofenac standard graph was constructed in 6.8 pH phosphate buffer analyzed the samples by UV spectrophotometer. An absorption maximum (λ_{max}) of 274.8 nm was observed.

DRUG - EXCIPIENTS COMPATIBILITY STUDIES

Fourier Transform Infra Red spectroscopy (FTIR):

The spectrum analysis of pure drug and physical mixture of drug and different excipients were studied. Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide, compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded using Shimadzu Corporation (Koyto, Japan) facilty (model - 8400S) from 4000 cm^{-1} to 500 cm^{-1} for 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

PREPARATION AND EVALUATION OF SOLID DISPERSIONS

Preparation of Solid Dispersions by Physical Mixture Method (PM) [1-5]

The physical mixtures (PM) of drug with different carriers were prepared by blending method as shown in **Figure 1**. The physical mixtures were prepared at various drug to carrier ratios with all the carriers in the increasing order of carrier amounts as given in **Table 1.**

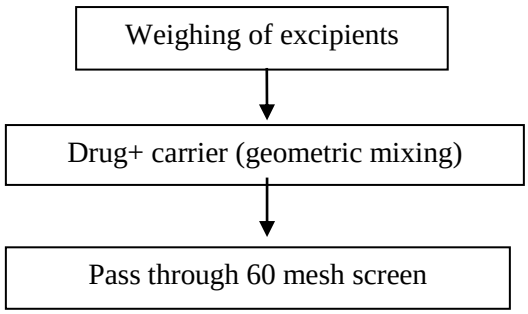

Figure 1: Physical mixture method

Table 1: Formulas of Aceclofenac solid dispersions (SDs) prepared by physical mixtures

Formulation code	Ratio of the mixture of drug and carrier (D:C)	Weight of the drug (mg)	Weight of the carrier (mg)
Aceclofenac with polaoxamer188			
ACP111PM	1:1	100	100
ACP112PM	1:2	100	200
ACP113PM	1:3	100	300
ACP114PM	1:4	100	400

ACP115PM	1:5	100	500
Aceclofenac with polaoxamer407			
ACP411PM	1:1	100	100
ACP412PM	1:2	100	200
ACP413PM	1:3	100	300
ACP414PM	1:4	100	400
ACP415PM	1:5	100	500
Aceclofenac with PEG6000			
ACPE611PM	1:1	100	100
ACPE612PM	1:2	100	200
ACPE613PM	1:3	100	300
ACPE614PM	1:4	100	400
ACPE615PM	1:5	100	500

NOTE: D-Drug (aceclofenac), C-Carrier (poloxamer188, poloxamer407 and PEG6000)

Preparation of Solid Dispersions by Kneading Method (KM)

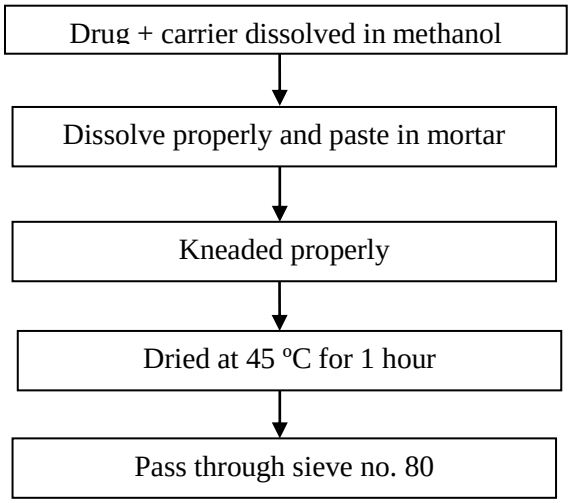

Figure 2: Kneading method

Table 2: Formulas of aceclofenac solid dispersions (SDs) prepared by kneading method

Formulation code	Ratio of the mixture of drug and carrier (D:C)	Weight of the drug (mg)	Weight of the carrier (mg)
Aceclofenac with poloxamer 188			
ACP111KM	1:1	100	100
ACP112KM	1:2	100	200
ACP113KM	1:3	100	300
ACP114KM	1:4	100	400
ACP115KM	1:5	100	500
Aceclofenac with poloxamer 407			
ACP411KM	1:1	100	100
ACP412KM	1:2	100	200
ACP413KM	1:3	100	300
ACP414KM	1:4	100	400

ACP415KM	1:5	100	500
Aceclofenac with PEG6000			
ACPE611KM	1:1	100	100
ACPE612KM	1:2	100	200
ACPE613KM	1:3	100	300
ACPE614KM	1:4	100	400
ACPE615KM	1:5	100	500

NOTE: D-Drug (aceclofenac), C-Carrier (poloxamer188) (poloxamer407) (PEG6000)

Preparation of Solid Dispersions by Solvent Evaporation Method (SM)

The solid dispersions of the drug were prepared with various carriers by solvent evaporation method using rotary flash evaporator (**Figure 3**). The solid dispersions were prepared with various drug to carrier ratios with all the carriers in the increasing order of carrier amounts (**Table 3**).

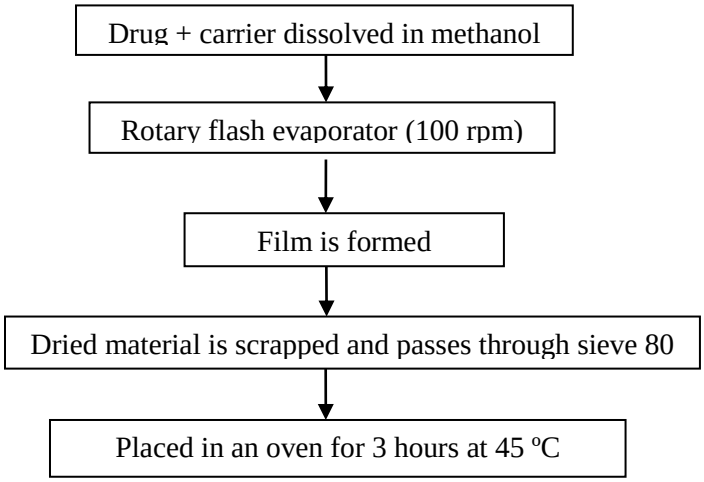

Figure 3: Solvent evaporation method

Table 3: Formulas of Aceclofenac solid dispersions (SDs) prepared by solvent evaporation method

Formulation code	Ratio of the mixture of drug and carrier (D:C)	Weight of the drug (mg)	Weight of the carrier (mg)
Aceclofenac with poloxamer188			
ACP111SM	1:1	100	100
ACP112SM	1:2	100	200
ACP113SM	1:3	100	300
ACP114SM	1:4	100	400
ACP115SM	1:5	100	500
Aceclofenac with poloxamer407			
ACP411SM	1:1	100	100
ACP412SM	1:2	100	200
ACP413SM	1:3	100	300
ACP414SM	1:4	100	400
ACP415SM	1:5	100	500

Aceclofenac with PEG6000			
ACPE611SM	1:1	100	100
ACPE612SM	1:2	100	200
ACPE613SM	1:3	100	300
ACPE614SM	1:4	100	400
ACPE615SM	1:5	100	500

NOTE: D-Drug (aceclofenac), C-Carrier (poloxamer188) (poloxamer407) (PEG6000)

Characterization of solid dispersions[6-10]

Assay:

Assay of the prepared solid dispersions was determined in distilled water. Accurately weighed amounts of solid dispersions equivalent to 100 mg of drug was taken in a 100 ml volumetric flask, 20 ml methanol was added and shaken for 20 min to dissolve the drug. The volume was made to 100 ml with 6.8 pH phosphate buffer. The dispersions were filtered and 1 ml aliquot of the above solutions were taken and diluted to 10 ml with 6.8 pH phosphate buffer. The absorbance of these solutions was determined at 274.8 nm against the blank as 6.8 pH phosphate buffer using UV-Spectrophotometer. The percentage of assay was calculated.

