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Original Article

OPTIMIZATION OF STATISTICALLY DESIGNED ACECLOFENAC FAST DISSOLVING TABLETS EMPLOYING STARCH GLUTAMATE AS A NOVEL SUPERDISINTEGRANT

R. SANTOSH KUMAR, SAHITHI MUDILI

GITAM Institute of Pharmacy, GITAM (Deemed to be University), Rushikonda, Visakhapatnam-45
Email: drsantoshrada@gmail.com

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ABSTRACT

Objective: To optimize aceclofenac fast dissolving tablets employing starch glutamate as novel superdisintegrant by 2^3factorial design to improve bioavailability and enhance patient compliance.

Methods: Starch glutamate was prepared by the esterification process**.** Starch glutamate physical and micromeritics properties had been evaluated and the prepared starch glutamate was used as a superdisintegrant for the formulation of the fast dissolving tablets of aceclofenac by direct compression method and optimized by employing 2^3factorial design. The prepared aceclofenac fast dissolving tablets were evaluated for post compression parameters as well as *in vitro* and *in vivo* release characteristics. Optimized formulation stability studies were performed at accelerated conditions for 6 mo as per ICH and WHO guidelines.

Results: The prepared starch glutamate was amorphous, insoluble in aqueous and organic solvents were tested. Fast dissolving tablets of aceclofenac were formulated by employing starch glutamate as a superdisintegrant showed good tablet properties and showed an increased dissolution efficiency of the drug. Among all the formulations (F1 to F8), the formulation F8 containing 5% concentration of starch glutamate, croscarmellose sodium and, crospovidone as a superdisintegrants showed 99.7±0.15% of drug release within 5 min. Whereas the formulation F2 containing 5% concentration of starch glutamate, drug release characters were comparable to the formulation F8. Optimized formulation F2 attained peak plasma concentration within a short period and showed increased relative bioavailability of the drug.

Conclusion: From the physical properties, disintegration time, *in vitro* dissolution studies and pharmacokinetic studies, it was concluded that fast dissolving tablets of aceclofenac tablets formulated by employing starch glutamate as a superdisintegrant enhanced the dissolution efficiency and improved the bioavailability of the drug as compared to the pure drug and stable.

Keywords: Superdisintegrant, Starch glutamate, *In vitro* dissolution, Pharmacokinetics

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INTRODUCTION

Fast dissolving drug delivery system which consists of fast dissolving tablets gaining popularity nowadays [1]. Fast dissolving tablets were defined as 'a solid dosage containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon tongue' [2]. Fast dissolving tablets show improved patient compliance by avoiding difficulties in swallowing for the all age groups, especially in old age people, children, bedridden patients, and mentally disabled patients [3]. Fast dissolving tablets can be easily administered without the aid of water and provides accurate dosing [4]. Fast dissolving tablets can provide the advantages of a liquid dosage form in the solid form [5]. Aceclofenac exhibits potent analgesic activity, effective in the treatment of painful inflammatory conditions, mostly administered orally. It is broadly prescribed for conditions rheumatoid arthritis, osteoarthritis, acute lumbago and dental pian [6]. Aceclofenac is a biopharmaceutical classification system class-II drug, and drug dissolution is the limiting step for its absorption. The work aimed to formulate and characterize fast dissolving tablets of aceclofenac by utilizing optimization techniques for rapid dissolution of the drug and absorption employing a new superdisintegrant i.e., starch glutamate.

Optimization has been defined as the implementation of systemic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions [7]. Optimization is a phenomenon of finding 'the best' possible composition or operating conditions. Optimization refers to changing one variable at a time, so to obtain a solution to a problematic formulation. Optimization technique will help in fixing the quantities or levels of excipients [8]. The present study deals with an attempt of systemic formulation approach for optimization aceclofenac fast dissolving tablets employing a novel superdisintegrant i.e. starch glutamate along with other superdisintegrants like croscarmellose sodium, and crospovidone. A statistical approach i. e 2^3 factorial design was applied to investigate the main and interaction effects of the three formulation variables, i.e. starch glutamate (A), croscarmellose sodium (B), and crospovidone (C) were independent variables and dissolution efficiency in 5 min and percentage dissolved in 5 min were dependent variables in each case to find the formula with less disintegration time and more dissolution efficiency 5 min. Pharmacokinetic parameters of optimized aceclofenac fast dissolving tablets were evaluated by performing in vivo studies on male wister rats. The optimized formulation of aceclofenac fast dissolving tablets were subjected to accelerated stability test by storing the tablets at a temperature of 40±2 ° C and 75±5% RH for 6 mo.

MATERIALS AND METHODS

Materials

Glutamic acid, potato starch, acetone, potassium dihydrogen phosphate, conc. HCl and Dimethyl sulfoxide, crospovidone, croscarmellose sodium, mannitol, microcrystalline cellulose were purchased from the SD fine chemicals, Hyderabad and aceclofenac pure drug purchased from Yarrow Chem, Mumbai.

