Dissolution enhancement of aceclofenac tablet by solid dispersion technique

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ABSTRACT

Present study was carried out to enhace the dissolution rate of poorly water soluble drug Aceclofenac (BCS –II), by solid dispersion technique using different carrier and super disintegrant by Kneading method.

Screening of carrier and super disintegrant having better dissolution effect was performed by Placket Burman Design. Carrier that were selected for the study include Hydroxypropyl Beta Cyclodextrin (HPBCD), premix of Lactose and Maize Starch and Mannitol. Similarly, as superdisintegrant, Sodium Starch Glycolate (SSG), Croscarmellose and Crospovidone were selected . Among the carriers and superdisintegrants, Mannitol and Crospovidone showed best effect on dissolution, respectively.

For optimizaton of concentration of Mannitol and Crospovidone in solid dispersion, Central Composite Design (CCD) was applied for two factor at two level which gave 13 formulation.Tablet were prepared and evaluated for physiochemical properties. Reponse surface plot and contour plot were drawn and an optimum formulation was selected, which contained 114.14 mg of Mannitol and 10.5 mg of Crospovidone.

The *in-vitro* dissolution studies of optimized formulation CCDF8 and the marketed product were carried out in USP Type II apparatus at different time interval of 5,15, 30 and 45 minute at 50 rpm in phosphate buffer, pH 7.5 (0.33M mixed).

Solid dispersion was evaluated by FTIR. It showed that the drug was stable in solid dispersion.

Hence, Solid dispersion technique can be sucessfully used for the improvement of the dissolution profile of Aceclofenac.

Keywords: Dissolution, Aceclofenac, Solid Dispersion

1. INTRODUCTION

Aceclofenac is an orally effective Non-Steroidal Anti-Inflammatory Drug (NSAID) of phenyl acetic acid group, which possesses anti-inflammatory, analgesic properties. It is well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. Unfortunately, it has low aqueous solubility (0.058µg/ml), leading to poor dissolution and insufficient oral bioavailability. It is an example of Biopharmaceutical Classification System (BCS) class II compound and its oral bioavailability is determined by dissolution rate in the gastrointestinal tract. Therefore, the improvement of Aceclofenac dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy [1].

Various approaches including physical, chemical and other modification have been attempted to improve the solubility and bioavailability of the drugs [2].

Among them, Solid dispersion is promising technologies to improve dissolution which is defined as the dispersion of active ingredient in an inert carrier in solid state. It is simple, scalable, convenient method and prepared using numerous processes [3].

Kneading is the simplest process for the preparation of solid dispersion where drug and appropriate polymers are triturated using a small volume of ethanol-water (1:1) solution to give a thick paste and dried at medium temperature (40 - 60) ^{0}C in an oven [3].

The characteristic of solid dispersion depends upon process used, type of carrier, drug and carrier ratio, type of interaction, degree of interaction between drug and carrier, composition of solvent, process conditions such as temperature, humidity and rate of cooling.

Carrier selection in solid dispersion is a difficult process. Highly water-soluble carriers are preferred for solubility, bioavailability and dissolution rate enhancement. On contrary, water insoluble or slowly soluble or swellable or enteric polymers are used to prepare controlled or delayed-release formulations. The carriers should be heat stable, freely water soluble or soluble in organic solvents, nontoxic and pharmacologically inert [4]. Interesting method to improve the dissolution of solid dispersion tablet with high drug load might be incorporation of superdisintegrants in solid dispersion; because tablet will rapidly disintegrate, prevent crystallization of the drug, don't irritate gastrointestinal tract and can be used at low amounts in formulation. [5]

Solid dispersions are characterized to ensure the type of dispersion (molecular, amorphous, crystalline) uniformity, miscibility, particle size, surface properties and stability. At present, several techniques are available which are used to characterize SDs such as X-ray diffraction, Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy, Scanning Electron Microscopy, Small-Angle X-Ray Scattering and Dissolution Testing [6-10].

The objective of this study was to prepare solid dispersion of Aceclofenac using different carriers and disintegrants to increase dissolution, study of effect of different excipients used in the formulation on the dissolution profile and formulation of Aceclofenac tablet using chosen carrier and disintegrant.

2. MATERIALS AND METHODS

2.1 Materials

Aceclofenac and its reference standard(RS) (Potency : 100.128 and Loss on drying: 0.019 %) and other excipients, Hydroxypropyl-β-Cyclodextrin, Lactose, Maize Starch, Mannitol, Avicel PH102, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, Sodium Lauryl Sulphate, Talcum, Colloidal Silicon Dioxide and Magnesium Stearate were received from Deurali-Janta Pharmaceuticals Pvt. Ltd, Dhapasi, Kathmandu, Nepal as gift samples. Marketed products were purchased from local retail pharmacy and were used as reference product for data analysis.

2.2 Methods

Analytical method development

Scanning for the determination of λ max for Aceclofenac

A 25 mg of Aceclofenac (RS) was weighed accurately and 60 ml of methanol was added in 100 ml volumetric flask then sonicated for 10 min. After that the volume was made to 100 ml with methanol and labeled as a stock solution. The resulting solution from the stock solution was prepared and labeled as standard working solution. The spectrum of this solution was run from 200 to 400 nm range in UV-visible spectrophotometer.