Solubility studies:

An excess of pure aceclofenac drug and prepared solid dispersions were added to screw capped bottles containing distilled water. Bottles are shaken mechanically at 26 $^{\circ}$C for 24 hours and aliquots are withdrawn, filtered and assayed for drug content at 274.8 nm using UV-Spectrophotometer**.**

***In vitro* Dissolution study of aceclofenac solid dispersion:**

Dissolution studies were performed with solid dispersions prepared by different methods and also compared with the pure aceclofenac drug. The conditions for dissolution test given below:

Parameter	**Condition**
Temperature	37 ± 0.5^{o}C
Dissolution media	6.8 pH phosphate buffer
Volume of dissolution media	900 ml
Aliquot withdrawn	5 ml
Aliquot replaced	5 ml of the fresh buffer solution
Dissolution apparatus	USP type II (paddle)
Revolutions per minute (speed)	100 RPM
Sampling time intervals	10 min., 20 min., 30 min., 40 min., 50 min. and 60 min.

Precompression parameters of the powder blend

Angle of repose (Ø):

100 gms of the blend was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel. The interrelationship between the angle of repose and flow properties of powder are shown in the **Table 4.** Angle of repose is calculated by the following formula given in **Equation 1.**

$$Ø = Tan^{-1}(h/r) \text{..... Equation 1}$$

Where, Ø = angle of repose, r=radius of the pile, h=height of the pile.

Table 4: Correlation of angle of repose with flow properties of powder

S. No	Angle of repose (ø)	Powder flow
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair
4	41-45	Passable
5	46-55	Poor
6	56-65	Very Poor
7	> 66	Extremely poor

Bulk density:

Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula given in **Equation 2**

$$*b = M/V* \text{..... Equation 2}$$

Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula given in **Equation 3**

$$*t = M/V_t \text{..... Equation 3}$$

Carr's index:

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the formula given in **Equation 4.** The correlation between the compressibility index and flow properties of powder are shown in the **Table 5.**

C.I (%) = Tapped density –Bulk density×100 ……..…… Equation 4

Tapped density

Table 5: Correlation between compressibility index and flow properties of powder

S. No	% Compressibility Index	Powder flow
1	< 10	Excellent
2	11-15	Good
3	16-20s	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very Poor
7	> 38	Extremely poor

Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the using the formula given in **Equation 5.** The correlation between the hausner's ratio and flow properties of powder are shown in the **Table 6.**

Hausner's ratio = *t/*d..... Equation 5

Where *t=tapped density and *d=bulk density

Table 6: Correlation of Hausner's ratio with flow properties

S. No	Hausner's ratio	Powder flow
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very Poor
7	> 1.60	Extremely poor

PREPARATION AND EVALUATION OF ACECLOFENAC TABLETS

Preparation of aceclofenac tablets by direct compression method:

The optimized solid dispersion i.e. 1:5 ratio solid dispersion containing drug and poloxamer 407 prepared by solvent evaporation method was taken and formulated into tablets. All other tablet excipients like diluent (mannitol), Direct compressive vehicle (MCC), binder (PVP), Sweetener (Sodium saccharin) and lubricants & glidants (Magnesium stearate and talc) given in **Table 7** were triturated individually in a mortar and passed through # 60 sieve. Then required quantity of all ingredients were weighed for a batch size of 50 tablets and mixed uniformly in a mortar. Finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed into tablets containing 100 mg of drug using 11.1 mm flat face surface punches on a Rimek-1

rotary tablet machine by direct compression method (**Figure 4**). Total weight of tablet was kept 650 mg.

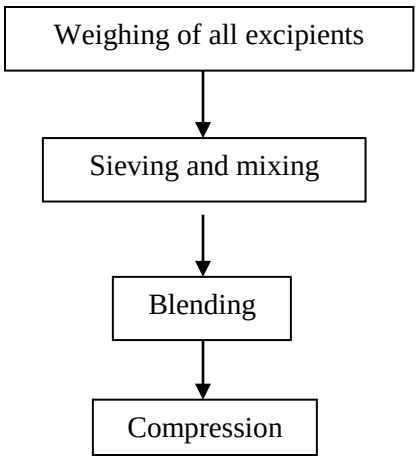

Figure 4: Flow chart of the direct compression method

Table 7: Formulations for ACP415SM tablet

FORMULA FOR ACP415SM TABLET	
Name of the ingredient	**Quantity (mg)**
Drug (equivalent amount of solid dispersion)(mg)	598
Microcrystalline cellulose (2%)	13
PVP (2%)	13
Mg. stearate (2%)	13
Talc(2%)	13
Total Wt. (mg)	**650**

NOTE: ACP415SM Formulations of tablets containing 1:5 of drug and poloxamer 407

Evaluation of aceclofenac tablets[11]

The prepared tablets can be evaluated for various parameters.

Weight variation:

20 tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated. The limits for weight variation mentioned in **Table 8**.

Table 8: Percentage deviation allowed for the tablets

Pharmaceutical Form	**Avg. Weight in mg**	**% Deviation**
Tablets	130 mg or less	10
	More than 130 mg	7.5
	More than 324 mg	5

Thickness:

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. The thickness of the tablet is related to the tablet hardness. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Hardness:

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability:

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (% F) is given by the formula given in **Equation 6**

$$\% \quad F = (1-W_0/W)\times 100 \quad \text{.....Equation 6}$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Content Uniformity:

Tablets are finely powdered and powder equivalent mg of drug is accurately weighed and transferred to 100 ml volumetric flasks containing solution of desired pH. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value is calculated.

Disintegration time:

Disintegration time was measured using a disintegration apparatus. For this purpose, a glass beaker was filled with 900 ml of media at $37^{\circ}C \pm 0.5^{\circ}C$. The tablet was carefully put in the centre of the tablet assembly and the time for the tablet to completely disintegrate into fine particles was noted.

***In-vitro* drug release:**

In-vitro drug release of aceclofenac tablets was determined by using USP dissolution test apparatus II (Paddle type) (Electro lab TDT-08L) and compared with marketed tablets (HIFENAC). The conditions for dissolution test given below:

Parameter	**Condition**
Temperature	37 ± 0.5°C
Dissolution media	6.8 pH phosphate buffer
Volume of dissolution media	900 ml
Aliquot withdrawn	5 ml
Aliquot replaced	5 ml of the fresh buffer solution
Dissolution apparatus	USP type II (paddle)
Revolutions per minute (speed)	100 RPM
Sampling time intervals	10 min., 20 min., 30 min., 40 min., 50 min. and 60 min.

Absorbance of solution was checked by UV Spectrophotometer (ELICO- 164 double beam spectrophotometer) at a wavelength of 274.8 nm and drug release was determined from standard curve.

Accelerated stability studies for aceclofenac tablets:

The optimized formulation of aceclofenac tablets was subjected to stability studies at 40°C±2°C/75%±2% RH for period of one month. Each tablet was individually wrapped in aluminum foil and packed in amber colored bottle and put at above specified condition in a heating humidity chamber for one month. The tablets were analyzed for the hardness, disintegration time, drug content and *in-vitro* drug release.

