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Formulation and Characterization of Aceclofenac Mouth Dissolving Tablet by QbD

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ABSTRACT

The purpose of this study was to develop fast dissolving tablets of Aceclofenac using different concentration of super disintegrants. Fast dissolving tablets of Aceclofenac were prepared by dry granulation technique using croscarmellose sodium together with avicel ph as superdisintegrants. The porous granules were then compressed in to tablets by direct compression technique. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and dispersion time. All the formulations showed low weight variation with dispersion time less than 90 seconds and rapid *in vitro* dissolution. The drug content of all the formulations was within the acceptable limits. The optimized formulation showed good release profile i.e. maximum drug being released at all-time intervals compared to other trial batches. It was concluded that fast dissolving tablets with improved dissolution could be prepared by dry granulation method of tablet.

Keywords: Aceclofenac, fast dissolving tablet, dry granulation, super disintegrants.

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INTRODUCTION

Oral drug delivery is the most advisable route for drug administration among all the routes used for drug delivery. Various types of dosage forms are prepared for administration of drug via oral route. Solid dosage forms are popular because of ease of administration, self medication, accurate dosage, pain avoidance and most importantly the patient compliance.[1] Dysphagia occurs in children due to undeveloped muscular and nervous system, geriatric patients suffering from Parkinson's disease, bedridden &mentally ill patients.[2]

To overcome these problems mouth dissolving tablets are the best choice of formulation. These tablets get disintegrated or dissolved in buccal cavity avoiding water consumption. This is a newer dosage form that gets dissolved in saliva in very few seconds. these tablets are also known as melt in mouth tablet (MMT), Fast melting tablet (FMT), Fast dissolving tablet (FDT), Orally Disintegrated tablet (ODT), Rapidly Disintegrated tablet (RDT).[3]

Aceclofenac,(2-[2-[2-(2,6- dichlorophenyl)aminophenyl] acetyl]oxyacetic acid), a nonsteroidal anti-inflammatory drug NSAID) has been indicated for various painful indications and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, result in a greater compliance with treatment[4].

Aceclofenac is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution.[5] In the present study, an attempt was made to develop mouth dissolving tablets of aceclofenac and to investigate the effect of different concentration of super disintegrants on the release profile of the drug by using 3^2 factorial design in design expert software.

MATERIALS AND METHODS

Materials

Aceclofenac was gifted by medley pharmaceuticals, croscarmellose sodium and avicel ph were gifted by signet chemical Mumbai. Lactose, sodium saccharine, magnesium stearate were purchased from S.D Fine Chem. Mumbai.

Method used

Mouth dissolving tablets of Aceclofenac were prepared by using two super disintegrants croscarmellose sodium and avicel ph, lactose as diluent, sodium saccharin as sweetening agent and magnesium stearate as a flow promoter.

Blending and tableting

Tablets containing 250 mg of Aceclofenac are prepared by dry granulation method and various ingredients used in the study are shown in Table 1. The drug, diluents, super disintegrants and sweetener are passed through sieve # 40 and then passed through sieve #20. All the above ingredients were properly mixed to obtain coherent mass. The powder blend was compressed in to tablets on twelve station rotary punch-tableting machine (Karnavati, Rimek Mini Press- 2) using 8 mm concave punches set. The hardness of tablets was taken between 3 and 4.5 kg/cm^2.

Table 1: Formulation Table

S.N.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Aceclofenac	100	100	100	100	100	100	100	100	100
2	Cross Carmellose Sodium	12.5	10	7.5	12.5	10	7.5	12.5	10	7.5
3	Sodium Saccharin	2	2	2	2	2	2	2	2	2
4	Micro Crystalline Cellulose	35	35	35	30	30	30	25	25	25
5	Mg Stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6	Lactose	86	88.5	91	91	93.5	96	96	98.5	101

RESULTS AND DISCUSSION

1. Authentication of Drug:

a. UV Spectrophotometry:The solution of aceclofenac in PBS (pH 7.4) was found to exhibit maximum absorption (λ_{max}) at 276 nm after scanning in the range of 200-400 nm by UV spectrophotometer.