Analytical Method Validation

UV visible-spectrophotometric method for assay was developed and validated. Assay method Validation was done in terms of Linearity, Specificity, Accuracy and Precision, Limit of detection (LD) and Limit of Quantification (LQ) and Range [11].

Linearity

Various concentrations of reference standard Aceclofenac solution were prepared in methanol. The absorbance of the solution was detected in UV–visible spectrophotometer. Absorbance versus concentration curve was plotted. The value of correlation coefficient (R^2) and linear equation was determined for the linearity of the plot.

Precision

Assay was done of both the formulated batches and optimized batches. Relative Standard Deviation (RSD) less than 2% indicated the precision.

Accuracy

The accuracy was performed by recovery studies at three different concentrations of samples of optimized batched. The test was performed by preparing the sample solution of 15, 20 and 25 µg/ml of Aceclofenac which was ±25% of target concentration. The test was carried out using the method of assay. Accuracy of the analytical method was indicated by recovery of analytical result. The recovery was determined by using equation 1.

$$\% \text{ Recovery} = \frac{\text{Analytical result}}{\text{True result}} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Specificity

The specificity test was carried out by scanning the spectrum of Aceclofenac reference standard, sample containing Aceclofenac and the placebo (blank) used in the formulation at the spectrum range 200-400 nm in UV visible spectrophotometer using methanol as the solvent. No peak of excipients except Aceclofenac should be obtained at wavelength 276 nm.

Limit of Detection

Various concentrations of Aceclofenac RS were prepared in methanol as mentioned in calibration curve. Limit of detection was calculated by using equation no 2.

$$\text{Limit of Detection} = \frac{3.3 \times \text{standard deviation of the blank}}{\text{slope of the calibration curve}} \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

Limit of Quantification

Various concentrations of Aceclofenac RS were prepared in methanol as mentioned in calibration curve. Limit

of quantification was calculated by using equation no 3.

$$\text{Limit of Quantification} = \frac{10 \times \text{standard deviation of the blank}}{\text{Slope of the calibration curve}} \quad \text{.....} \quad (3)$$

Range

Various concentrations of Aceclofenac RS were prepared in methanol and absorbance was measured in assay method. The range was determined as value of limit of quantification as minimum and the value obtained from the linearity data as maximum.

Design of Experiment (DOE)

Minitab 16.2.3 software was used for DOE. Initially, ten excipients (Lactose: Maize Starch, Mannitol HP-β-CD, Sodium starch Glycolate, Crospovidone, Croscarmellose, Sodium Lauryl Sulphate (SLS), Aerosil, Talcum and Magnesium Stearate) were used for Plackett-Burman Design (PBD) to determine their role in dissolution of tablet and to sort out the most effective carrier and superdisintegrant.

After that, Central Composite Design was used to find out the optimum concentration of Carrier and super disintegrant.

Solid Dispersion Preparation

Carrier (Mannitol, HPBCD, Lactose and maize starch premix) and disintegrant (Crospovidone, Croscarmellose and Sodium Starch Glycolate) were passed through sieve no 60. Aceclofenac, carrier and disintegrant of each formulation listed in Table I and Table II, was mixed in polybag for 10 minute and kneaded thoroughly for 30 minute in a mortar by the use of ethanol and water (1:1) ratio as solvent. The paste so formed was dried at 40 °C in hot air oven. Dried granules were pulverized through 14 mm mesh.

Mixing Solid dispersion with other Excipients

Excipients were sieved before mixing with solid dispersion. Sodium Lauryl Sulphate was sieved through 100 mesh, Aerosil and Avicel PH 102 were sieved through 40 mesh. Dry granule mixing was performed for 5 minute using Aerosil, Sodium Lauryl Sulphate (SLS) and Avicel 102. After that, Magnesium Stearate and Talcum (in Placket Burman only) were sieved through 100 mesh and lubricated for 2 minutes. Micromeritic properties of Aceclofenac blend were studied.

***In- Vitro* dissolution studies**

The dissolution test was carried out using IP Apparatus 1 (paddle) as per IP 2010; 900 ml of phosphate buffer pH 7.5(0.33 M) was used as dissolution medium maintained at 37±0.5°C and 50 rpm. Five ml of the sample was taken out at different interval of dissolution time and passed through Whatsman filter paper no. 1. Absorbance was measured at 273 nm using UV spectrophotometer.

Preparation of optimized formulation

On the basis of distance based optimality, surface response plot and contour plot in Minitab 16.2.3 optimization of concentrations of Mannitol and Crospovidone were carried out.

Similarity factor

It was determined by using following equation.

$$F_s = 50\, X log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}(Rj - Tj)^2\right]^{-0.5} X\ 100\right\} \quad \text{.....} \quad (4)$$

Where n is the sampling number, R_j and T_j are the % dissolved of reference and the test products at each time points j respectively. f_s value higher than 50 and close to 100 show the similarity of the dissolution profiles.

Difference Factor

It was determined by using following equation.

$$F_d = \left[\frac{\sum_{i=1}^{n}(Rj - Tj)}{\sum_{i=1}^{n} Rj}\right] X100 \quad \text{.....} \quad (5)$$

The percentage error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. F_d values should be close to 0 to be similar. In general the values lower than 15 or between 0 and 15 show the similarity of the dissolution profiles.