RESULTS AND DISCUSSIONS

Drug-excipient compatibility studies by FTIR

FTIR studies were done to verify if there was any interaction between the pure drug and various excipients employed. The FTIR graphs of pure drug and various excipients were mixed and the blend was formulated into IR pellet and scanned using FTIR. The spectra shown in **Figure 5, 6, 7, 8** results depicted in **Table 9, 10, 11, 12.**

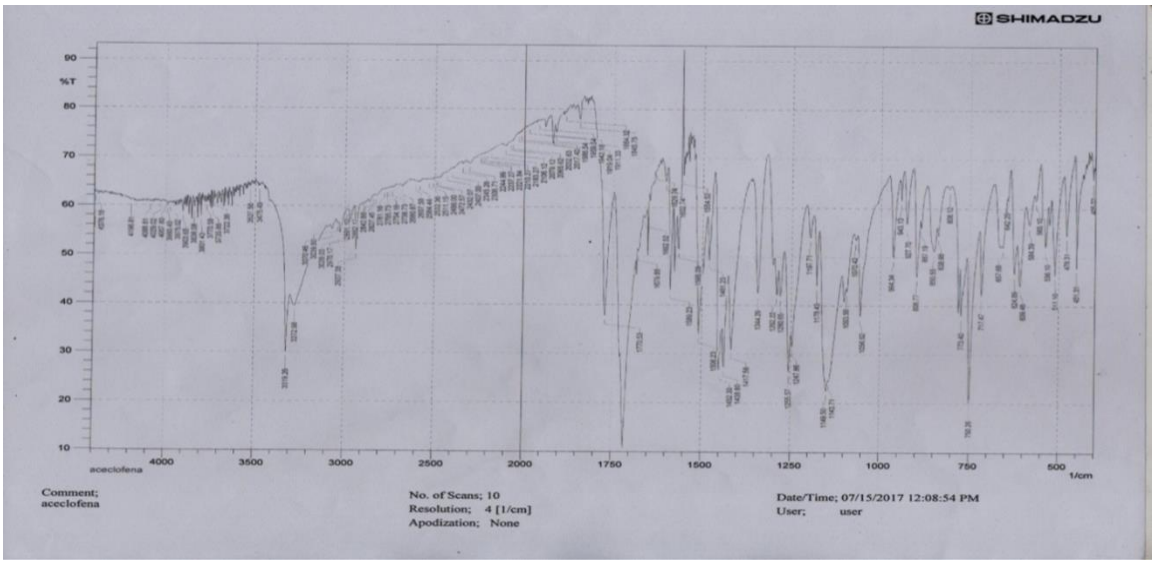

Figure 5: FTIR graph of aceclofenac (Pure drug)

Table 9: Interpretation of FTIR graph of pure drug aceclofenac

S. No	Region in cm^{-1}	Type of vibration	Functional group present
1	3319.26	N-H Stretch	Amine
2	750.26	C-H bend	Aromatic
3	1149.50	C=C bend	Aromatic

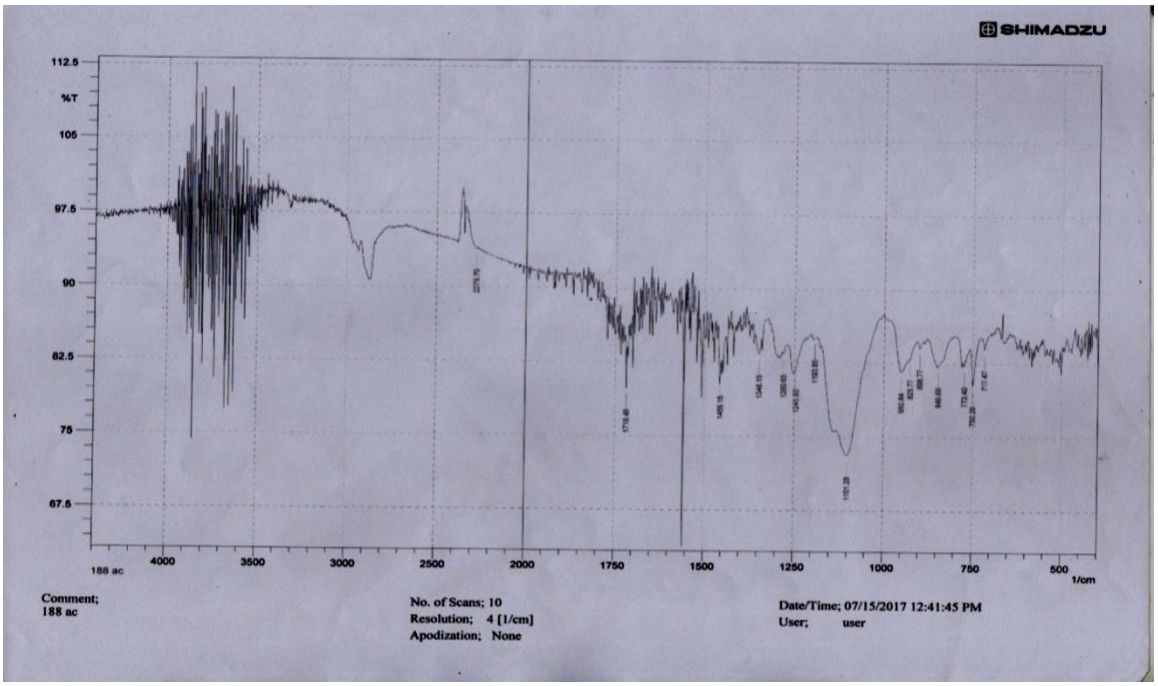

Figure 6: FTIR graph of aceclofenac and poloxamer188

Table 10: Interpretation of FTIR graph of aceclofenac and poloxamer188

S. No	Region in cm^{-1}	Type of vibration	Functional group present
1	1718.46	C=C bend	Aromatic
2	1101.28	C-O stretch	Ether

3	750.26	C-H bend	Aromatic

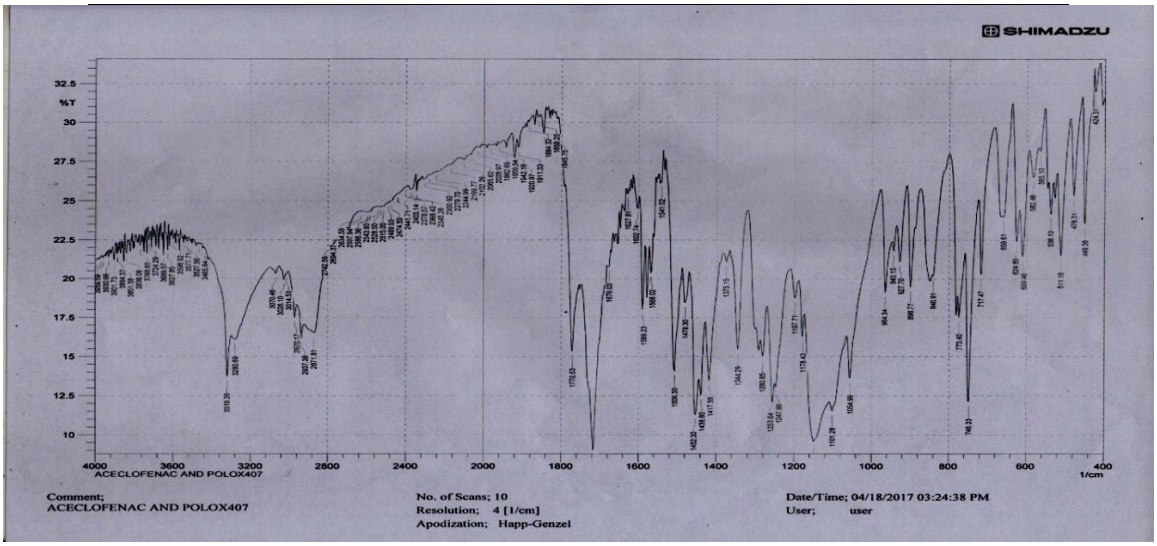

Figure 7: FTIR graph of aceclofenac and poloxamer407

Table 11: Interpretation of FTIR graph of aceclofenac and poloxamer407

S. No	Region in cm^{-1}	Type of vibration	Functional group present
1	748.33	C-H bending	Aromatic
2	3319.26	N-H Stretch	Amine
3	1770.53	C=O Stretch	Carboxylic acid