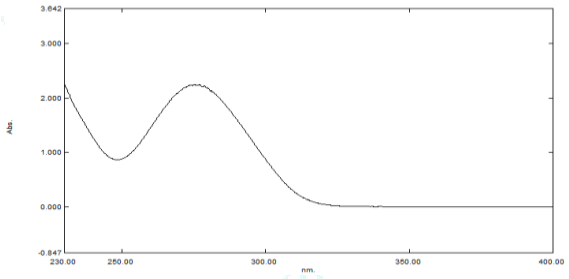

Fig 1: UV spectrum of Aceclofenac

b. Fourier transmission infrared (FT-IR) spectroscopy: Identity of the drug was confirmed by comparing IR spectrum of drug with reported spectrum of Aceclofenac as shown in Fig.

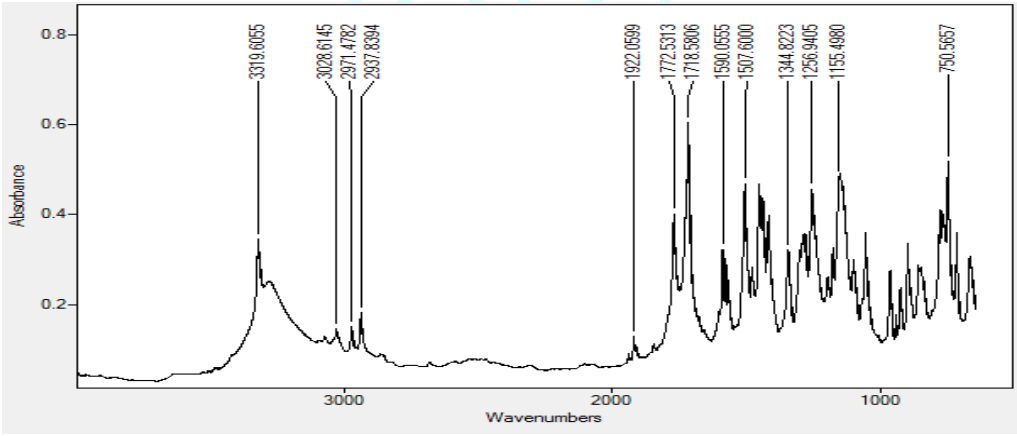

Fig 2: FT-IR spectrum of Aceclofenac

Table 2: IR Frequency range

Functional groups	Ranges
C-C streching bond	1772
C=O bond	1718
C=C bond	1589
-COOH bond	1590
-NH bond	1507
C-Cl bond	748

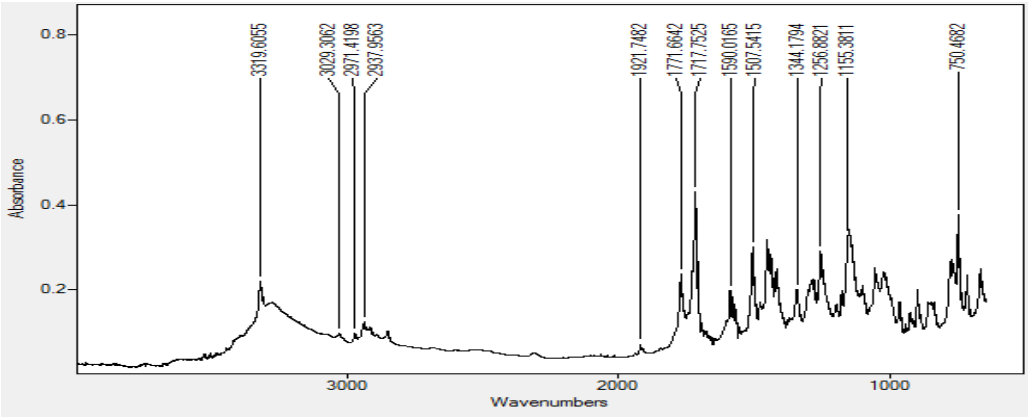

Fig 3: IR spectra of formulation

Table 3: IR Frequency range

Functional groups	Ranges
C-C streching bond	1921
C=O bond	1771
C=C bond	1590
-COOH bond	1717
-NH bond	1510
C-Cl bond	750