Fourier Transform IR (FTIR) Spectroscopy

FTIR spectroscopy has been used to study the interaction between drug and carrier. FTIR spectra of Aceclofenac , Mannitol, Crospovidone , physical mixture of optimized batch and Solid dispersion of optimized batch were analyzed**.** The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Stability Study

Accelerated Stability study has been performed as per WHO technical report series No 953 on the optimized batch [12]**.**

3. RESULTS AND DISCUSSION

Validation of Analytical Method

Linearity

Absorbance was measured by UV Visible Spectrophotometer at 276 nm of the solutions of 7.5, 10, 15, 20, 25 µg/ml. From the working standard solution, the curve was plotted by taking absorbance on y-axis and concentration on x-axis (Figure I). The graph shows that there is linear relationship between concentration and the absorbance with correlation coefficient (R^2) 0.999 and regression equation 6.

$$y = 0.033x \quad \text{.....} \qquad (6)$$

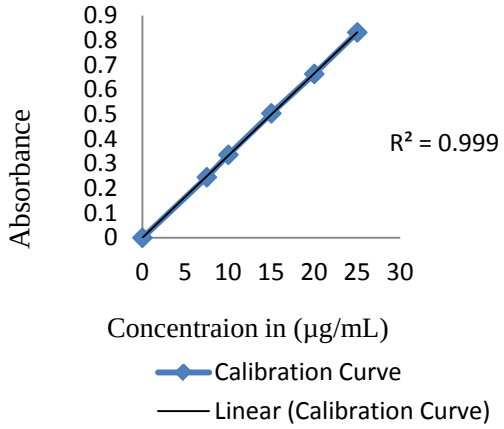

Figure I. Standard calibration curve of Aceclofenac in methanol.

Specificity

After scanning the reference standard solution, sample solution and placebo solution in the range of 200-400 nm, in the UV-visible spectrophotometer, a prominent peak was observed by the reference standard solution and sample solution at 276 nm in methanol, while a flat line was observed in the placebo at the same range of wavelength. These showed that analytical method is specific and free of interference from excipients.

Accuracy and Precision

The method of analysis was found to be accurate as the mean recovery values laid within the limit of 98.00 to 102.00% with a lower limit of 100.26% and upper limit of 101.51% while the relative standard deviation (RSD) was found to be 0.884%. Thus, the method of analysis was found to be accurate and precise.

Limit of Detection (LOD)

By using the data from linearity curve and using the equation 2. The Detection limit was found to be 0.068 µg/ml.

Limit of Quantification (LOQ)

By using the data from linearity curve and using the equation 3.The Quantification limit was found to be 0.23µg/ml.

Range

The range of analytical procedure was determined from the data obtained from the Limit of Quantification and Linearity Curve. The range of concentration for the quantification of Aceclofenac in this analytical procedure is 0.23 µg/ml to 30µg/ml.

Experimental Design

Placket Burman design

During the statistical evaluation, the excipients required for maximum drug release were determined employing main effect plot of Plackett-Burman design. The results are shown in Figure II. The result of the main effect plot showed that Mannitol, Crospovidone and SLS are significant factors affecting dissolution. Lactose: Maize Starch, HPBCD and SSG are found insignificant with negative coefficients for drug release. Talcum, Croscarmellose and Magnesium Stearate affected dissolution with minimal coefficient for drug release.

The amount of SLS in the formulation had to be high for immediate release of the drug which may lead to gastrointestinal tract irritation [5]. Therefore, Mannitol and Crospovidone were taken for further optimization; SLS, Aerosil and Magnesium Stearate were kept constant in subsequent experiments. Since Lactose: Maize starch, HPBCD, Croscarmellose and SSG decreased drug release; it was removed from further formulation design.

Avicel PH 102 was used as diluent to compress tablet at 400 mg in Placket Burman Design. PBF8, without carrier and disintegrant, showed 86 % dissolution at 10 minute. This is due to high amount of Avicel PH 102 present in the formulation as diluent. Therefore, for the further optimization in Central Composite Design, Avicel PH 102 was used as diluents.