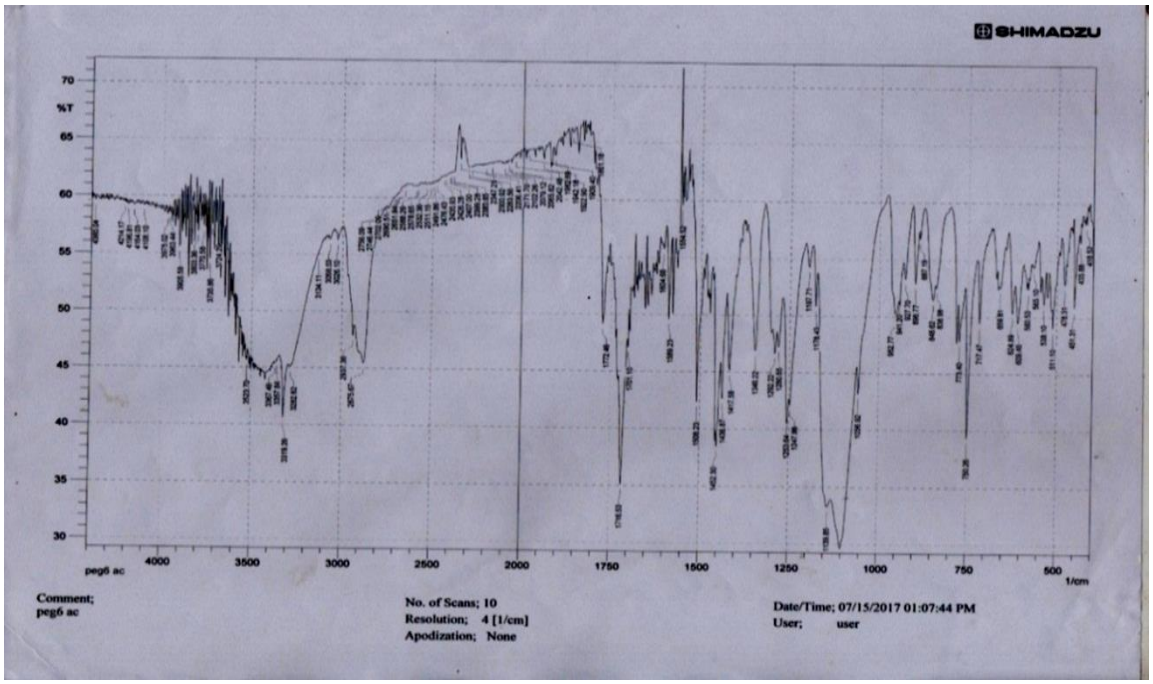

Figure 8: FTIR graph of aceclofenac and PEG6000

Table 12: Interpretation of FTIR graph of aceclofenac and PEG6000

S. No	Region in cm^{-1}	Type of vibration	Functional group present
1	3319.26	N-H stretch	Amine

2	1716.53	C=C bend	Aromatic
3	750.26	C-H bend	Aromatic
4	1452.30	C=C bend	Aromatic

From the above IR graphs the peaks representing the pure drug were found similar in formulation graph (ACP415SM) suggesting that there is no interaction and the pure drug is not altered functionally.

Thermal analysis by DSC

The nature of the prepared of solid dispersions of aceclofenac with poloxamer407 (ACP415SM) was studied by DSC. The melting point, peak onset and appearance of any peak were noted. Similarly, the plain drug was analyzed by DSC in the same manner and the melting point and onset of peak values were noted. The thermograms of the solid dispersions were superimposed with the plain drug to compare the results.

DSC of the pure drug showed a sharp peak at 8.8.25 cal. DSC of ACP415SM showed peak characteristic of the drug with no additional peaks. From the DSC it can be concluded that the drug and carrier showed no interaction. Thermograms showed in the **Figures 9 & 10**

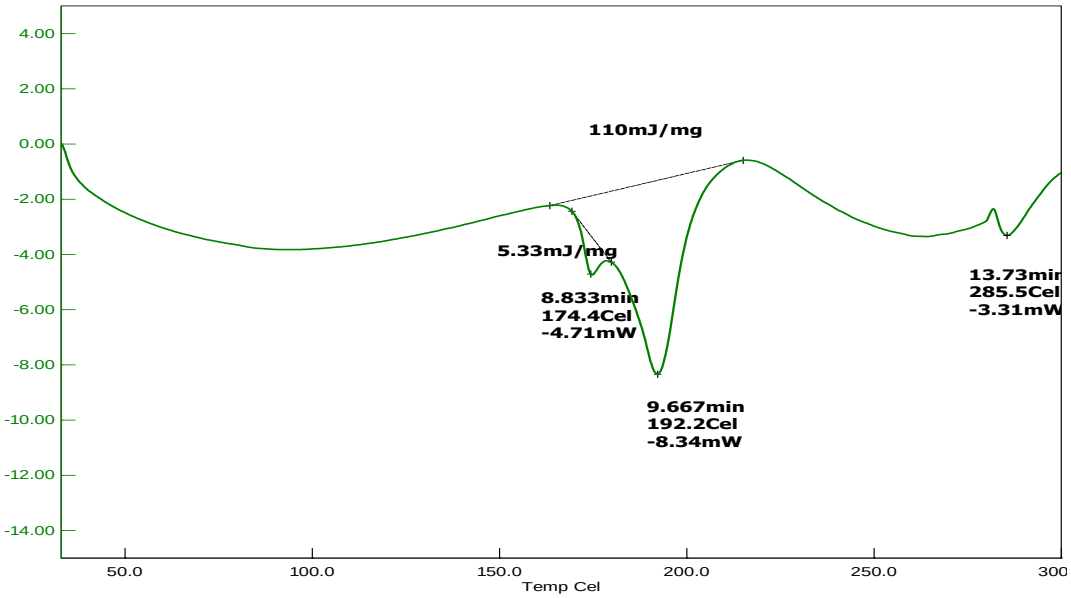

Figure 9: DSC graph of pure drug (aceclofenac)