Preparation of starch glutamate

The starch slurry was prepared by dispersing the starch into distilled water. Glutamic acid was taken and it was dissolved in the distilled water and this was added to the pre-prepared starch slurry. The glutamic acid and starch slurry pH was adjusted to 3.5by using 10 ml sodium hydroxide. After pH adjustment, this slurry was conditioned for 16 h and unreacted glutamic acid was removed by washing it with distilled water. The obtained solid mass was dried at 60 °C temperature to form starch glutamate. Dried starch glutamate was passed through #120 sieve and stored in a desiccator.

Characterization of starch glutamate

The prepared starch glutamate was evaluated for the physical and micromeritics parameters like solubility, pH, melting point, viscosity, swelling index, gelling property, moisture absorption, particle size determination, density, compressibility index and angle of repose [9].

Fourier transform infrared spectroscopy (FTIR)

FTIR spectrum of starch glutamate was measured with the help of Bruker FTIR (Tokyo, Japan) at the spectrum from 4000-500 cm^{-1} [10].

X-ray diffraction

X-ray diffraction pattern of the prepared starch glutamate was measured by using the X-ray diffractometer (Panalytical spectris Pvt. Ltd., Singapore) at full scale 200 [10].

Scanning electron microscopy

The surface morphology of the starch and prepared starch glutamate were observed with the help of scanning electron microscopy [10].

Drug and excipient compatibility studies

Drug and excipient compatibility studies between the starch glutamate and aceclofenac drug were done by using Fourier transform infrared spectrum (FTIR), and differential scanning calorimetry (DSC) [11].

Preparation of aceclofenac fast dissolving tablets

Aceclofenac fast dissolving tablets employing starch glutamate was formulated as per 2^3 factorial design. In this 2^3 factorial design, three were independent variables (Starch glutamate (A), croscarmellose sodium (B) and crospovidone (C)) and two were dependent variable i.e. dissolution efficiency in 5 min and percent dissolved in 5 min. For the formulation of aceclofenac fast dissolving tablets, superdisintegrants were selected in two levels, one is lower level, i.e. zero and another level is higher level i.e. 5% concentration. To attain uniformity in particle size, each ingredient was passed through #100 mesh. Accurately weighed starch glutamate, crospovidone and croscarmellose sodium (superdisintegrants), mannitol (diluent) and microcrystalline cellulose (directly compressible vehicle) were thoroughly mixed in a mortar by using the pestle. To this mixture, aceclofenac drug was added and finally talc (glidant), magnesium stearate (lubricant) was added to this powder mixture and compressed into tablets by using eight-station compression machine (Karnawathi Machineries Pvt, Ltd., Ahmedabad, India). The composition of the different formulation of aceclofenac fast dissolving tablets were shown in table 1 [12].

Table 1: Formulae of aceclofenac fast dissolving tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	100	100	100	100	100	100	100	100
Starch glutamate (A)	---	25	---	25	---	25	---	25
Croscarmellose sodium (B)	---	---	25	25	---	---	25	25
Crospovidone (C)	---	---	---	---	25	25	25	25
Mannitol	130	105	105	80	105	80	80	55
Microcrystalline cellulose	250	250	250	250	250	250	250	250
Talc	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10
Total weight	500	500	500	500	500	500	500	500

Evaluation tests for the aceclofenac fast dissolving tablets

Hardness test

Hardness test of the tablet was done by using the Monsanto hardness tester. Tablets were placed in the hardness tester and the breaking point was recorded. The average breaking point of 10 tablets was noted, from this hardness of the tablet evaluated [13].

Friability test

Friability test was performed in Roche fribilator. In this, previously weighed 20 tablets were placed in the fribilator and rotated at 25rpm speed for 100 revolutions and again tablets were weighed after completion of the set revolutions. Then, percentage weight loss was calculated by using the following formula [14].

$$F = 100x\frac{[W(initial) - W(final)]}{W(initial)}$$

Where W (initial) = initial weight of the tablets

W (final) = Final weight of the tablets

Drug content uniformity test

Ten tablets were weighed and powdered, a quantity powder equivalent to 10 mg weight of the aceclofenac was taken and diluted with pH 7.4 phosphate buffer absorbance was measured at 276 nm with UV-Vis spectrophotometer (Shimadzu) [14].

Wetting time

Wetting time is the time required to wet tablet completely. Five Whatman tissue papers were placed in a petri dish, and in this 10 ml amaranth solution was added. Later tablet was placed on the tissue paper and time required for the tablet to wet completely was noted [15].

Water absorption ratio

The water absorption ratio was noted by pre-weighing the tablet before placing it on tissue paper which was kept in petri-dish containing 6 ml of distilled water and allowed it to wet completely and the wet weight of the tablet was noted after complete absorption of water. The water absorption ratio of the tablet was measured by using the following formula [15].

$$R = 100\frac{W_d - W_e}{W_e}$$

Where

R = water absorption ratio

W_d = weight of the tablet after water absorption

W_e = weight of the tablet before water absorption.