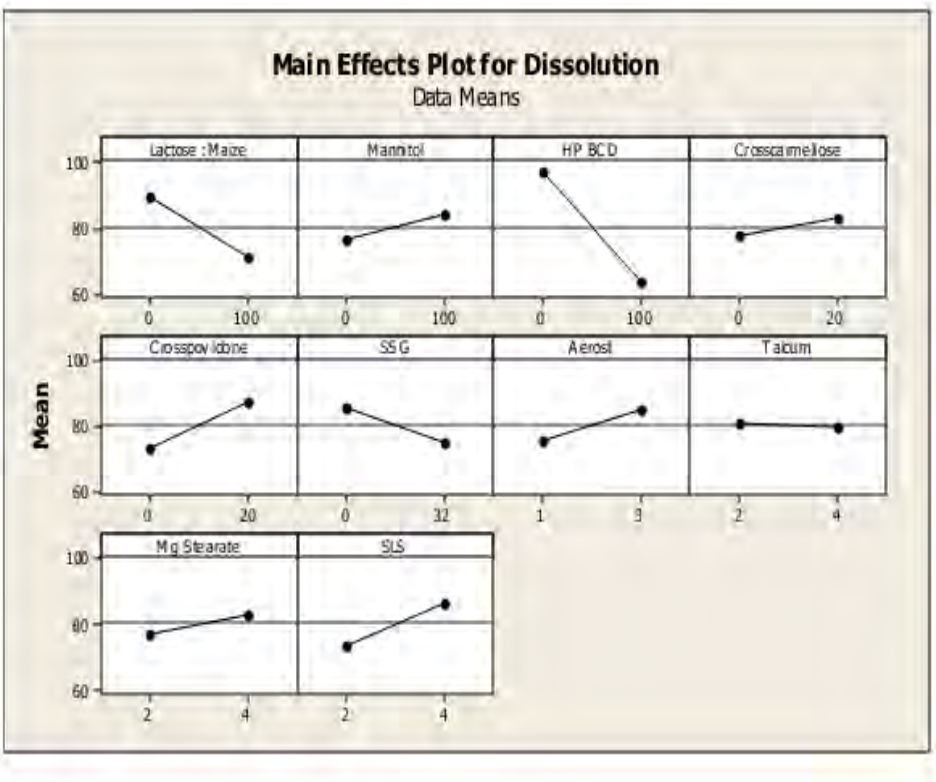

Figure II. Main effect plot showing effect of different factors on dissolution of Aceclofenac tablets at 10 mins.

Central Composite Design

Significant factors Mannitol and Crospovidone as per the result of Plackett-Burman design, contribute in drug release were further optimized by response surface methodology using Minitab 16.2.3. Two level full factorial central composite design with 4 cube points (α= 1.41421), 5 centre point and 4 axial points with 1 replication resulting in a total of 13 experiments were used to optimize the chosen key factors that affects drug release given in Table II.

Physicochemical Properties of Tablet of Central Composite Design (CCD)

Pre-compression parameter like, initial density, tapped density, Carr's Index, Hausner's ratio of the formulation were evaluated. The initial density of granule was between 0.51g/ml of formulation CCDF1 and 0.56g/ml of formulation CCDF12.The tapped density of granule was between 0.66g/ml of formulation CCDF11 and 0.84g/ml of formulation CCDF4. Formulations CCDF2, CCDF10, CCDF11 and CCDF12 exhibited good flow properties for compression with the Carr's index value of 16.67, 15.49, 16.59 and 16.37 respectively. CCDF4 and CCDF7 formulation show poor flowability. Remaining formulations were fair passable. The value of Hausner's ratio of formulation CCDF10, CCDF11, CCDF12, CCDF13 and CCDF2 showed below 1.25 which indicates better flow property. Compressed tablets of all formulation had uniform weight due to uniform die fill which were within acceptable limit i.e. % deviation was within ±7.5% as per IP.

***In*-Vitro Dissolution**

Comparison was made between all thirteen CCD formulations for dissolution time as shown in Figure III and IV. All the formulation showed similar kind of drug release pattern i.e immediate release at earlier and constant after that. From the Figure III and IV, at 5 min F6 showed the highest drug release and F5 showed the lowest. Similarly at 15 min F8 showed the higest where as F5 showed the lowest. In 30 min, F5 showed the slowest where as F10 showed the highest .At 45 min ,F8 showed the highest where as F5 showed the lowest. Drug release from F5 was less than other formulation, it is due to crospovidone which is water insoluble disintegrant present in higher concentration in the formulation.

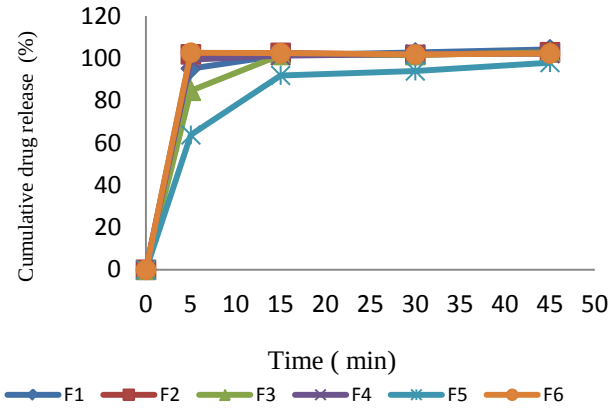

Figure III. Showing dissolution profile of CCDF1 to CCDF6

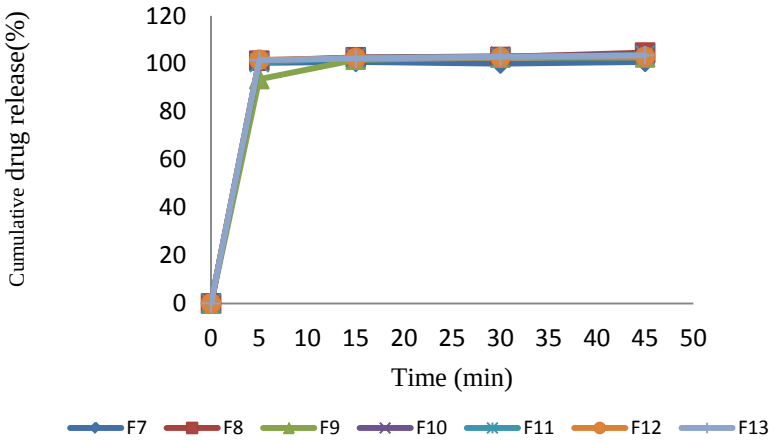

Figure IV .Showing dissolution profile of CCDF7 to CCDF13

Immediate release of Aceclofenac from tablet can be ascribed to several factors, such as lack of crystallinity of Aceclofenac after Solid dispersion preparation, reduction of aggregation and agglomeration by incorpoarating Crospovidone in solid dispersion, reduction of interfacial tension between hydophobic drug and dissolution medium, increase wettability and effective surface adsorption of drug on hydrophilic carrier (Mannitol).