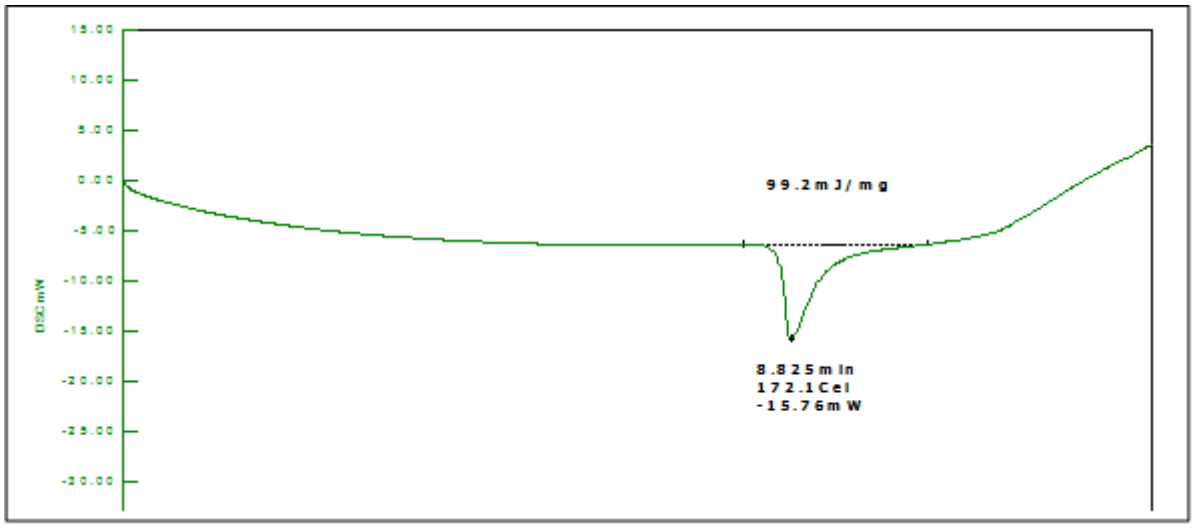

Figure 10: DSC graph of formulation ACP415SM

Crystallinity by XRD

The crystallinity of the prepared solid dispersions of aceclofenac is studied by XRD. The change in degree of crystallinity was studied. The pure drug and solid dispersions were also analyzed by XRD in same manner and the peak intensity and presence of new peaks were noted. The XRD pictures depicted in **Figures 11 & 12** for pure drug and ACP415SM respectively.

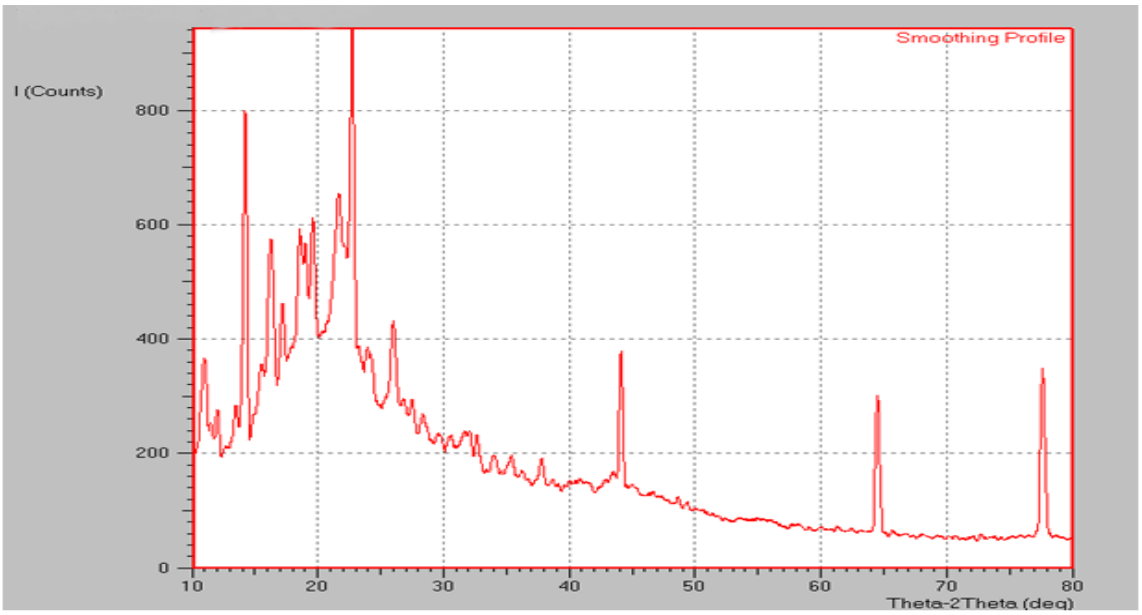

Figure 11: XRD of pure drug

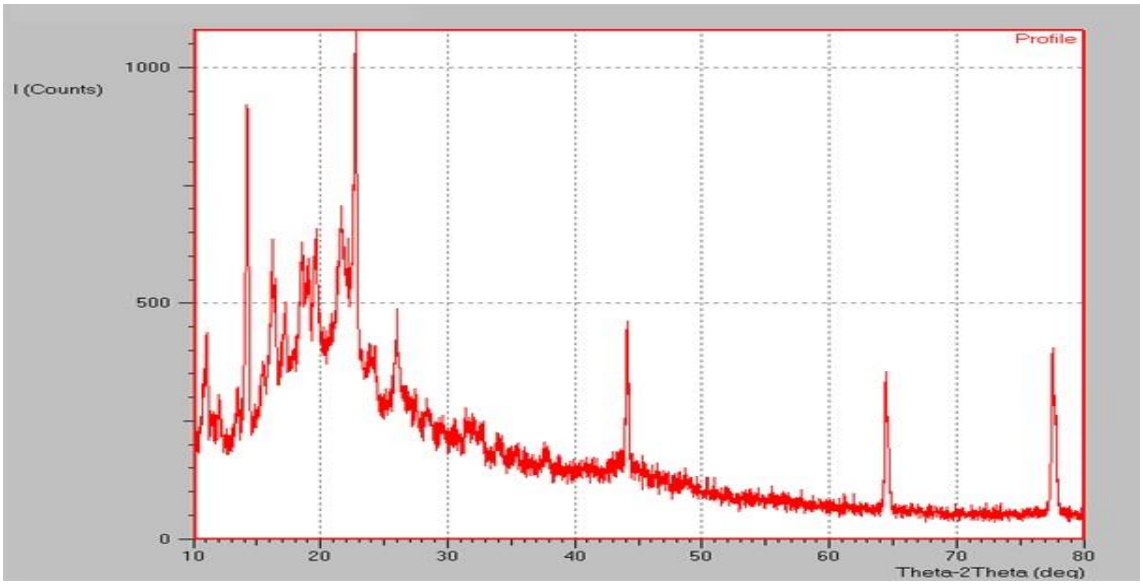

Figure 12: XRD of ACP415SM

EVALUATION OF SOLID DISPERSIONS (SDs)

Solid dispersions were prepared by physical mixture, kneading and solvent evaporation methods were evaluated for assay, solubility, dissolution studies and pre-compression parameters.