***In vitro* disintegration time**

In vitro disintegration test was performed by using USP disintegration apparatus basket rack assembly. Phosphate buffer (pH 7.4) was used as a disintegration medium which is maintained at a temperature of 37±0.2 °C. Six tablets were selected randomly and placed one in each of the tubes of the basket rack assembly which contain the disintegration media and the time was noted in seconds for the complete disintegration of the tablet without leaving any residue [16].

***In vitro* dissolution studies**

In vitro dissolution studies were performed by using 8 station dissolution test apparatus (Electro TDL-08L) which was fitted with the paddle. Fast dissolving tablets were placed in the dissolution media i. e 7.4 pH phosphate buffer (900 ml) at a temperature of

37±0.5 °C and 50rpm. The samples (5 ml each time) were withdrawn at the predetermined time intervals 5, 10, 15, 30, 45 and 60 min and filtered through 0.45µ membrane filter. The samples were analyzed at 274 nm by using UV-Vis spectrophotometer (Shimadzu) [17].

Factorial design

The polynomial regression algorithm equation was drawn to co-relate the independent variables, i.e. superdisintegrants starch glutamate (A), croscarmellose sodium (B), crospovidone (C) and dependent variables like percent dissolved in 5 min and dissolution efficiency in 5 min. Contour plots and surface plots were drawn with the help of Design Expert 7.11 version software. Based on the results of statistical analysis, the optimum formulation was selected.

***In vivo* studies**

The optimized formulation of aceclofenac fast dissolving tablets employing starch glutamate was tested on male Wister rats along with the pure drug. Male Wister rats were selected as an animal model. This pre-clinical study protocol was approved by the Institutional Animal Ethical Committee, GITAM Institute of Pharmacy, GITAM (Deemed to be University), and Visakhapatnam (Approval No: 1287/PO/Re/S/09/CPCSEA). Male Wister rats with body weight 200-250g were housed in a wire cage by keeping three rats in one cage and provided with free access to food and water. These animal cages were placed in a clean room with controlled room temperature (20-25 °C) and animals were exposed to 12hr light cycle and 12hr dark cycle in a day.

Male Wister rats with a bodyweight of 200-250g selected randomly and divided into two groups each group containing 6 rats. In two groups, one group treated with the pure drug (10 mg/Kg body weight in 0.5% CMC) and another group was treated with an optimized formulation (10 mg/Kg body weight in 0.5% CMC). Before the commencement of the study, rats were fastened for 12 h and during the study, they had limited access to food and water. A two-way crossover design was selected for the study, the dose was administered to the Wister rats by dispersing the drug in distilled water and through the oral feeding pipe. After drug administration, blood samples were collected from a lateral tail vein of the rat at specified time intervals, i.e. zero (pre-dose), 0.5, 1, 2, 3, 4, 5, 6 and 7th hour by anesthetizing the rats with mild ether. These blood samples were collected in the microcentrifuge tubes which containing 6 mg of EDTA (anti-coagulant) to prevent the blood clotting in microcentrifuge tubes. Plasma from these blood samples was separated by centrifugation at a speed of 5000 rpm for 25 min and these plasma samples were stored at-20 °C until further analysis. The plasma samples were analyzed using a validated HPLC method to determine pharmacokinetic parameters.

Stability studies

As per ICH and WHO guidelines optimized formulation of aceclofenac fast dissolving tablets were subjected to accelerated stability test by storing the tablets at a temperature of 40±2 ° C and 75±5% RH for 6 mo in HDPE bottles. Before and after storing for 6months these samples were analyzed for change in physical properties and drug release characteristics [18].

RESULTS AND DISCUSSION

The synthesized novel superdisintegrant starch glutamate was found to be insoluble in all aqueous and organic solvents which were tested and pH of 1% aqueous dispersion is 2.88. Starch glutamate was free-flowing and amorphous. It was having a high swelling index, i.e. 1200, which helps in the quick breakup of the tablet into smaller particles and helps in faster disintegration and increase rate of dissolution of the drug. Starch glutamate did not exhibit any gelling nature with good compressibility index and excellent flow property. Results of physical and micromeritics properties were given in table 2.

FTIR spectrum of potato starch and starch glutamate was analyzed and shown in fig. 1, 2. In the FTIR spectrum of starch glutamate, a peak was observed at 1619.29 cm^{-1}, characteristic of the ester group. Whereas no peak was observed in the FTIR spectrum of potato starch, from this it was concluded that an ester (starch glutamate) was formed when potato starch was treated with glutamic acid. X-ray diffraction pattern of the starch glutamate was evaluated to know its molecular structure and shown in fig. 3. X-ray diffraction pattern of starch glutamate did not show any characteristic peaks indicating the amorphous nature of the novel superdisintegrant. Scanning electron microscopy (SEM) of the starch and starch glutamate was shown in fig. 4, 5 respectively. SEM of the starch glutamate indicates the amorphous nature of it. From the results of physical, micromeritics and structural properties of starch glutamate it was concluded that starch glutamate has all the characteristic properties of an ideal superdisintegrant, so it can be used in the formulation of fast dissolving tablets as a superdisintegrant.