Optimization of Formulation

For the optimization, distance based optimality in Minitab 16.2.3 was used, which gave CCDF8 as optimum point. 114.14 mg Mannitol and 10.5 mg Crospovidone concentration of CCDF8 was located in contour plot and surface plot (Figure V and Figure VI) and showed the desired target dissolution i.e. 100-105%. Therefore, CCDF8 was chosen as an optimized batch.

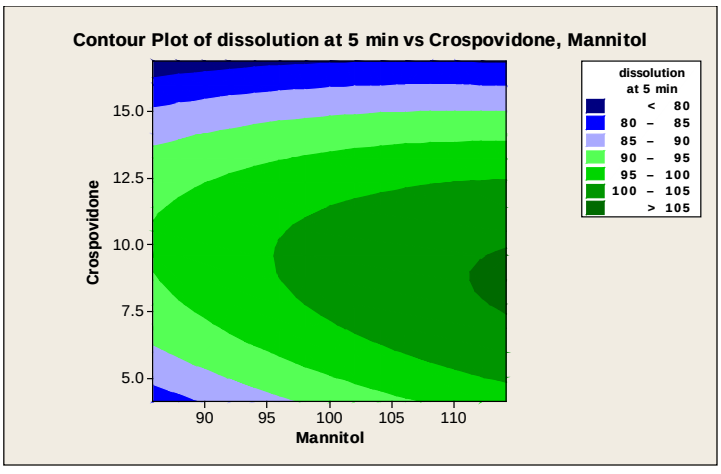

Figure V. Contour Plot of Dissolution at 5 mins vs. Crospovidone, Mannitol

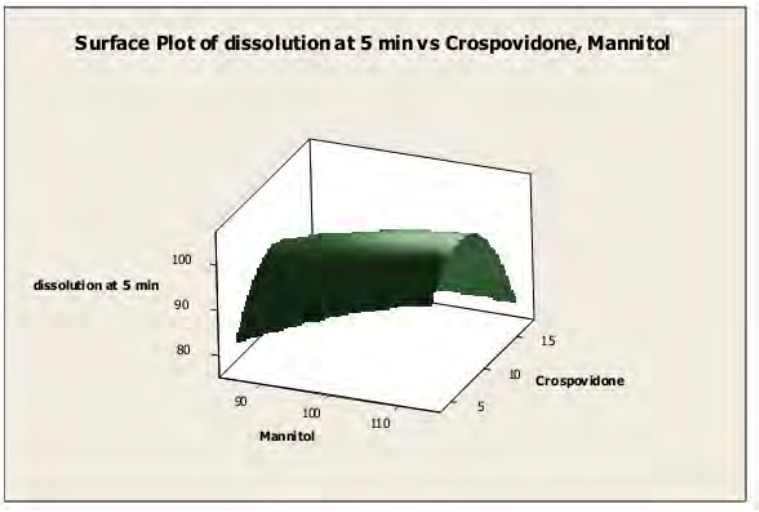

Figure VI. Surface Plot of Dissolution at 5 mins vs. Mannitol, Crospovidone

FT-IR Study

FTIR spectrum of pure Aceclofenac, physical mixture of optimized batch, solid dispersion of optimized batch and optimized batch are shown in figure VII, VIII, IX and X.

The spectrum of Aceclofenac showed characteristic bands at

- 3319.49 cm^{-1}(N-H stretching),
- 3282.84 cm^{-1} (O-H stretching),
- 1714.72 cm^{-1} (C=O stretching),
- 1589.34 cm^{-1} (Skeleton vibration of aromatic C-C stretching),
- 1282.66 cm^{-1} (C-N aromatic amine),
- 1344.38 cm^{-1} (O-H in plane bending)
- 750.31 cm^{-1} (Aromatic out plane bending for C-H)
- 2937.59 cm^{-1} (C-H Stretching)
- 1452.4 cm^{-1} (Aromatic ring stretch)
- 1658.78 cm^{-1} (C=C stretch)

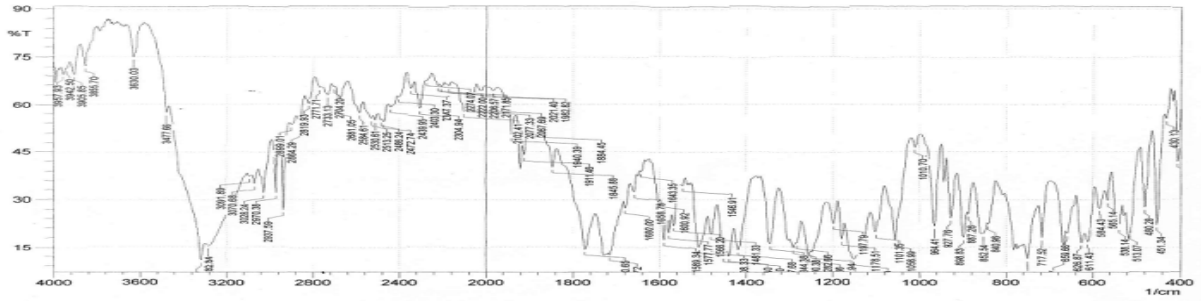

Figure VII: IR spectrum of pure Aceclofenac

These peaks were also shown by physical mixture, solid dispersion and optimized batch. These confirm the stability of the drug.