c. Melting point of Drug: Melting point of the drug was determined by capillary method and was found to be approximately 152±0.5°C. This was within the limits as per literature. This confirms purity of drug substance.

d. Solubility study: Solubility study was performed in water, ethanol, methanol, chloroform.

2. Construction of calibration curve: Calibration curve for aceclofenac drug was determined in PBS (pH 7.4) by UV method.

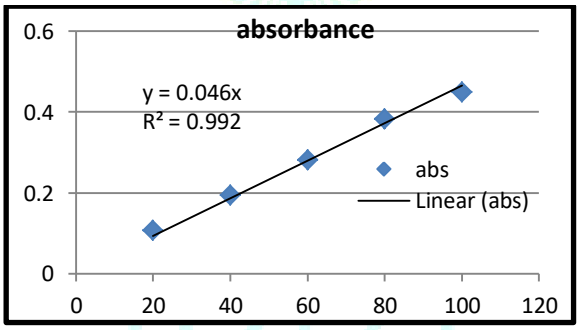

Fig 4: Calibration curve of aceclofenac

Table 4: Absorbance values of Aceclofenac

Concentration (ug/ml)	Absorbance
20	**0.107**
40	**0.194**
60	**0.282**
80	**0.383**
100	**0.450**

3. Drug-Excipients compatibility study

Compatibility studies of pure drug with superdisintegrants and other excipients were carried out prior to the preparation of tablets. The pure drug was mixed with each excipients in the ratio of 1:1 individually. The drug-excipient mixtures were taken in the vials which was previously washed, cleaned and completely dried in an oven.

Table 5: Drug excipients compatibility studies

Sr No	Drug + Excipients	Observation	Result
1	Drug + Crosscarmellose sodium	White to off white powder	Compatible
2	Drug + Micro crystalline cellulose	White to off white powder	Compatible
3	Drug + Lactose	White to off white powder	Compatible
4	Drug +Magnesium stearate	White to off white powder	Compatible
5	Drug +Sodium saccharine	White to off white powder	Compatible

EVALUATION TEST FOR FAST DISSOLVING TABLET [9-13]

1. PRE-COMPRESSION PARAMETERS

Table 6: Precompression evaluation of Aceclofenac mouth dissolving tablets

Formulation	Angle of repose()	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio
F1	28.59 ± 0.27	0.625 ± 0.023	0.758 ± 0.017	17.55 ± 0.21	1.21 ± 0.03
F2	26.57 ± 0.35	0.641 ± 0.016	0.758 ± 0.023	15.44 ± 0.14	1.18 ± 0.02
F3	26.70 ± 0.28	0.610 ± 0.028	0.735 ± 0.028	17.01 ± 0.19	1.20 ± 0.04
F4	28.32 ± 0.24	0.625 ± 0.017	0.735 ± 0.007	14.97 ± 0.07	1.18 ± 0.06
F5	26.70 ± 0.18	0.595 ± 0.029	0.694 ± 0.009	14.27 ± 0.08	1.17 ± 0.05
F6	27.74 ± 0.30	0.610 ± 0.024	0.714 ± 0.020	14.57 ± 0.16	1.17 ± 0.04
F7	28.59 ± 0.29	0.658 ± 0.014	0.781 ± 0.024	15.75 ± 0.13	1.19 ± 0.02
F8	28.94 ± 0.17	0.490 ± 0.025	0.595 ± 0.017	17.65 ± 0.09	1.21 ± 0.03
F9	28.41 ± 0.21	0.481 ± 0.018	0.581 ± 0.008	17.21 ± 0.24	1.21 ± 0.05

Angle of repose

The angle of repose of the drug powder was in the range of 26.57 ± 0.35 to 28.94 ± 0.17, which indicates good flow of the drug powder.