In-vitro dissolution studies in 6.8 pH phosphate buffer

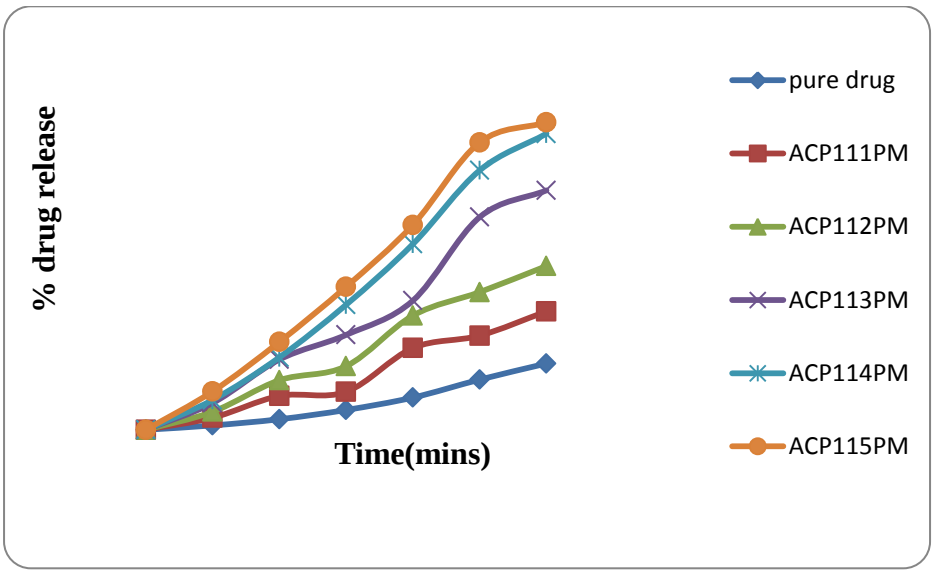

Figure 13: Dissolution profiles of aceclofenac SDs by PMM with poloxamer188

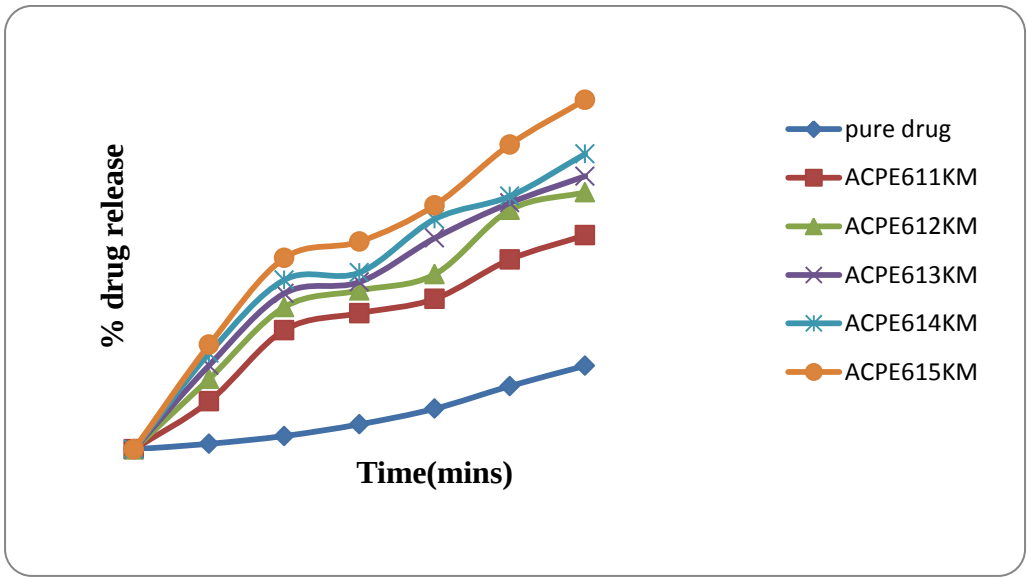

Figure 14: Dissolution profiles of aceclofenac SDs by KM with PEG6000

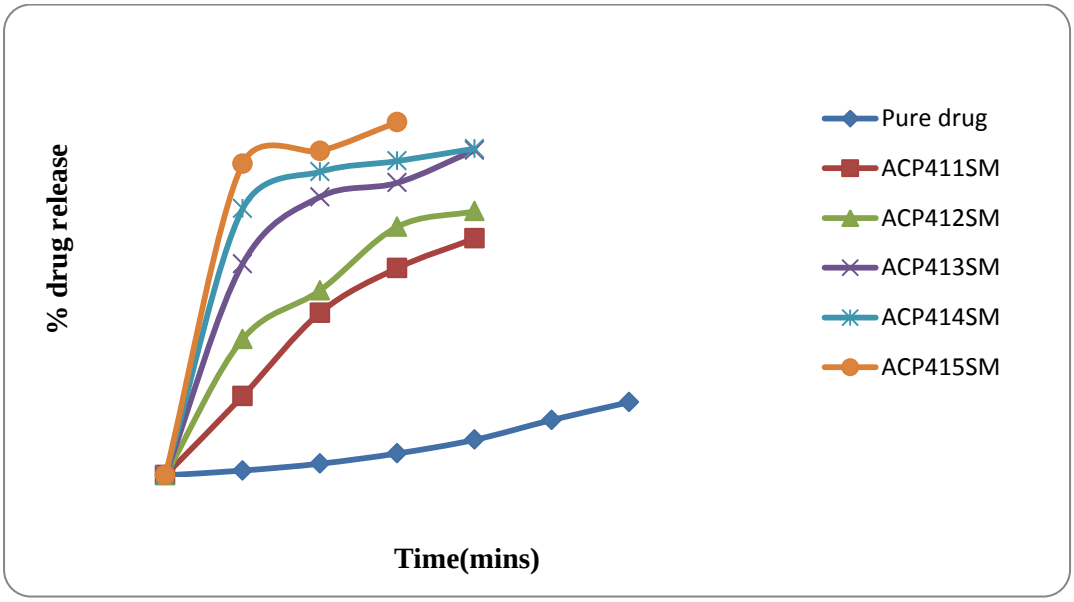

Figure 15: Dissolution profiles of aceclofenac SDs by SM with poloxamer407

From the above dissolution studies, formulation ACP415SM-aceclofenac by solvent evaporation method with poloxamer407 in 1:5 ratio showed 99% release in 30 minutes in 6.8 phosphate buffer when compared to pure drug which may be due to increased wettability of the drug by using such hydrophilic carriers and more drug getting available for dissolution. Pure aceclofenac due its hydrophobic nature and poor solubility tends to form aggregates and float on the surface leading to reduced effective surface area and thereby decreased dissolution. It was also evident that as the poloxamer407 concentration got increased, the release of aceclofenac from the SM got increased due to more carrier available for coating. Hence, ACP415SM was taken as optimized formulation.

Assay

The prepared solid dispersions complied with the requirements of assay. The result for assay for ACP415SM was 99.14±13%. These percentage drug values indicated that the drug content is uniform in all the batches. Formulation ACP415SM showed maximum assay value than other formulations.

Solubility studies

Solubility of aceclofenac by physical mixture method, formulation ACP115PM showed maximum solubility of 0.272±0.11 mg/ml. By kneading method, formulation ACPE615KM showed 0.308±0.12 mg/ml. By solvent evaporation method, formulation ACP415SM showed 0.331±0.006 mg/ml. It has been observed, as the concentration of carrier (poloxamer407) increased, the solubility was enhanced. Among the three different methods, solvent evaporation method showed maximum solubility of 0.331±0.006 mg/ml when compared with pure drug (0.0265 mg/ml). Formulation ACP415SM showed maximum solubility in distilled water. Solubility studies of aceclofenac solid dispersions results showed in **Table 13.**

