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VARIOUS APPROACHES TO ENHANCE *IN-VITRO* DISSOLUTION OF ACECLOFENAC AND OPTIMIZATION BY APPLYING THREE SQUIRE (3^2) FACTORIAL DESIGN

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ABSTRACT

The aim of the present study is to enhance the solubility and dissolution rate of Aceclofenac using its solid dispersions (SDs) with hydrophilic carriers like polyethylene glycol (PEG 6000) and Poly Vinyl Pyrrolidone K 30 (PVP K 30) and Inclusion complex with β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrin. The SDs of Aceclofenac with PVP K 30 were prepared at 1:1 w/w (Aceclofenac / PVP K 30) ratios by physical mixture and solvent evaporation methods. The batch of solvent evaporation method gave better dissolution profile than the batch of physical mixtures. So, further five batches were prepared by solvent evaporation method with varying PVP K 30 ratios. Similarly, SDs of Aceclofenac with PEG 6000 were prepared at 1:1 w/w (Aceclofenac /PEG 6000) ratios by physical mixture, melting and solvent evaporation methods. The batch of solvent evaporation method gave better dissolution than others. So further five batches were prepared by solvent evaporation method with varying PEG 6000 ratios. The Inclusions of Aceclofenac with β-Cyclodextrin ware prepared by physical mixture, co-grinding and kneading method at 1:1 w/w ratio. It was clear that kneading method would be the best method for the preparation of inclusion complex of Aceclofenac with β-CD. Hence kneading method was selected for further studies with varying molar ratio of β-CD. Aceclofenac inclusion complex with HP β-CD was prepared by co-grinding and kneading method at ratios 1:1 w/w. The batch of grinding method has shown better dissolution than other batches. Finally, the optimization was carried out by considering drug to PEG 6000 and molar ratio of β-CD from batch F1 to F9 and applied 3^2 factorial design. All evaluation of the properties of the SDs and Inclusion complex were performed by using Phase solubility study, dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and short-term stability studies.

KEY WORDS

Aceclofenac; Solid dispersion; Inclusion complex; Phase solubility study; Dissolution; Stability study and Factorial design.

INTRODUCTION:

Sufficient aqueous solubility is a necessary tool for effective oral delivery of any therapeutic agent. However, low soluble and highly permeable drug molecules are gradually becoming prevailing in the development pipelines of pharmaceutical companies. Such drug molecules fall into Biopharmaceutics Classification System (BCS) Class II, for which the dissolution is usually the rate-limiting step for gastrointestinal absorption. The solubility can be increased using various techniques which include solid dispersion, solvent disposition, co solvents, salt formation, pH control, micronization, co-grinding. However, all these techniques have potential limitations. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation.

Decreasing particle size increases solubility but they show poor wetting and flow. Solid dispersions have certain advantages to overcome these problems. The terms solid dispersion refers to a group of solid products consisting of at least two different components, usually a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Aceclofenac, a non-steroidal anti-inflammatory drug (NSAID) has been recommended orally for the treatment of various kinds of pain, inflammation, rheumatoid arthritis and osteoarthritis. It has specific inhibitory action against cyclo-oxygenase-2 (COX-2) than cyclo-oxygenase-1 (COX-1). The present study is aimed at improving the dissolution rate of poorly water-soluble drug Aceclofenac using different carriers PVPK 30, PEG-6000, β-CD and HP β-CD. In order to characterize the prepare dispersions, Fourier transform infrared (FTIR) spectroscopy, Differential scanning Calorimetry (DSC) as well as saturation solubility, dissolution studies, stability study and factorial design were carried out.

MATERIALS AND METHODS:

Aceclofenac was obtained as a gift sample from Lustre Pharmaceuticals, Ahmadabad, PVP K 30 , Dichloromethane (DCM) and PEG 6000 were purchased from Krishna Chem, Baroda, β-Cyclodextrin and HP β-Cyclodextrin were obtained as gift samples from Cadila Pharmaceuticals, Ahmedabad, Hydrochloric acid was purchased from Purvi enterprise, Ahmedabad, Absolute alcohol was procured from Shri Chalthan Mandali Ltd., Surat, Sodium Starch Glycolate, Crospovidone and Talc were purchased from Astron Chemical, Ahmedabad. All other ingredients used were of analytical grade.