The compatibility of the prepared starch glutamate with aceclofenac was evaluated by Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). The FTIR spectrum of aceclofenac and aceclofenac-starch glutamate was shown in fig. 6, 7. FTIR spectrum of the aceclofenac showed characteristic bands at 1769.91(-COO), 1719.91(-C=O), 1581.86(-C=C), 3274.64(-OH), 3317.22 (-NH) and 747.44(Aromatic-Cl) whereas in the FTIR spectrum of aceclofenac-starch glutamate exhibited same characteristic bands at 1770.42(-COO), 1719.34(-C=O), 1584.46(-C=C), 3276.76(-OH), 3317.22 (-NH) and 751.12(Aromatic-Cl). From the FTIR spectra, it was concluded that starch glutamate did not show any interaction with the selected drug.

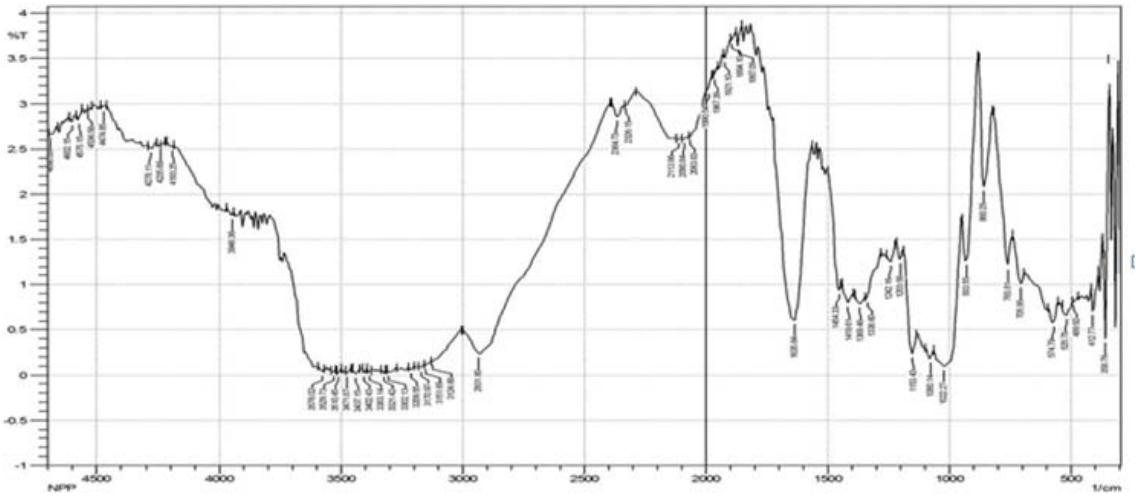


Fig. 1: Fourier transform infrared (FTIR) spectrum of potato starch

Table 2: Physical and micrometric properties of starch glutamate

Parameter	Observation
Solubility	Insoluble in all aqueous and organic solvent (alcohol, dichloromethane, chloroform, acetone and, petroleum ether)
pH (1% aqueous dispersion)	2.88
Melting point	Charred at 325 °C
Viscosity (1%w/v aqueous dispersion)	1.08cps
Swelling index	1200
Gelling property	It did not exhibit any gelling property as that of potato starch.
Moisture absorption	4.4%
Particle size	158µm (80/120 mesh)
Density	0.584g/cc
Bulk density	0.562g/cc
Angle of repose	27.47 °
Compressibility Index	14.23%