Table 13: Solubility studies of aceclofenac solid dispersions

Formulation code	Solubility by physical mixture (PM) in mg/ml	Solubility by kneading method (KM) in mg/ml	Solubility by solvent evaporation method (SM) in mg/ml
Aceclofenac with poloxamer188			
ACP111	0.210±0.10	0.270±0.10	0.295±0.006
ACP112	0.224±0.14	0.286±0.15	0.298±0.009
ACP113	0.243±0.11	0.295±0.09	0.303±0.012
ACP114	0.258±0.13	0.297±0.12	0.314±0.008
ACP115	0.272±0.11	0.300±0.11	0.325±0.009
Aceclofenac with poloxamer407			
ACP411	0.222±0.12	0.252±0.11	0.298±0.009
ACP412	0.237±0.14	0.267±0.15	0.301±0.006
ACP413	0.242±0.10	0.286±0.10	0.310±0.009
ACP414	0.253±0.11	0.298±0.18	0.326±0.008
ACP415	0.267±0.10	0.305±0.17	0.331±0.006
Aceclofenac with PEG6000			
ACPE611	0.228±0.09	0.262±0.10	0.298±0.009
ACPE612	0.236±0.08	0.277±0.18	0.302±0.012
ACPE613	0.246±0.10	0.283±0.15	0.311±0.011
ACPE614	0.253±0.11	0.292±0.14	0.316±0.010
ACPE615	0.266±0.13	0.308±0.12	0.320±0.008

Note: All values expressed in mean ±SD, (n=4)

Pre compression parameters

Solid dispersions prepared by physical mixture method, kneading method and solvent evaporation method were evaluated for precompression parameters, mainly flow properties. Precompression parameters of the aceclofenac powder blend containing SDs by physical mixture, kneading method and solvent evaporation method shown in **Table 14, Table 15 and Table 16** respectively.

Table 14: Precompression parameters of the aceclofenac powder blend containing SDs by physical mixture

Formulation code	Angle of repose(Ø)	Bulk density gm/cm^3	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Assay (%)
Poloxamer188						
ACP111PM	38.0±0.11	0.325±0.02	0.349±0.01	1.20±0.02	16±0.01	97.42±0.08
ACP112PM	36.0±0.04	0.329±0.04	0.348±0.03	1.19±0.18	19±0.12	96.35±0.11
ACP113PM	35.0±0.05	0.321±0.01	0.352±0.11	1.22±0.21	17±0.09	97.65±0.12
ACP114PM	34.0±0.12	0.345±0.05	0.364±0.14	1.19±0.18	18±0.01	96.73±0.09
ACP115PM	33.0±0.06	0.325±0.09	0.367±0.02	1.24±0.04	20±0.02	97.51±0.10
Poloxamer407						
ACP411PM	33.0±0.01	0.327±0.01	0.342±0.02	1.04±0.01	4.08±0.12	98.25±0.11
ACP412PM	40.0±0.12	0.329±0.02	0.334±0.02	1.01±0.05	6.20±0.11	96.32±0.14
ACP413PM	37.0±0.01	0.330±0.02	0.369±0.12	1.11±0.10	10±0.03	97.36±0.15
ACP414PM	35.0±0.21	0.332±0.11	0.357±0.01	1.07±0.15	9.32±0.15	97.43±0.25
ACP415PM	33.0±0.02	0.336±0.10	0.364±0.04	1.08±0.04	8.56±0.11	96.67±0.02
PEG 6000						
ACPE611PM	35.0±0.12	0.328±0.15	0.348±0.01	1.06±0.08	5.74±0.01	97.53±0.09
ACPE612PM	33.0±0.11	0.331±0.01	0.351±0.12	1.06±0.10	5.69±0.09	98.67±0.12
ACPE613PM	34.0±0.25	0.335±0.04	0.355±0.15	1.05±0.05	5.63±0.11	96.33±0.08
ACPE614PM	32.0±0.01	0.341±0.04	0.357±0.01	1.04±0.11	4.48±0.14	97.58±0.11
ACPE615PM	30.0±0.15	0.352±0.12	0.359±0.02	1.01±0.15	1.98±0.06	98.69±0.15

Note: All values expressed in mean ±SD, (n=4)

The angle of repose of above physical mixture formulations ranged between 30.0±0.15 to 38.0±0.11 inferring fair flow property. Carr's index ranged from 1.98±0.06 to 16±0.01 inferring fair flow property. Hausner's ratio ranged from 1.01±0.05to 1.19±0.18 inferring fair flow property.

Table 15: Precompression parameters of the powder blend of aceclofenac containing solid dispersions by kneading method

Formulation code	Angle of repose(Ø)	Bulk density gm/cm^3	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Assay (%)
Poloxamer188						
ACP111KM	38.0±0.12	0.350±0.01	0.359±0.01	1.02±0.01	15±0.12	97.12±0.12
ACP112KM	39.0±0.11	0.332±0.12	0.351±0.12	1.05±0.14	17±0.09	98.11±0.09
ACP113KM	40.0±0.09	0.341±0.04	0.355±0.15	1.04±0.16	18±0.01	96.54±0.09
ACP114KM	36.0±0.15	0.335±0.01	0.357±0.11	1.06±0.09	16±0.08	98.62±0.11
ACP115KM	37.0±0.12	0.328±0.15	0.359±0.12	1.09±0.11	15±0.06	97.74±0.12

Poloxamer407						
ACP411KM	42.0±0.11	0.326±0.11	0.356±0.02	1.09±0.01	8±0.11	98.10±0.09
ACP412KM	39.0±0.04	0.330±0.01	0.349±0.04	1.05±0.15	5±0.09	97.13±0.07
ACP413KM	37.0±0.03	0.331±0.14	0.352±0.15	1.06±0.10	6±0.08	96.32±0.10
ACP414KM	35.0±0.01	0.337±0.02	0.342±0.11	1.01±0.12	1±0.10	98.59±0.11
ACP415KM	34.0±0.12	0.341±0.12	0.366±0.09	1.07±0.11	6±0.12	98.76±0.05
PEG 6000						
ACPE611KM	36.0±0.11	0.426±0.09	0.375±0.11	0.88±0.11	13±0.12	97.26±0.11
ACPE612KM	39.0±0.10	0.426±0.10	0.364±0.10	1.02±0.15	17±0.11	98.41±0.10
ACPE613KM	36.0±0.15	0.478±0.11	0.395±0.09	1.04±0.10	21±0.10	96.69±0.12
ACPE614KM	37.0±0.12	0.456±0.06	0.374±0.08	1.02±0.16	21±0.09	98.89±0.10
ACPE615KM	38.0±0.08	0.342±0.08	0.310±0.06	1.0±0.08	10±0.10	97.55±0.09

Note: All values expressed in mean ±SD, (n=4)

The angle of repose of above formulations ranged between 34.0±0.12 to 42.0±0.11inferring fair flow property. Carr's index ranged from 10±0.10 to 21±0.10 inferring fair flow property. Hausner's ratio ranged from 0.88±0.11to 1.09±0.11 inferring excellent flow property.