Preliminary Studies:

1. Preparation of Standard Curve:

Aliquots of stock solution of Aceclofenac (1-10.0 ml) were transferred into a series of volumetric flasks and their volumes were made up to 50 ml each with 0.1 N HCl (i.e. 2-20 µg/ml). The absorbances were measured at 273 nm against 0.1 N HCL as blank solution using Double UV – Vis Spectrophotometer, Shimadzu-1800, Japan.

2. Solubility Determination:

Solubility of Aceclofenac was determined in different media including distilled water, 0.1 N HCL and Phosphate buffer pH 7.5. Excess amount of Aceclofenac was added into three different conical flask containing 100 ml of distilled water, 0.1 N HCL and phosphate buffer pH 7.5 respectively. These solutions were shaken for 48h at room temp on a magnetic stirrer. After equilibrium, the suspensions were filtered through 0.45 µm Millipore membrane filters. The first 15% of the filtrate was discarded to avoid any potential loss of the drug, because of absorption by the filter until and the subsequent filtrate was collected. The filtrate was appropriately diluted and the concentration of the Aceclofenac in the filtrate was determined by UV spectrophotometer at 273 nm.

3. Phase Solubility Study:

Phase solubility study for Aceclofenac was performed as described by Higuchi and Connors. Excess amount of Aceclofenac was added into 100 ml 0.1 N HCL containing carrier at various concentrations and shaken for 48h at room temperature on a magnetic stirrer. Phase solubility studies were carried out for different carriers like PEG 6000, PVP K 30, β-Cyclodextrin (β-CD) and Hydroxy Propyl β-Cyclodextrin (HP β-CD).

Formulation of Solid Dispersion of Aceclofenac with Different Carriers: -

1. Solid Dispersions of Aceclofenac with PVP K 30:

Preparation of physical mixture:

The required quantity of drug and PVP K 30 (1:1) were weighed, mixed and passed through 80 #. The prepared mixture was stored in an air tight container. (Batch S1)

Preparation of solid dispersion by solvent evaporation method:

Aceclofenac and the PVP K 30 in given ratio (1:1) were weighed and dissolved in dichloromethane and alcohol in proportion of 1:1. The solvent was evaporated under vacuum at 60° C. The solid dispersions were stored for 24 hrs in a desiccator containing fused calcium chloride as desiccating agent. The resultant solid was pulverized and then passed through 80 # sieve. The co precipitates were stored in air tight container at room temperature. (Batch S2)

2. Solid Dispersion of Aceclofenac with PEG 6000

Preparation of physical mixture:

The required quantity of drug and PEG 6000 (1:1) were weighed, mixed and passed through 80 #. The prepared mixture was stored in an air tight container. (Batch P1)

Preparation of solid dispersion by melting method

Accurately weighed Aceclofenac and PEG 6000 (1:1) were mixed evenly in petridish and heated on the sand bath till all the solid melts. Then the melt was cooled

rapidly in the ice bath. The solid dispersion was aged for 2 days, crushed, and then passed through 80 # sieve. The powder equivalent to 100 mg of Aceclofenac was weighed and filled in the capsule by hand filling method. (Batch P2)

Preparation of solid dispersion by solvent evaporation method:

Aceclofenac and the PEG 6000 in given ratio (1:1) were weighed and dissolved in dichloromethane and alcohol in equal proportion. The solvent was evaporated under vacuum at 60° C. The solid dispersions were stored for 24 hrs in a desiccator containing fused calcium chloride as desiccating agent. The resultant solid was pulverized and then passed through 80 # sieve. The co precipitates were stored in air tight container at room temperature. (Batch P3)

3. Formulation of Aceclofenac Inclusion Complex with β-Cyclodextrin (β-CD)

Preparation of Physical mixture

The required quantity of Aceclofenac and Molar ratio of β-CD with respect to drug (1:1) were weighed and mixed properly by spatula and passed it through 80 # sieve.

Preparation of Co-grinding mixture:

The required quantity of Aceclofenac and Molar ratio of β-CD with respect to drug (1:1,1:0.5,1:1.5) were weighed and pass it through 80 #. The drug and carrier were mixed in mortar for 5 minutes and stored in a glass jar.

Preparation of inclusion complex by kneading method

The required quantity of β-CD (molar) was weighed and water added to get a dough like consistency. To the paste, weighed quantity of Aceclofenac was added with respect to drug in the ratio of (1:1,1:0.5,1:1.5). The mixer was kneaded in glass mortar for 1 hour and then completely dried in oven at 60^0 C. The dry product was sieved through 80 # to obtain powder and stored in a glass jar.