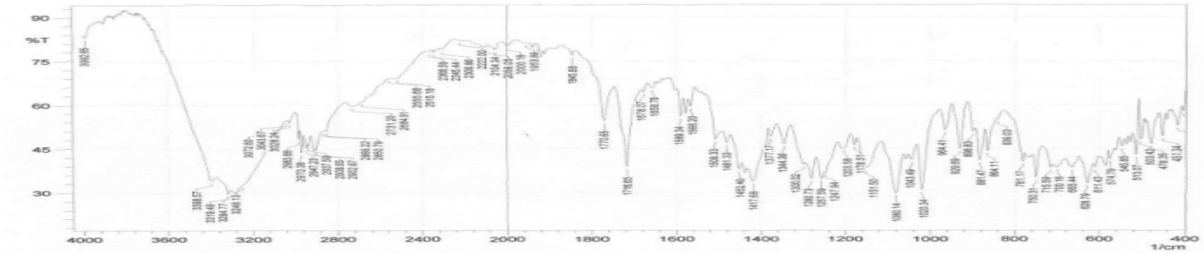

Figure VIII: IR spectrum of Physical mixture

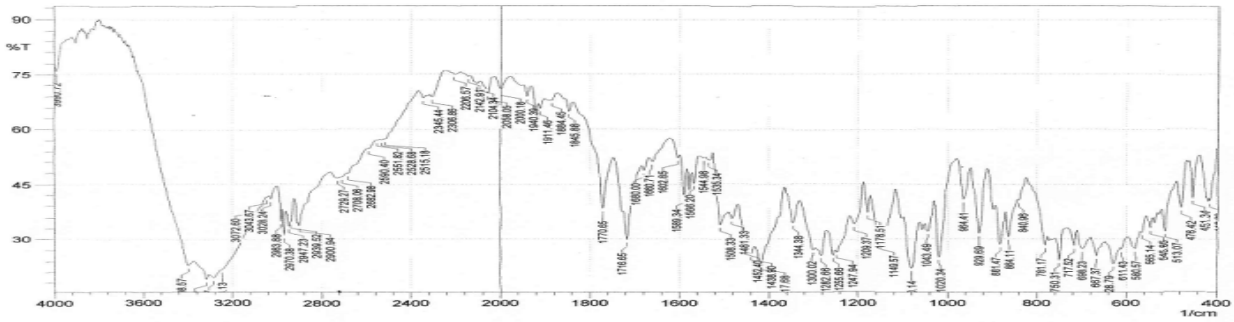

Figure IX: IR spectrum of Solid dispersion

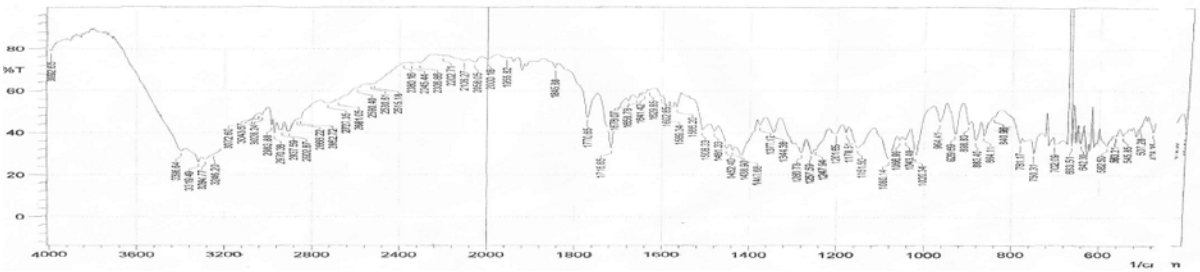

Figure X: IR spectrum of optimized batch

Solid dispersion were prepared from Mannitol, Crospovidone and Aceclofenac.The spectra of Mannitol and crospovidone are shown in figure XI,XII and characteristec bands are listed below:

Mannitol Characteristic absorption peaks at

- 3400.5 cm^{-1}(O-H stretching)
- 2947.23 cm^{-1} (C-H stretching)
- 1053,1070.49 cm^{-1}(C-O stretching)

Distinct peak of Mannitol was observed at 3400.5 cm^{-1} for OH stretching. This peak was shifted to lower frequency 3398.5 cm^{-1} in solid dispersion. The reason for this observation interpreted as a consequence of hydrogen bonding between hydrogen and oxygen molecules of Aceclofenac and Mannitol.