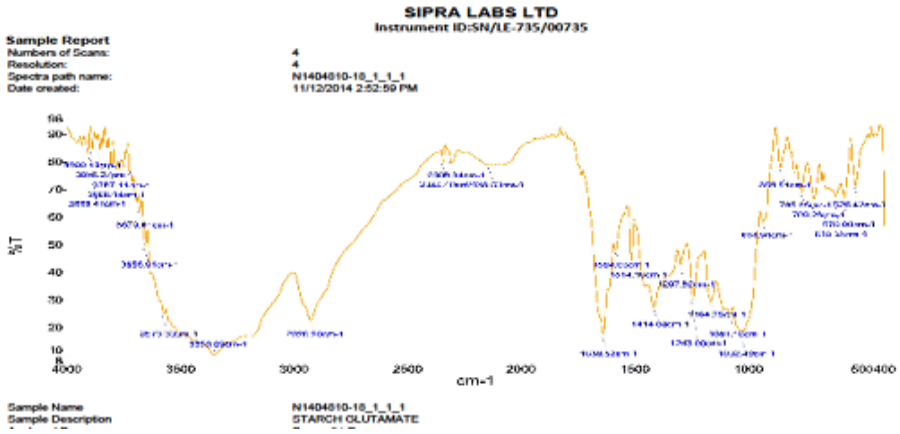


Fig. 2: Fourier transform infrared (FTIR) spectrum of starch glutamate

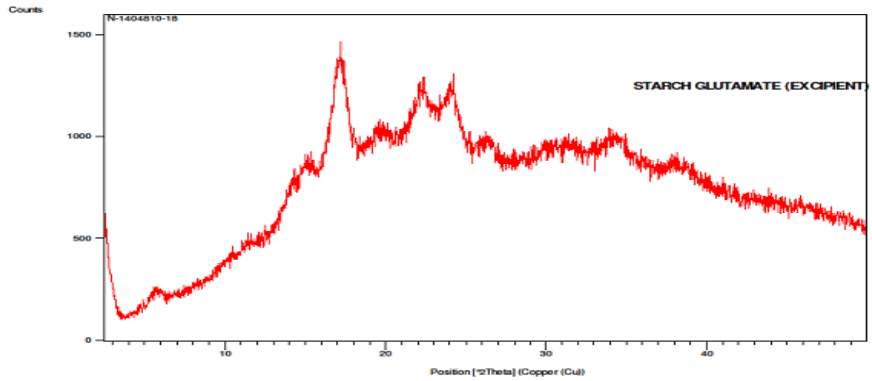


Fig. 3: XRD spectrum of starch glutamate

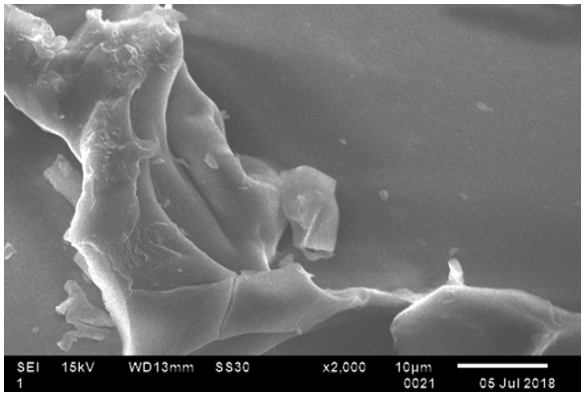


Fig. 4: Scanning electron microscopy of potato starch

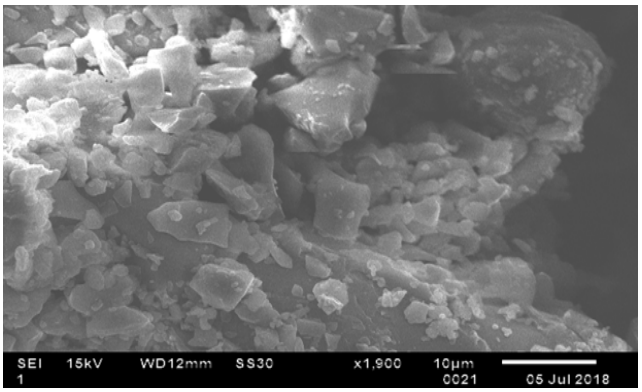


Fig. 5: Scanning electron microscopy of starch glutamate

DSC thermograms of the aceclofenac and aceclofenac–starch glutamate were shown in fig. 8, 9 and it was found that DSC thermogram of the aceclofenac showed a sharp exothermic peak at 152.57 °C and this same sharp exothermic peak was found in the DSC thermogram of aceclofenac-starch glutamate too at 152.51 °C. The exothermic peaks in this region correspond to the melting point of the aceclofenac drug i.e. 149-153 °C, from this it was evident that starch glutamate did not show any interaction with the selected drug.

FTIR and DSC studies of starch glutamate indicated that the prepared superdisintegrant i.e. starch glutamate was compatible.