4. Formulation of Aceclofenac Inclusion Complex with HP β-Cyclodextrin (HP β-CD)

Preparation of Co-grinding mixture

The required quantity of Aceclofenac and HP β-CD (1:1) were weighed and passed it through 80 #. The drug and carrier were mixed in mortar for 5 minutes and stored in a glass jar.

Preparation of inclusion complex by kneading method

The required quantity of HP β-CD was weighed, and water added to get dough like consistency. To the paste weighed quantity of Aceclofenac was added. The mixer was kneaded in glass mortar for 1 hour and then completely dried in oven at 60^0 C. The dry product was sieved through 80 # to obtain powder and stored in a glass jar.

5. Adaptation of Factorial Design:

To achieve complete dissolution of Aceclofenac and to optimize the concentration of PEG 6000 and β-CD when used in combination, the factorial design was adopted.

Formulation of batches:

A 3^2-full factorial design was used to optimize variables that were thought to affect the release of Aceclofenac. Each of the factor and level was coded in such a way that the high level of each factor was (+1), medium level was (0) and low level was (-1). Nine factorial batches were prepared, and their solubility was evaluated. The formulation of the batches and the transformed values are shown in Table No-1.

Procedure:

Required quantity of Aceclofenac as calculated according to Table No-2 was dissolved in dichloromethane and alcohol in proportion of 1:1. To that solution, required amount of PEG 6000 was added and mixed to dissolve. This solution was evaporated under vacuum at 60^0 C. The dry mass obtained was pulverized, passed through 80 # sieve and stored in air tight container. In another petridish weighed amount of β-Cyclodextrin was taken and water added with mixing to make a paste. To this paste weighed amount of above solid dispersion was added. The kneading of paste was continued for 1 hour. Then the paste was dried in hot air oven at 60^0 C, pulverized and sieved through 80 #.

6. Formulation of Tablet from the Optimized Batch of Factorial Design (F9)

The complex was prepared as per procedure and composition of batch F9. The dried mass obtained from the batch F9 was pulverized and passed through 40 # sieve and collected over 100 # sieve. From collected fines 15% were added to the granules. Other excipients such as Sodium Starch Glycolate Batches of B1, B2, B3 (2%,4%,8%), Crospovidone of B4, B5 (2%,4%), with 2% talc in all the batches were added to granules. The granules formed were evaluated for angle of repose, Hausner's ratio, Carr's Index and then compressed into the tablets. The results are depicted in Table No-3. The optimized batch from factorial design and the optimized tablet was compared for dissolution profile in Figure no-5.

***In Vitro* Dissolution Studies: -**

The pure drug/solid dispersion/inclusion complex (equivalent to 100 mg of Aceclofenac) was filled in hard gelatin capsule by hand filling method and placed into the type-I (Basket type) dissolution test apparatus USP XXIII. The tablet containing Aceclofenac equivalent to 100 mg was placed in type–II (paddle type) dissolution test apparatus USP XXIII. The 900 ml of 0.1 N HCl was used as dissolution medium maintained at 37±0.5°C. The stirring speed was kept 100 RPM.5ml of the samples were withdrawn at time intervals of 10, 20, 30, 40, 60, 90 and 120 minutes. The sample was filtered through Whatman paper (0.7 µ size). The volume of the dissolution fluid was adjusted by replacing 5ml of dissolution medium after each sampling. The absorbance of the solution was measured at 273 nm using dissolution medium as reference standard. The concentration of Aceclofenac was calculated by using Standard curve equation.

Differential Calorimetry Studies (DSC)

The possibility of any interaction between the drug and the carriers during preparation of Physical mixture, Co-grinded mixture and solid dispersion were assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture, Co-grinded mixture and solid dispersion using DSC. DSC was performed by Perkin-Elmer 7 series thermal analysis system for the drug (Aceclofenac) and solid dispersion of drug with carriers (PVPK 30, PEG-6000, β-CD & HP β-CD). Samples were scanned at 20^0C to 300^0C at a rate of 10^0C/minute in a N_2–(Nitrogen) environment.

Fourier Transforms Infrared Spectroscopy (FTIR):

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the conventional KBr pellet method. FTIR spectra of pure drug, polymer, physical mixture, co grinded mixture and solid dispersion product for both the carriers were obtained with Schimadzu spectrophotometer. The spectra were scanned over a frequency range 4000-500cm^{-1}.