Bulk density

Bulk density of the drug powder was found to be in the range of g/ml 0.481 ± 0.018 to0.658 ± 0.014 g/ml.

Tapped density

Tapped density of the drug powder was found to be in the range of 0.581 ± 0.008g/ml to 0.781 ± 0.024 g/ml.

Carr's compressibility index

The Carr's index was found to be in the range of 14.27 ± 0.08% to17.65 ± 0.09 % indicating good flow of the powder blends.

Hausner ratio

Haunser's ratio was found in the range of 1.17 ± 0.04 to 1.21 ± 0.05 indicates good flow of the powder blends.

2. POST COMPRESSION PARAMETERS.

Table 7: Post compression evaluation of Aceclofenac mouth dissolving tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content
F1	3.98 ± 0.06	9.06 ± 0.05	2.17 ± 0.29	249.11 ± 3.15	0.765 ± 0.020	88%
F2	4.06 ± 0.08	9.04 ± 0.07	2.17 ± 0.29	245.78 ± 2.36	0.748 ± 0.009	90%
F3	4.30 ± 0.12	9.15 ± 0.06	2.17 ± 0.29	242.89 ± 2.68	0.758 ± 0.013	95%
F4	4.01 ± 0.05	9.04 ± 0.03	2.17 ± 0.29	253.56 ± 1.17	0.753 ± 0.012	90%
F5	4.19 ± 0.07	9.14 ± 0.02	2.17 ± 0.29	253.78 ± 1.88	0.772 ± 0.010	91%
F6	4.10 ± 0.08	9.11 ± 0.04	2.17 ± 0.29	252.22 ± 2.35	0.780 ± 0.018	92%
F7	4.47 ± 0.05	9.03 ± 0.03	2.33 ± 0.29	256.78 ± 1.58	0.776 ± 0.013	94%
F8	4.33 ± 0.03	9.11 ± 0.01	2.17 ± 0.29	253.44 ± 2.49	0.571 ± 0.017	93%
F9	4.06 ± 0.10	9.13 ± 0.07	2.17 ± 0.29	251.78 ± 2.48	0.588 ± 0.011	90%

DISINTEGRATION TIME:

Table 8: Disintegration time

Batch no	Disintegration time (sec)
F1	78
F2	50
F3	47
F4	67
F5	56
F6	96
F7	85
F8	63
F9	60

IN VITRO DISSOLUTION STUDIES

Table 9: In vitro dissolution Graphs (F1-F9)

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	3	1	1.5	3.2	2	0	0
5	10	12	15	12.5	20	13.2	16	18.9	20
10	30	29	31.83	27.23	25	19	30	30	33.5
15	43.82	30	36.5	33.5	29.2	27	39	42.1	42.5
30	46.21	57.89	46.69	40.23	39.33	30	47.19	53.22	52.89
45	53.12	74.56	79.82	53.91	51.9	38	53.11	72.56	68.3
60	70	93	94	68	69.9	42	69.01	91.63	83