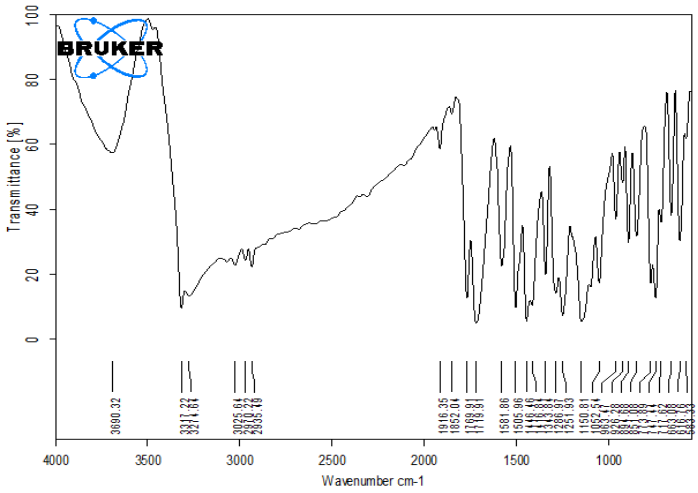


Fig. 6: FTIR spectrum of aceclofenac pure drug

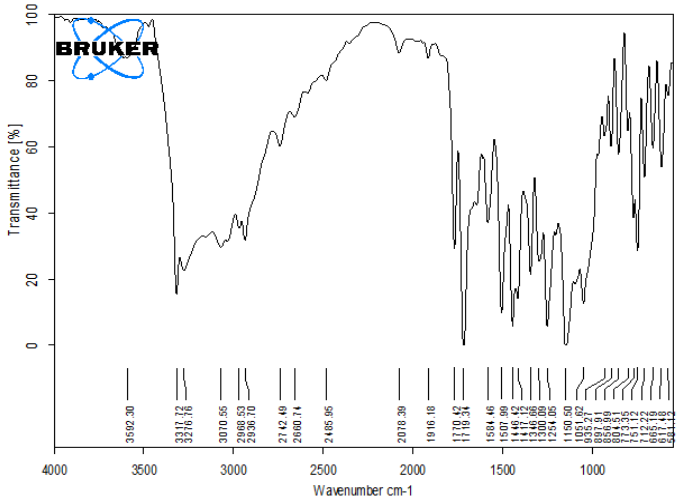


Fig. 7: FTIR spectrum of aceclofenac-starch glutamate

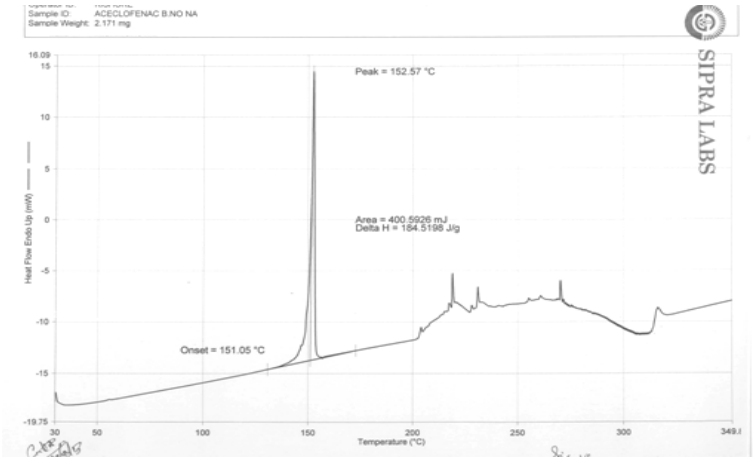


Fig. 8: DSC thermogram of aceclofenac pure drug

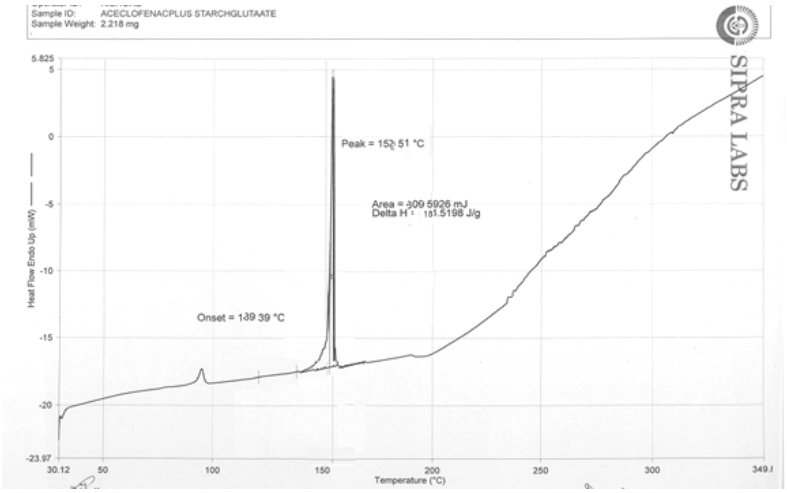


Fig. 9: DSC thermogram of aceclofenac-starch glutamate

Evaluations tests for aceclofenac fast dissolving tablets

Hardness

The hardness of aceclofenac fast dissolving tablets was found to be in between 3.7±0.02 to 3.9±0.02 Kg/cm^{2}and passed the official IP hardness test. Hardness results were tabulated in table 3. All the formulations of aceclofenac possessed sufficient strength which helps to withstand handling, packing, storage, and transportation without getting broken.

Friability

Friability of aceclofenac fast dissolving tablets were found to be in-between 0.11±0.011 to 0.12±0.012%, which have passed the official IP friability test. Friability results were tabulated in table 3. All the tablets possessing good mechanical strength as per IP and withstands mechanical shocks during handling and transportation.

Drug content uniformity

Drug content uniformity of aceclofenac fast dissolving tablets was found to be in between 98.28±0.51 to 99.41±0.21 mg/tab. Drug content uniformity results were tabulated in table 3. All the aceclofenac fast dissolving tablets passed the official IP drug content uniformity test (i.e. 85 to 115% of the average content).

Wetting time and water absorption ratio

Water absorption ratio and wetting time of aceclofenac fast dissolving tablets depends on the superdisintegrant used in the formulation. Wetting time and water absorption ratio results of aceclofenac fast dissolving tablets were given in table 3. From the results, it was concluded that the formulation which contains the novel superdisintegrant have less wetting time and more water absorption ratio compared to the formulation with no superdisintegrant added. The wetting time and water absorption ratio of formulations F8 and F2 were found to better than the aceclofenac fast dissolving tablets formulated by Hazarika *et al.* [19].