Stability Study of Optimized Batch:

In order to determine the change in dissolution profiles on storage, stability study of batch B5 was carried out at 45^0 C (Batch B5a) and at room temperature (Batch B5b) for 4 weeks. During the stability study the tablets were placed in their final container. The tablets were evaluated for the change in *in-vitro* dissolution profile. The results are depicted in Table No-8.

RESULTS AND DISCUSSION:

Phase Solubility Study:

The solubility profiles of Aceclofenac in 0.1 N HCL were influenced by carrier material concentration at room temperature. All experimental trials have shown that there was increase in solubility of Aceclofenac by addition of hydrophilic carrier and this increase in solubility having a linear correlation with conc. of carrier. The solubility curve with correlation coefficient squared values (r^2) >0.95 (r^2=0.95) was regarded as a straight line (AL type) (Higuchi and Connors, 1965). Most of the hydrophilic polymers including PEG 6000, PVP K 30 and β-CD, HP β-CD show r^2 value more than 0.95 having AL type of curve. Solubility of Aceclofenac showing improvement in case of PEG 6000 compare to that of PVP K 30. While β cyclodextrin and hydroxy propyl β cyclodextrin showed an enormous improvement in solubility of Aceclofenac. This might be attributed to its surface-active property, wetting property, inclusion of drug in cavity of cyclodextrin. But from the phase solubility data it was concluded that alone β cyclodextrin can't produce satisfactory solubility and dissolution rate enhancement and hence PEG 6000 is used as hydrophilic carrier along with β cyclodextrin.

Solid Dispersion of Aceclofenac with Different Carriers

Aceclofenac: PVP K 30 solid dispersions-

The dissolution rate of pure drug is very poor and during 120 minutes a maximum of about 6.1 % of drug was dissolved from capsule. The reason for poor dissolution of pure drug could be intrinsic insolubility and hydrophobicity of Aceclofenac due to its chemical nature, agglomeration of the particles and poor wettability.

An attempt for dissolution enhancement was made by using carrier PVP K 30. The figure No 7 has shown the comparison of physical and solvent evaporation method for ACE: PVP K 30 (1:1) solid dispersion. From data received it can be concluded that solvent method is better than physical mixing method. So further batches PV1 toPV5 batches were prepared by solvent evaporation method using different weight fraction of carrier viz,1, 3,5,7,9 for 1 part of drug. Form solubility data it can be concluded that dissolution increases with increasing the proportion of the PVP K 30 being used, but the drug dissolution has not increase significantly. It

might be due to the fact that drug might present in crystalline form which hampers dissolution.

Aceclofenac: PEG 6000 solid dispersions-

The comparison of physical, melting and solvent evaporation method for Aceclofenac: PEG 6000 (1:1) solid dispersion (Batch P1-P3) and data received from them, it can be concluded that solvent method was better than physical and melting method. So further batches of PE1 to PE5 were prepared by solvent evaporation method using different weight fraction of carrier viz 1 to 5 for 1 part of drug. The comparative dissolution profile for Aceclofenac: PEG 6000 prepared by solvent evaporation method were studied. It can be concluded that there were increase in dissolution rate as the amount of the carrier increases. The enhanced dissolution rate may be due to enhanced wettability, dispersibility of drug in dissolution medium and solubilization effect by the carrier.

Aceclofenac: β-Cyclodextrin inclusion complex -

From the dissolution profile of 1:1 Aceclofenac: β-CD inclusion complex prepared by physical mixing (Batch-C1), co-grinding(Batch-C2) and kneading method(Batch-C3) it was clearly evident that kneading method has given highest dissolution among the three methods of prepared inclusion complex. The dissolution profile of 1:1 Aceclofenac: HP β-CD inclusion complex prepared by co-grinding (Batch-H1) and kneading method(Batch-H2). From experimental data it was clearly understood that co-grinding method is better than kneading method. It observed that Batch H1 which is co-grinded product of drug and HP β-CD has shown almost similar dissolution profile to that of Batch C3 which is kneaded product of drug and β-CD. As the weight of Batch H1 about 496 mg which was more than that of Batch C3 about 421 mg. So, it was decided to go with β-CD rather than HP β-CD to decrease bulk of tablet and also HP β-CD is high priced than β-CD.