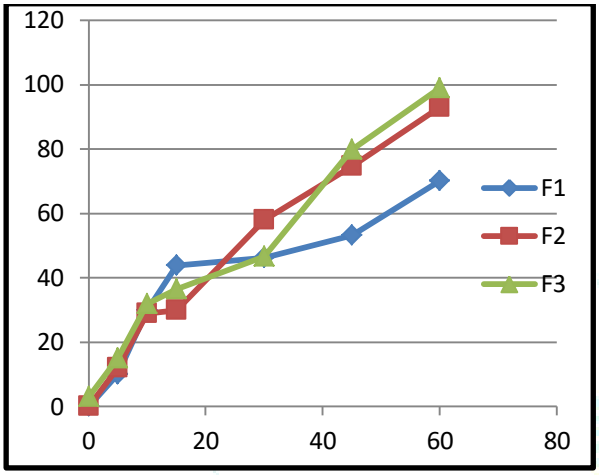

Fig 5: Dissolution graph F1-F3

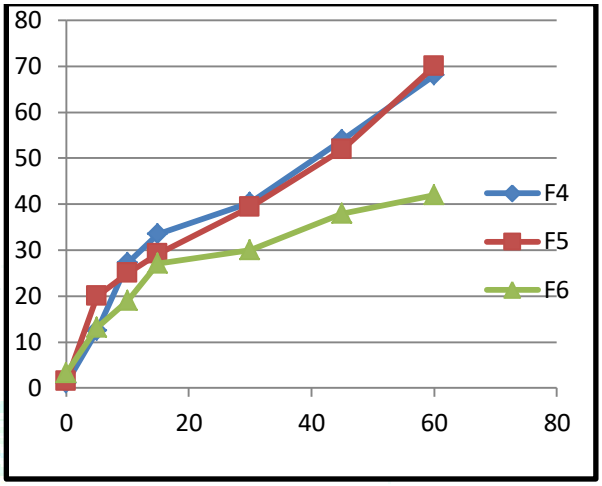

Fig 6: Dissolution graph F4-F6

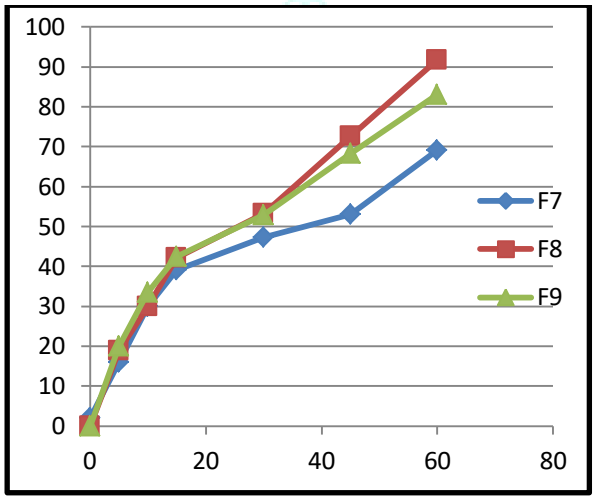

Fig 7: Dissolution graph of F7-F9

RELEASE KINETICS DATA OF OPTIMIZED BATCH:

Table 10: Release Kinetic Model

Release Kinetic Model	Regression Coefficient $(R)^2$
Zero Order	0.923
First Order	0.979
Higuchi Model	0.994
Hixscon-Crowell Model	0.972
Koresmeyers- Peppas Model	0.808

6. TABLET FORMULATION AND DEVELOPMENT BY USING 3^2 FACTORIAL DESIGNS

The present study consisted of a three-level two-factorial (3^2) design for experimentation. Statistical experimental design was performed using a software DESIGN EXPERT® version 11 (Stat-Ease Inc., Minneapolis, USA). Response surface graphics were used to show the factor interaction between the considered variables. Selected independent variables studied were the concentration of microcrystaline cellulose and croscarmelose sodium in varying concentrations viz. (X_1) and (X_2) respectively. Three factorial levels coded for low, medium and high settings (−1, 0 and 1, respectively) were considered for two independent variables. The selected dependent variables investigated were the drug release in 1hrs (Y1) and disintegration time (Y2). The number of trials required for the study is based on the number of independent variables selected. A total of 9 experimental runs were required for analyzing the interaction of each level on formulation characters and to optimize. [6, 7, 8]