***In vitro* disintegration time**

In vitro disintegration times of the aceclofenac fast dissolving tablets were given in table 3. From the results, it was concluded that disintegration time depends on the concentration of the superdisintegrants added to the formulation. Among all the formulations, the formulation (F8) which containing the 5% concentration of each superdisintegrant i.e. starch glutamate, croscarmellose sodium and crospovidone resulted into less disintegration time i.e. 4±0.58 sec. whereas the formulation F2 with a novel superdisintegrant i.e. starch glutamate in the concentration range of 5% was also comparable to the formulation F8. Both the formulations F2 and F8 showed less disintegration time compared to the aceclofenac tablets prepared employing βCD and Kolliphor HS15 by Chowdary *et al.* [20].

***In vitro* dissolution studies**

The formulation F8, formulated by employing 5% concentration of starch glutamate, 5% concentration of croscarmellose sodium and 5% concentration of crospovidone showed 99.7±0.15% of drug release within 5 min, whereas formulation F2 with novel superdisintegrant i.e.

starch glutamate in the concentration range of 5% was also comparable to the formulation F8. Therefore, when compared to F8, F2 was found to be more economical with single novel superdisintegrant i.e. starch glutamate and it was considered as good fast dissolving formulations of aceclofenac which was found to better than the aceclofenac fast dissolving tablets formulated by Hazarika *et al.*[19]. Cumulative percentage drug release and dissolution parameters of the aceclofenac fast dissolving tablets were given in table 4 and represented in fig. 10, 11. ANOVA results of disintegration time (table 5.1), wetting time (table 5.2), water absorption ratio (table 5.3) and dissolution efficiency in 5 min (table 5.4) were given and from these results it was concluded that, individual effects of starch glutamate (A), croscarmellose sodium (B) and crospovidone (C) as well as combined effects of AB, BC, AC, and ABC, were showed significant effect on the wetting time, water absorption ratio, disintegration time and on dissolution efficiency in 5 min.

Table 3: Physical properties of aceclofenac fast dissolving tablets

Formulation	Hardness (kg/cm^2) n±SD	Friability (%) n±SD	Drug content (mg/tab) n±SD	Wetting time (Sec) n±SD	Water absorption ratio (%) n±SD	Disintegration time (sec) n±SD
F1	3.8±0.02	0.11±0.012	98.28±0.51	191±2.65	0.29±0.05	318±1.00
F2	3.9±0.02	0.12±0.011	99.1±0.53	8±1.00	9.81±0.10	23±1.00
F3	3.8±0.02	0.12±0.011	99.21±0.25	7±1.00	1.40±0.03	8±1.00
F4	3.9±0.02	0.11±0.013	98.74±0.32	6±0.58	1.25±0.12	9±1.00
F5	3.7±0.02	0.12±0.011	99.41±0.21	27±3.06	0.98±0.02	25±1.00
F6	3.8±0.02	0.12±0.011	99.22±0.04	8±1.00	0.92±0.00	7±1.00
F7	3.9±0.01	0.12±0.012	99.11±0.37	32±1.00	1.60±0.43	26±2.65
F8	3.9±0.02	0.11±0.011	99.16±0.12	4±1.00	1.96±0.02	4±0.58

*All the values are expressed as mean±SD, where n=3, SD: Standard Deviation.

Table 4: Dissolution parameters of the aceclofenac fast dissolving tablets formulated using starch glutamate as superdisintegrant

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
PD_5	7.3±1.05	86.0±1.00	98.0±1.03	99.3±0.12	96.4±0.50	99.05±0.03	47.0±1.06	99.7±0.15
DE_5%	6.4±0.23	85.2±0.20	93.6±1.19	94.9±0.12	94.3±0.51	94.5±0.61	47.4±0.57	94.9±0.72
No of folds increase in DE_5%	-	13.3	14.6	14.8	14.7	14.7	7.4	14.8
K_1 (min^{-1})	0.020±0.001	0.535±0.144	0.804±0.104	1.004±0.033	0.399±0.011	0.931±0.007	0.144±0.014	1.126±0.147
No of folds increase in K_1 (min^{-1})	-	26.75	40.2	50.2	19.95	46.55	7.2	56.3

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation. PD_5-Percent dissolved in 5 min, DE_5%-Dissolution efficiency in 5 min, K_1-First order rate constant.