Optimization by Three Squire (3^2) Factorial Design:

It was observed that β-cyclodextrin alone was not sufficient for complete solubilization of this drug. Hence it was decided to use another carrier i.e. PEG 6000 along with β-CD for complete dissolution of Aceclofenac. To achieve complete dissolution of Aceclofenac and to optimize the concentration of PEG 6000 and β-CD when used in combination, the factorial design was adopted.A 3^2 full factorial design was used to optimize variables that were thought to affect the release of Aceclofenac.The dissolution pattern for each batch was carried out and comparative dissolution profile is studied.A 3^2 factorial design was used to optimize concentration of PEG 6000 and β- Cyclodextrin. The attribute i.e. the response studied for the evaluation of best batch among the optimization set was Q_{90}.Q_{90} values show a variation from 57.0 % to 96.88 %, indicating that the selected variables exert considerable effect on drug dissolution (Table-5). The co-efficient for the equation of this optimization set was calculated as per the procedure recommended by Bolton (Table-6).

The equation for the full model was as follows

$$Y = 80.507 + 11.178X_1 + 9.039X_2 - 1.357X_1X_1 - 2.295X_2X_2 + 0.002X_1X_2$$

A polynomial equation was generated by linear multiple regression that quantitatively explain the effect of different variables on the dissolution. The equation for the reduced model was,

$$Y = 80.507 + 11.178X_1 + 9.039X_2 - 1.357X_1X_1 - 2.295X_2X_2$$

The R square value for the reduced model was 0.9992, which complied with the R square value of full model. To validate the equation, Batch F10 was prepared using X1 = 0.5 (i.e. 250 mg PEG) and X2 = 1.25 (i.e. 401 mg β-CD). Then Q_{90} of prepared checkpoint batch was evaluated in the same manner.

From the Table no 5-7 it can be concluded that experimental and predicted Q_{90} values of solubility of Aceclofenac are almost similar. Hence it can be said that the evolved model taking Q_{90} as the response is valid.

As evident from the Factorial design the optimized batch is F9 as far as percentage drug release is concerned. This batch has been further formulated and evaluated for the tablet dosage form.

Result From FT-IR Spectrum and DSC Studies

The FT-IR spectrum of pure Aceclofenac and optimized batch F9 were shown in Figure 2 and Figure 3. The results of IR analysis of pure Aceclofenac and batch F9 has shown similar peaks of Aceclofenac in both the spectrum. This indicates the absence of chemical interaction between Aceclofenac and the carriers used in the complex. Supporting evidence for complex formation was also obtained from DSC studies in Figure 4. The DSC thermogram showed endothermic peak of Aceclofenac at 156°C, which corresponded to its melting point. While the β-CD peak near to 100°C assigned to its dehydration process. The endothermic peak of Aceclofenac is almost disappeared in batch F9 indicating the formation of true inclusion complex.

Evaluation of Tablet Dosage Form of the Optimized Batch (F9)

From Table 3,4 and 8 it can be seen that drug –complex with 8 % SSG as disintegrant have very high Disintegration time (DT). However, disintegration time increased with increase in the level of sodium starch glycolate from 2 % to 8 % in the tablets. It indicates that increase in the level of sodium starch glycolate had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by sodium starch glycolate might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing sodium starch glycolate.

The disintegration time of crospovidone containing tablets are comparatively lower than those containing sodium starch glycolate. The faster disintegration of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus, these results suggest that the disintegration times can be decreased by using wicking type of disintegrants (crospovidone). So, among the batches shown in Table 3, batch B5 was selected as the optimum batch.

Stability Study:

The comparative release profile of the batch B5 and the batches after storage of 4 weeks at 45^0 C (Batch B5a) and at room temperature (Batch B5b) are shown in Fig. 5.

The student 't' test was performed on the data of *in vitro* dissolution to determine if the difference between the dissolution patterns of fresh and aged samples was significant or not. The result shows that the calculated value of 't_{cal}' is lower than the t_{tab} at 5 % probability level. Hence, there was no significant difference in the dissolution pattern after stability test.

The model independent method introduced by Moore and Flanner for evaluating similarity between two dissolution profiles was also calculated. As shown in Table 8 both Similarity factor (F2) and Difference factor (F1) lies within the normal limit of 50-100 and 0-50 respectively. Therefore, it can be concluded that the selected best batch (B5) is not significantly affected by storage conditions.