Table 11: Formulation Code

Formulation Code	X_1	X_2	Microcrystaline cellulose (X1)	Croscarmelose sodium (X2)
F1	-1	-1	25	7.5
F2	0	-1	30	7.5
F3	1	-1	35	7.5
F4	-1	0	25	10
F5	0	0	30	10
F6	1	0	35	10
F7	-1	1	25	12.5
F8	0	1	30	12.5
F9	1	1	35	12.5

Formulation design

Tablets were made by direct compression method. The various batches were prepared by using 2 super disintegrants namely avicel ph(microcrystalline cellulose), croscarmellose sodium . All the ingredients were passed through 40 # and 60# mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets to 250 mg by direct compression method by using 8mm flat punch.

EXPERIMENTAL DESIGN & STATISTICAL ANALYSIS

ANOVA for Linear model

Response 1: Dissolution

Table 12: Analysis of variance table of dissolution [Partial sum of squares- Type III]

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2167.15	2	1083.57	27.68	< 0.0001	significant
A-MCC	373.83	1	373.83	9.55	0.0114	
B-S.D	1793.32	1	1793.32	45.82	< 0.0001	
Residual	391.42	10	39.14			
Lack of Fit	391.42	6	65.24			
Pure Error	0.0000	4	0.0000			
Cor Total	2558.56	12				

Factor coding is Coded.
Sum of squares is Type III - Partial

The Model F-value of 27.68 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

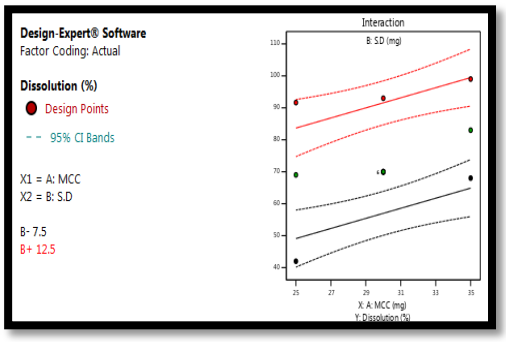

Fig 8: Interaction plot

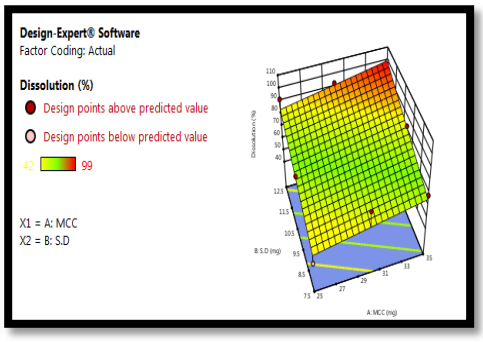

Fig 9: 3D plot

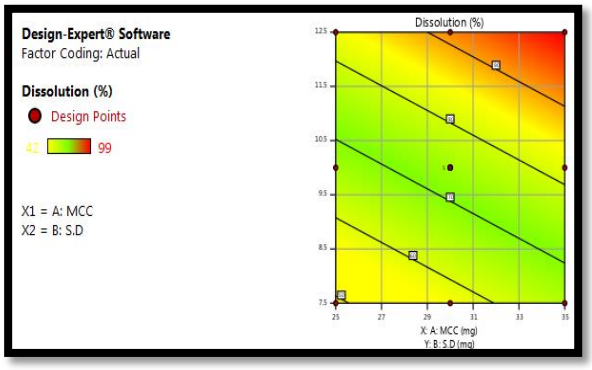

Fig 10: Counter plot

Response 2: Disintigration time

Table 13: Analysis of variance

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	216.67	2	108.33	112.37	< 0.0001	significant
A-MCC	66.67	1	66.67	69.15	< 0.0001	
B-CCS	150.00	1	150.00	155.59	< 0.0001	
Residual	9.64	10	0.9641			
Lack of Fit	9.64	6	1.61			
Pure Error	0.0000	4	0.0000			
Cor Total	226.31	12				