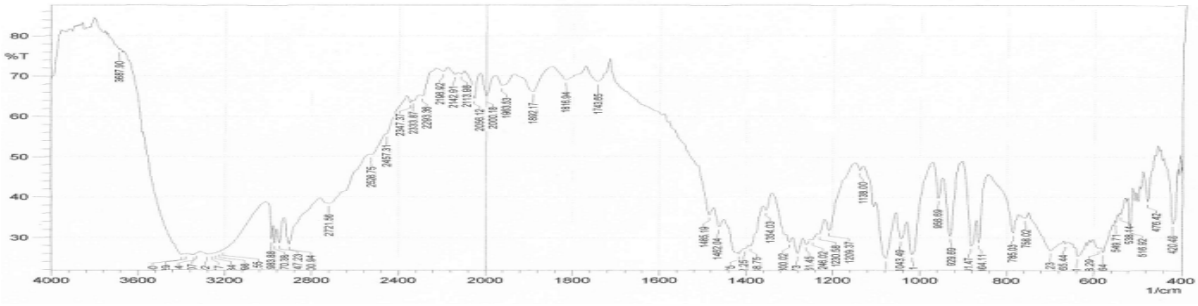

Figure XI: IR spectrum of Mannitol

Charcteristic absorption peaks of Crospovidone are

- 3469.94 cm^{-1} (N-H stretching)
- 2976.16 cm^{-1} (C-H stretching)
- 1643.35 cm^{-1}(C=O stretching)
- 1170.79 cm^{-1}(C-N stretching)
- 1114.86 cm^{-1}(C-C stretching)

C=O stretching peak of Crospovidone was observed at 1643.35 cm^{-1}. This peak was shifted to lower frequency 1641.42 cm^{-1} in solid dispersion. The reason for this observation interpreted as a consequence of hydrogen bonding between hydrogen and oxygen molecules of Aceclofenac and Crospovidone

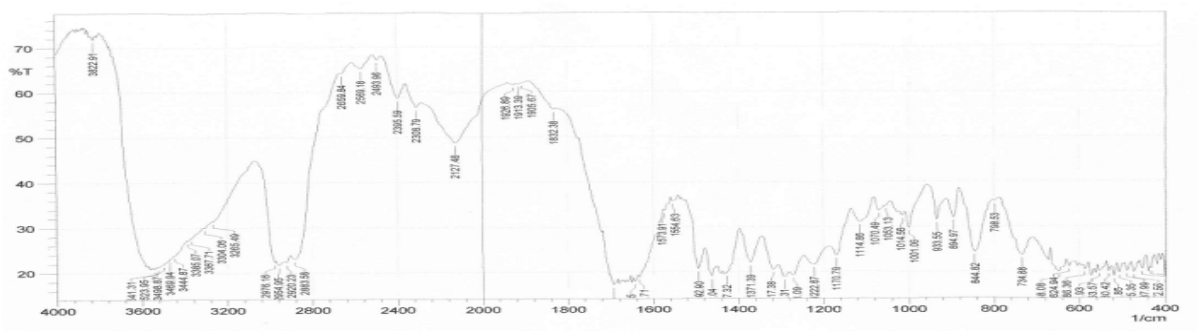

Figure XII: IR spectrum of Crospovidone

Study of In-vitro Dissolution of optimized batch, optimized formulation without Avicel and Physical Mixture of optimized formulation

Figure XIII shows dissolution profile of optimized formulation with and without Avicel, have similar kind of drug release. From this we can conclude that Avicel PH 102 have less effect in this formulation.

While comparing physical mixture of optimized formulation and optimized formulation in Figure XIII, at 5 min physical mixture show less than 40 % of drug release where as in optimized formulation release was equal to 100%. From this, we can conclude that Solid dispersion is useful technique to enhance dissolution.

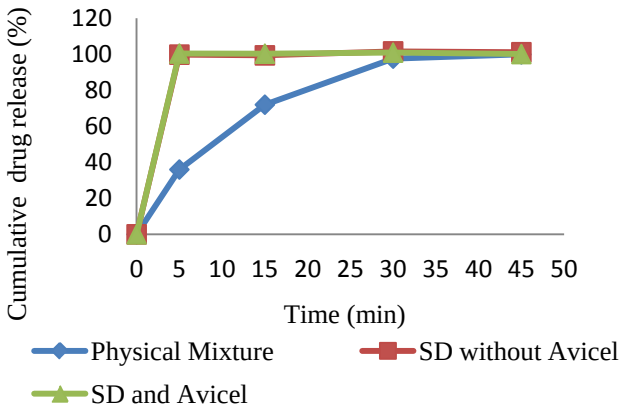

Figure XIII. Study of in-vitro dissolution of Physical mixture, Optimized formulation without Avicel and Optimized formulation

Real time and accelerated stability studies of optimized batch

The three months real time and accelerated stability study of optimized batch was performed. It was found that all the parameter tested were within the acceptable limits. The values obtained are shown in Table III.

While performing dissolution of CCDF8 stored at different storage condition as shown in Figure XIV, it was found that there was no significant difference observed in stability. From this output, we can conclude that for Aceclofenac stability is not a problem in different storage condition.

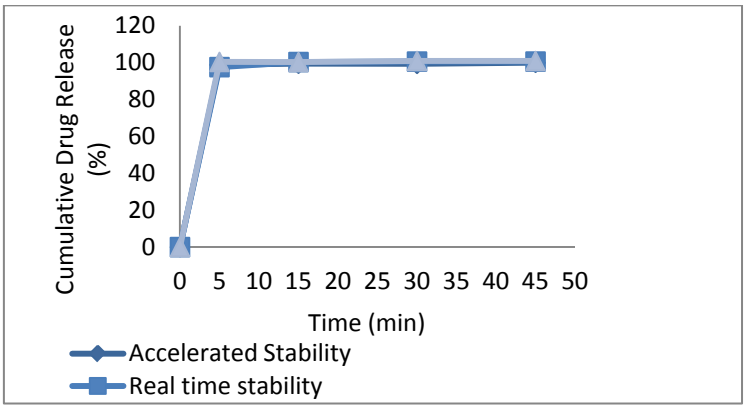

Figure XIV. Comparison of Dissolution profile of CCDF8 for zero time, real time and accelerated stability

Comparison of Dissolution Profile of Optimized Formulation with Market Product

Comparison of dissolution profiles of the market product and optimized formulation is shown in Figure XV which shows that the dissolution profile of the market product and the optimized formulation have similar pattern of drug release.