Stability study for one month was carried out at 45^0 C and at room temperature. From student't' test, F2 and F1 value it was concluded that batch B5 & batch B5b exhibited similar dissolution profile before and after stability study.

SUMMARY AND CONCLUSION:

The present study was performed to improve the solubility and its bioavailability of Aceclofenac which is a poorly soluble drug. To accomplish the purpose investigations were carried out by preparing physical mixtures, solid dispersion of drug with different hydrophilic carriers such as polyethylene glycol 6000 and Poly Vinyl Pyrrolidone K 30 and inclusion complexes with β-cyclodextrin and HP β-cyclodextrin. The Phase solubility studies of different batches ware evaluated and to select the optimized batch amongst the batches which exhibits good dissolution profile full factorial design was applied. The absence of chemical interaction was confirmed by IR spectrum and DSC studies. After selection of optimized batch, tablet dosage form was prepared, and its dissolution profile was evaluated. Finally, the stability study for one month was carried out at 450 C and at room temperature. The above studies concluded that the complexation of Aceclofenac with β-CD enhance its dissolution profile, which in turn has the potential to produce a faster onset of action and would also be helpful in reducing frequent dosing.

Table No-1: The formulation of the batches (F1-F9) and their transformed values

Batch Code	Real Values		Transformed Values	
	Drug: PEG 6000 ratio	Molar ratio of β-CD with respect to drug	X1	X2
F1	1:1	0.5	-1	-1
F2	1:1	1.0	-1	0
F3	1:1	1.5	-1	1
F4	1:2	0.5	0	-1
F5	1:2	1.0	0	0
F6	1:2	1.5	0	1
F7	1:3	0.5	1	-1
F8	1:3	1.0	1	0
F9	1:3	1.5	1	1

Table No-2: Compositions of Factorial Batches

Batch code	Aceclofenac (mg)	PEG6000 (mg)	β-CD (mg)
F1	100	100	161
F2	100	100	321
F3	100	100	481
F4	100	200	161
F5	100	200	321
F6	100	200	481
F7	100	300	161
F8	100	300	321
F9	100	300	481

Table No-3: Formulation and Evaluation Parameters of granules and Tablets

Formulation	**Batch Nos.**				
	B1	**B2**	**B3**	**B4**	**B5**
Drug complex as F9 **(Drug: PEG 6000 ratio) + Molar ratio of β-CD with respect to drug (1:3+1:1.5)**	881	881	881	881	881
Sodium Starch Glycolate	2%	4 %	8 %	_	_
Crospovidone	_	_	_	4 %	8 %
Talc	2%	2%	2%	2%	2%
Parameters					
For flow properties of granules					
Angle of Repose	25.758	26.218	28.218	23.465	21.837
Hausner's ratio	1.166	1.163	1.235	1. 121	1.035
Carr's Index	16.012	16.003	17.146	12.426	12.00
For evaluation of tablets					
Disintegration time (mins)	7.38	9.45	13.38	6.22	5.15
Crushing strength (kg)	3-4	3-4	3-4	3-4	3-4
Friability (%)	0.68	0.58	0.37	0.52	0.41

Table No-4: Comparative In-vitro dissolution profile of capsule and tablet dosage form of the optimize batch

Time (min)	**Cumulative percentage release (CPR)**	
	Batch F9 Cap	**Batch B5 Tab**
0	0.000	0.000
10	40.950	38.623
20	47.028	46.812
30	66.188	65.236
40	77.128	76.837
60	79.126	80.134
90	96.884	95.714
120	98.088	96.147

Table No-5: Q_{90} values of batches from F1 to F9

Batch no	X1	X2	X11	X22	X12	Q_{90}
F1	-1	-1	1	1	1	57.00
F2	-1	0	1	0	0	67.71
F3	-1	1	1	1	-1	74.62
F4	0	-1	0	1	0	68.54
F5	0	0	0	0	0	80.85
F6	0	1	0	1	0	87.54
F7	1	-1	1	1	-1	79.26
F8	1	0	1	0	0	90.25
F9	1	1	1	1	1	96.88

Table No-6: Results of multiple linear regression analysis

Regression Output:					
Intercept : 80.507					
Std error of Y Est.: 0.555					
Multiple R : 0.9996					
R- Square value : 0.9992					
	b_1	b_2	b_{11}	b_{22}	b_{12}
X-Coefficient	11.178	9.039	-1.357	-2.295	0.002
Std Err of Coeff.	0.226	0.226	0.392	0.392	0.277