Factor coding is Coded.
Sum of squares is Type III - Partial

The **Model F-value** of 112.37 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A and B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

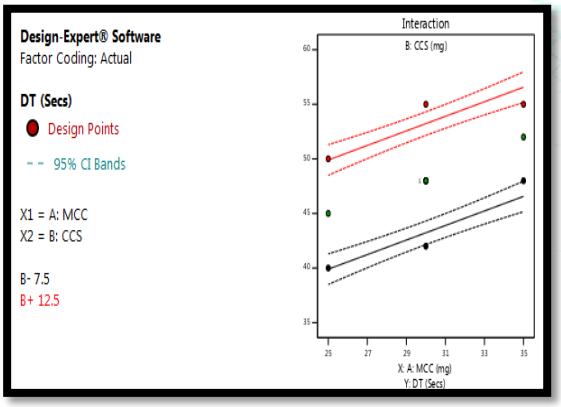

Fig 11: Interaction Plot

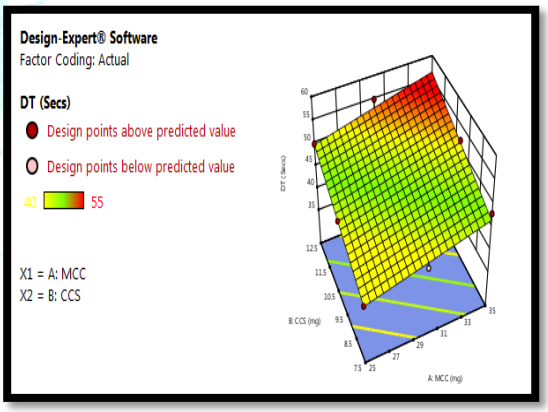

Fig 12: 3D Plot

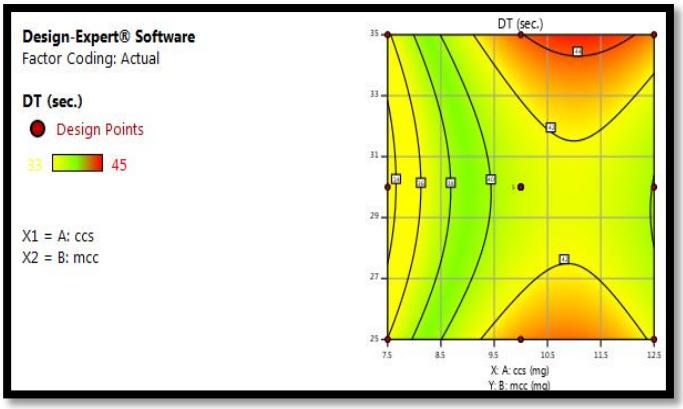

Fig 13: Contour plot

CONCLUSION

1. Aceclofenac Mouth dissolving tablets were prepared by using Cross carmellose sodium and Micro crystalline cellulose as superdisintgrants, Lactose as Diluent, Magnesium stearate as flowing aid and sodium saccharin as sweetner.
2. Aceclofenac MDT was prepared for fast release and quick action for inflammatory conditions.
3. The optimized batch followed Higuchi model for release kinetics.
4. In conclusion, it is suggested that Aceclofenac MDT with crosscarmellose sodium and avicel ph can be a better option in inflammatory conditions.
5. It was concluded that fast disintegrating tablets of Aceclofenac can be successfully prepared using selected superdisitegrants in order to improve disintegration/dissolution of the drug in oral cavity and hence better patient compliance and effective therapy.

CONFLICTS OF INTERESTS:

The authors declare that there is no conflict of interests regarding the publication of this paper.

AUTHORS CONTRIBUTION:

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Mr Shravan Yadav collected the data, and analysed the data. Dr. (Mr.) Asish dev proof-read the whole manuscript, and suggested the necessary changes, and helped in designing manuscript.

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