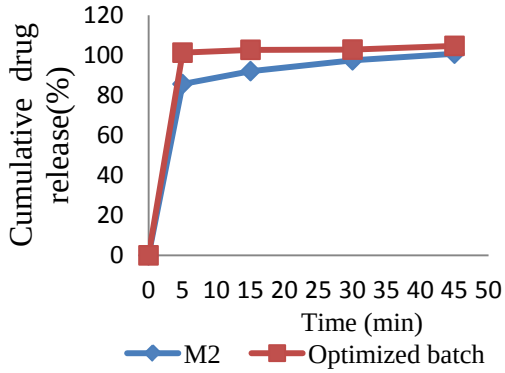

Figure XV. Showing dissolution profile of M2 market product and optimized batch

Similarity and Dissimilarity Factors

For more adequate dissolution profile comparison, similarity and dissimilarity factors were applied. Formulations that were similar to the market product M2 include F1, F2, F3, F4, F6, F7, F8, F9 F10, F1, F12 and F13. The values of the similarity and dissimilarity factor of the formulations are given in table IV which clearly indicates that the drug release profile of M2 market product and these formulations are identical as the range of Fs value is 50 to 100 and the range of Fd is 0 to 15.

4. CONCLUSION

Fast dissolving tablet is a promising approach with a view of obtaining faster action of the drug. Among all formulations, formulation CCDF8 prepared by solid dispersion of drug, Mannitol and Crospovidone at concentration of 100 mg, 144.14 mg and 10.5 mg respectively was the optimized batch. Thus it can be concluded that combination of carrier and superdisintegrant to solid dispersion of drug is promising approach to enhance dissolution of tablet of poorly water soluble drug Aceclofenac and such other poorly water soluble drugs.

5. ACKNOWLEDGEMENTS

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Formulation Code	Aceclofenac Mg	Lactose: Maize Starch (1:0.5) mg	Mannitol mg	Hp BCD mg	Croscarmellose mg	Crospovidone mg	SSG mg	Aerosil mg	Talcum mg	Mg Stearate mg	SLS mg	Avicel(102) mg	Total
PBF1	100	0	100	100	0	20	0	1	2	4	4	69	400
PBF2	100	0	100	100	20	0	32	3	2	4	2	37	400
PBF3	100	100	0	0	0	20	32	3	2	4	4	135	400
PBF4	100	100	100	0	20	0	0	1	4	4	4	67	400
PBF5	100	100	0	100	20	0	32	1	2	2	4	39	400
PBF6	100	0	0	100	20	20	0	3	4	2	4	147	400
PBF7	100	100	0	100	0	0	0	3	4	4	2	87	400
PBF8	100	0	0	0	0	0	0	1	2	2	2	293	400
PBF9	100	0	0	0	20	20	32	1	4	4	2	217	400
PBF10	100	100	100	100	0	20	32	1	4	2	2	0	461
PBF11	100	0	100	0	0	0	32	3	4	2	4	155	400
PBF12	100	100	100	0	20	20	0	3	2	2	2	51	400

Table I: Formulation of tablet as per factors considered during Placket Burman Design

Formulation Code	Aceclofenac Mg	Mannitol mg	Crospovidone mg	SLS mg	Aerosil mg	Mg Stearate mg	Avicel 102 mg	Total mg
CCD F1	100	90	6	3	3	3	95	300
CCD F2	100	100	10.5	3	3	3	80.5	300
CCD F3	100	85.86	10.5	3	3	3	94.64	300
CCD F4	100	110	6	3	3	3	75	300
CCD F5	100	100	16.86	3	3	3	74.13	300
CCD F6	100	90	15	3	3	3	86	300
CCD F7	100	110	15	3	3	3	66	300
CCD F8	100	114.14	10.5	3	3	3	66.36	300
CCD F9	100	100	4.14	3	3	3	86.87	300
CCD F10	100	100	10.5	3	3	3	80.5	300
CCD F11	100	100	10.5	3	3	3	80.5	300
CCD F12	100	100	10.5	3	3	3	80.5	300
CCD F13	100	100	10.5	3	3	3	80.5	300

Table II. Formulation of Tablet as per Central Composite Design

Conditions	**Zero time study**	**Room temperature (25°C)**	**Accelerated (75±5% RH,40±2°C)**
Assay	100.34%	99.51%	98.23%
DT	35	15	10
Hardness	8.42	7.21	6
Friability	0.56	0.6	0.9
Moisture Content	1.90%	2.23%	2.46%

Table III. Parameter of stability testing

Formulation	Similarity factor	Dissimilarity factor
F1	59	5
F2	50	9
F3	63	4
F4	53	8
F5	47	8
F6	50	9
F7	53	7
F8	50	9
F9	58	7
F10	50	9
F11	51	9
F12	50	9
F13	50	9

Table IV: Similarity and dissimilarity Factor