Table No-7:

Batch F10		
Response	**Predicted**	**Experimental**
Q_{90}	92.60	91.73

Table No-8: Comparative dissolution profiles of stability study batches

Time (min)	**Cumulative percentage release (CPR)**		
	Batch B5	**Batch B5a**	**Batch B5b**
0	0	0	0
10	38.623	35.411	36.417
20	46.812	44.721	46.02
30	65.236	60.132	64.138
40	76.837	72.624	75.626
60	80.134	77.231	80.121
90	95.714	88.808	94.283
120	96.147	89.942	94.973
T_{cal}	0 .24	0.06	
T_{obs}	2.14	2.14	
F2 value	68.61	91.01	
F1 value	6.13	1.60	

Fig.1: Comparative Dissolution Profile of Batch F1-F9.

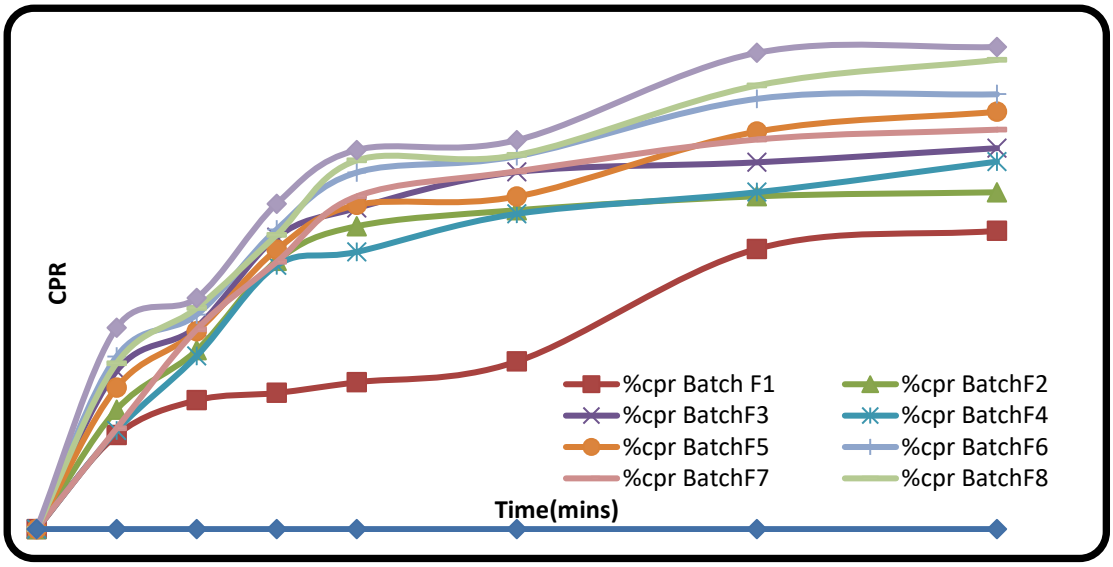


Fig. 2: FTIR spectrum of Pure Aceclofenac

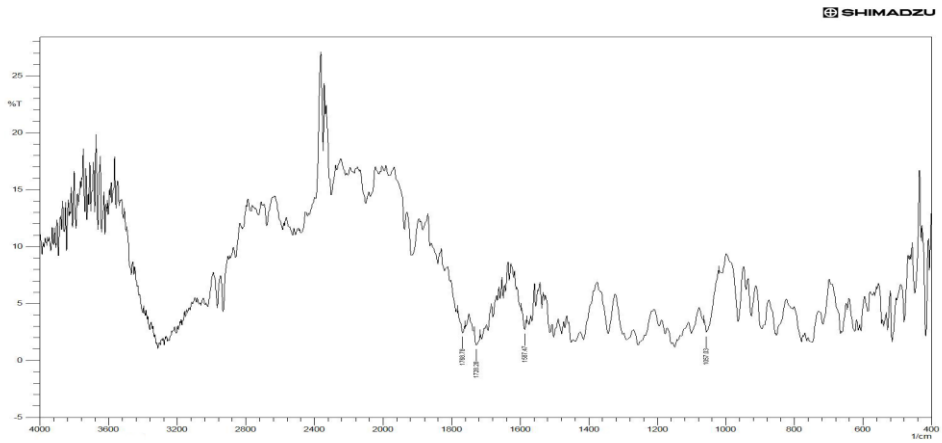


Fig. 3: FTIR spectrum of Optimized Batch F9

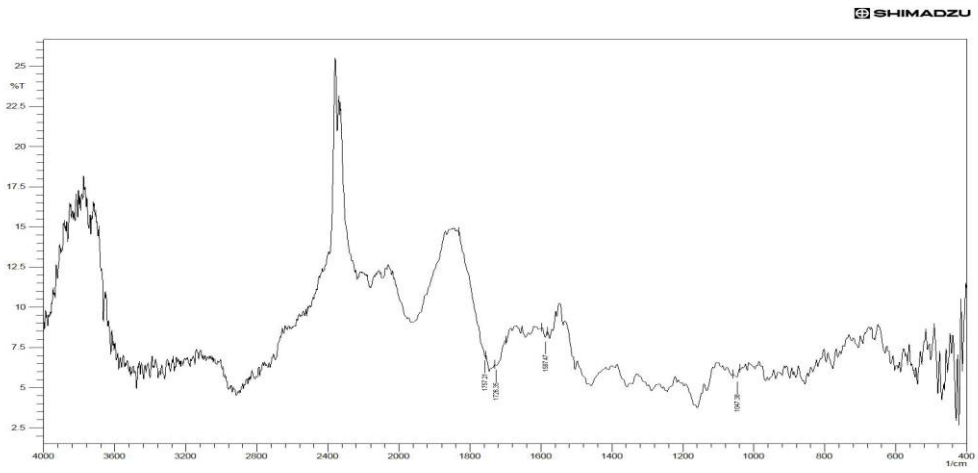


Fig .4: Thermal Analysis result of Optimized Batch F9

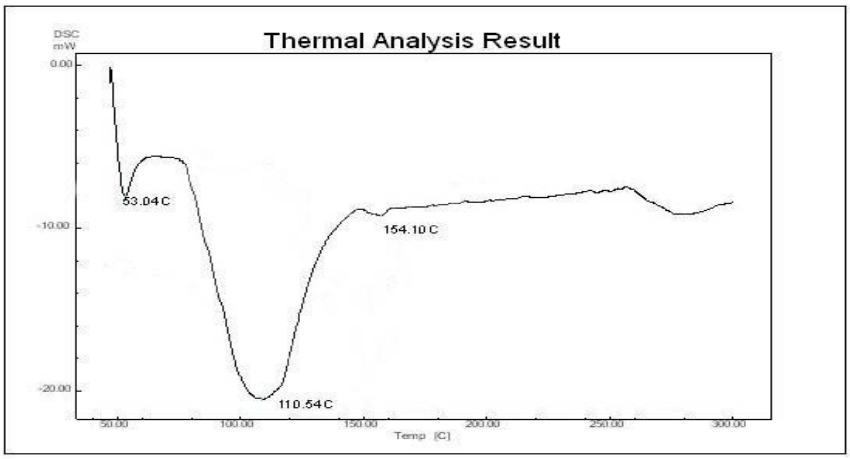
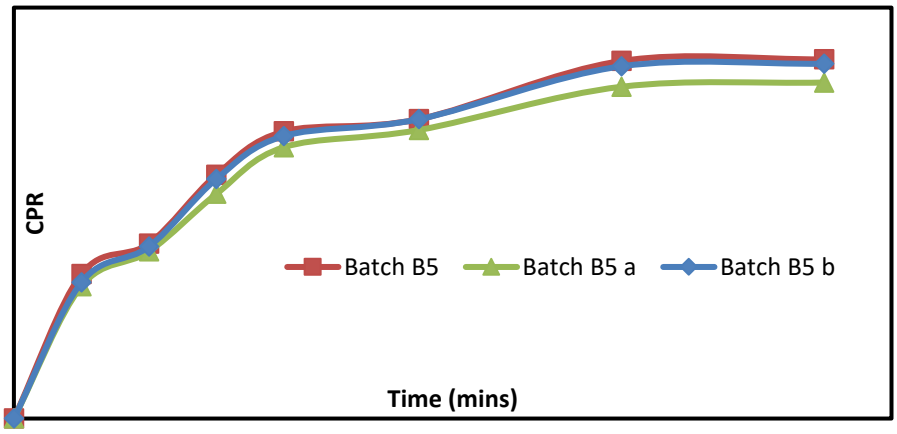


Fig. 5 : Comparative Dissolution of Stability study batches



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