Table 16: Precompression parameters of the powder blend of aceclofenac containing solid dispersions by solvent evaporation method

Formulation code	Angle of repose(Ø)	Bulk density gm/cm^3	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Assay (%)
Poloxamer188						
ACP111SM	39.0±0.11	0.450±0.16	0.395±0.10	1.12±0.06	12±0.05	97.14±0.11
ACP112SM	36.0±0.15	0.422±0.11	0.415±0.09	1.10±0.10	13±0.15	99.14±0.10
ACP113SM	35.0±0.10	0.436±0.18	0.425±0.11	1.11±0.11	14±0.01	98.15±0.21
ACP114SM	40.0±0.14	0.458±0.09	0.380±0.14	1.18±0.12	14±0.01	99.51±0.13
ACP115SM	37.0±0.13	0.415±0.15	0.398±0.12	1.15±0.14	15±0.17	98.57±0.17
Poloxamer407						
ACP411SM	35.0±0.10	0.412±0.11	0.369±0.15	1.20±0.09	11±0.02	97.22±0.14
ACP412SM	37.0±0.11	0.420±0.14	0.421±0.10	1.09±0.06	14±0.01	98.48±0.11
ACP413SM	40.0±0.14	0.416±0.12	0.387±0.12	1.15±0.08	15±0.15	99.13±0.10
ACP414SM	35.0±0.15	0.400±0.10	0.399±0.09	1.19±0.14	13±0.10	98.11±0.16
ACP415SM	36.0±0.10	0.417±0.09	0.404±0.08	1.12±0.10	12±0.09	99.14±13
PEG 6000						
ACPE611SM	36.0±0.10	0.396±0.10	0.355±0.08	1.11±0.11	11±0.11	97.24±0.14
ACPE612SM	34.0±0.11	0.385±0.15	0.386±0.09	1.13±0.10	10±0.15	98.25±0.14
ACPE613SM	37.0±0.14	0.401±0.11	0.425±0.10	1.10±0.08	5±0.09	97.66±0.10
ACPE614SM	35.0±0.12	0.420±0.13	0.415±0.11	1.12±0.10	1±0.12	98.41±0.11
ACPE615SM	40.0±0.13	0.410±0.11	0.418±0.09	1.18±0.14	1±0.14	97.42±0.13

Note: All values expressed in mean ±SD, (n=4)

The angle of repose of above formulations ranged between 34.0±0.11 to 40.0±0.14 inferring fair flow property. Carr's index ranged from 1±0.12 to 15±0.17 inferring good flow property. Hausner's ratio ranged from 1.10±0.10 to 1.20±0.09 inferring good flow property.

The precompression parameters were found to be good as related to other formulations. The solubility of the drug is increased markedly and is nearer to that of the optimized formulation ACP415SM (0.331±0.006 mg/ml). Poloxamer407 is a hydrophilic nonionic surfactant, hence it enhances the solubility of the drugs having poor solubility, by imparting its hydrophilic nature.

Evaluation of Aceclofenac Tablets

The optimized solid dispersions in 1:5 ratio containing poloxamer407 prepared by solvent evaporation method (ACP415SM) showed better results compared to other formulations. Hence tablets of the formulation ACP415SM were prepared by direct compression method. Tablets were evaluated for various parameters like weight variation, hardness, friability, drug content, disintegration time and in vitro drug release studies.

The hardness of the tablets was found to be to 5±0.11 kg/cm^2 and friability was found to be below 1% indicating good resistance. All tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. 498 ± 5 %. The drug content was found to be 99.14±13%, indicating uniform distribution of drug in the tablets. The most important parameter that needs to be optimized in the development of tablets is the disintegration time of tablets. In the present study, disintegration time of found to be 10 min. It was observed that less disintegration time was observed when poloxamer407 was used as carrier, may be due to swelling at faster rate upon contact with water. Dissolution studies were performed in 6.8 pH phosphate buffer. Formulation ACP415SM showed maximum percentage drug release 99.62±0.15% in 30 minutes in 6.8 pH phosphate buffer as shown in **Figure 16** and results shown in **Table 17.**

Table 17: Evaluation of ACP415SM tablet

Tablet Parameters	Formulation ACP415SM
Weight variation(mg)	498±5
Hardness (kg/cm^2)	5±0.11
Friability (%)	0.438±0.15
Disintegration time (min)*	10±0.15
Content uniformity(%)	99.14±13

*Percentage drug released ±SD (n=4)

***In vitro* dissolution studies of prepared aceclofenac tablets (ACP415SM) with marketed tablet (HIFENAC 100mg)**

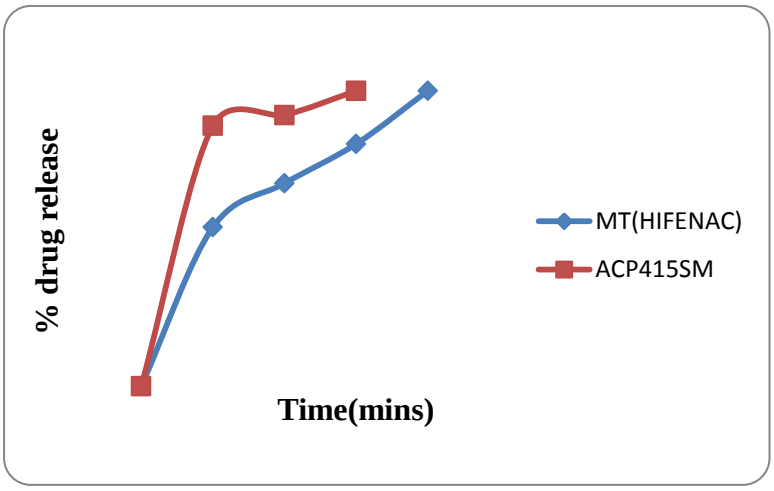

Figure 16: Comparitive dissolution profiles of prepared aceclofenac tablets with marketed tablet (HIFENAC 100mg) in 6.8 pH phosphate buffer

Accelerated stability studies

Toable 18: Accelerated stability studies

Parameters	**0 (Initial)**	**1st month**
Physical appearance	**No change**	**No change**
Hardness (kg/cm^2)	5±0.11	4.5±0.11
Disintegration time (min)	10±0.15	9±0.18
Drug content (%)	99.14±13	98.82±0.15
In-vitro drug release (%)	99.62±0.15	98.52±0.28

Note: All values expressed in mean ±SD, (n=4)

The stability of the optimized formulation ACP415SM tablets was known by performing stability studies for one month at accelerated conditions of 40±0.69°C/75±2% RH on optimized formulation. The formulation was found to be stable, with insignificant change in the hardness, disintegration time, drug content and in-vitro drug release in 6.8 pH phosphate buffer.

CONCLUSION

To enhance solubility of aceclofenac, solid dispersions with different carriers used and were prepared by physical mixture, kneading method and solvent evaporation methods. The aceclofenac drug solubility in distilled water 0.0265 mg/ml in distilled water and % drug release in 6.8 pH phosphate buffer is 26.60±0.12% in 60 mins. Solid dispersions by solvent evaporation method (ACP415SM, 1:5 ratio) showed enhanced solubility to 0.331 mg/ml in distilled water and % drug release in 6.8 pH phosphate buffer is 99.62±0.10 in 30 minutes. Drug-excipient compatibility studies conducted for solid dispersion by FTIR, DSC and XRD. From the FTIR studies results showed that there was no interaction between the drug and carrier. Poloxamer407 increased the solubility, dissolution rate of the drug (aceclofenac) by solid dispersion technique by solvent

evaporation method compared with that of the pure drug. Optimized solid dispersion of aceclofenac by solvent evaporation method (ACP415SM) containing 1:5 ratio of drug and poloxamer407 as a carrier was selected and tablets were prepared by direct compression technique. Formulation of tablets evaluated for various physicochemical characteristics and compared with marketed tablets (Hifenac). Tablets showed disintegration time within 10±0.15 min, % drug release 99.62±0.10% in 30 min when compared with pure drug shows 26.60±0.12% in 60 mins and marketed tablet (Hifenac) shows 99.64±0.07% in 40 minutes in 6.8 pH phosphate buffer.

By using poloxamer407 in the formulation of solid dispersion of aceclofenac, we can the dissolution rate or solubility enhancement of aceclofenac.

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