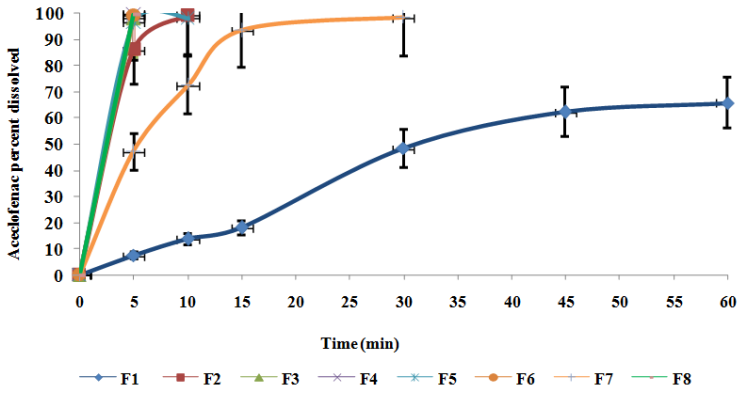


Fig. 10: Dissolution profile of aceclofenac fast dissolving tablets prepared by employing starch glutamate (F1-F8) (n=3, mean±SD)

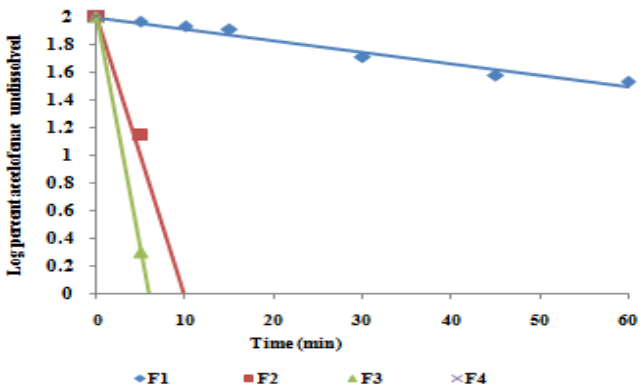


Fig. 11(A): Time vs log percent undissolved plots for aceclofenac fast dissolving tablets prepared by employing starch glutamate (F1-F4) (n=3, mean±SD)

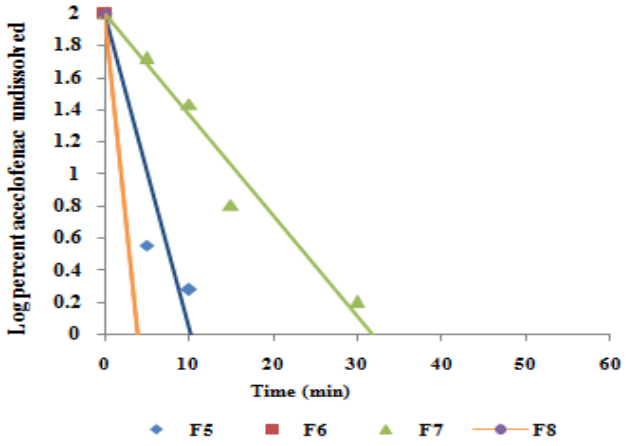


Fig. 11(B): Time vs log percent undissolved plots for aceclofenac fast dissolving tablets prepared by employing starch glutamate (F5-F8) (n=3, mean±SD)

Table 5.1: ANOVA of disintegration time of aceclofenac fast dissolving tablets formulated by employing starch glutamate

Source of variation	d. f	Sum of squares	Mean S. S	Variance ratio	Result
Replicates	2	3.583	1.79	1.087	P>0.05
Treatments	7	243439.29	34777.04	21095.26	P<0.05
Starch glutamate (A)	1	41917.04	41917.04	25426.28	P<0.05
Croscarmellose sodium (B)	1	39935.04	39935.04	24224.03	P<0.05
Starch glutamate x croscarmellose sodium (AB)	1	31901.04	31901.04	19350.72	P<0.05
Crospovidone (C)	1	32930.04	32930.04	19974.90	P<0.05
Starch glutamate x crospovidone (AC)	1	24130.04	24130.04	14636.94	P<0.05
Croscarmellose sodium x crospovidone (BC)	1	38801.04	38801.04	23536.16	P<0.05
Starch glutamate x croscarmellose sodium x crospovidone (ABC)	1	33825.04	33825.04	20517.79	P<0.05
Error	14	23.08	1.65	--	--
Total	23	--	--	--	--

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation. d. f-Degree of freedom, *S. S-Sum of Square, *M. S. S-Mean Sum of Square, P>0.05 indicates non-significance, P<0.05 Indicates Significance, ANOVA-Analysis of Variance.

Table 5.2: ANOVA of wetting time of aceclofenac fast dissolving tablets formulated by employing starch glutamate

Source of variation	d. f	Sum of squares	Mean S. S	Variance ratio	Result
Replicates	2	18.75	9.38	5.340	P<0.05
Treatments	7	85398.29	12199.76	6948.60	P<0.05
Starch glutamate (A)	1	20126.04	20126.04	11463.16	P<0.05
Croscarmellose sodium (B)	1	12927.04	12927.04	7362.84	P<0.05
Starch glutamate x croscarmellose sodium (AB)	1	11223.38	11223.38	6392.48	P<0.05
Crospovidone (C)	1	7385.04	7385.04	4206.29	P<0.05
Starch glutamate x crospovidone (AC)	1	7038.38	7038.38	4008.84	P<0.05
Croscarmellose sodium x crospovidone (BC)	1	13113.38	13113.38	7468.97	P<0.05
Starch glutamate x croscarmellose sodium x crospovidone (ABC)	1	13585.04	13585.04	7737.62	P<0.05
Error	14	24.58	1.76	--	--
Total	23	--	--	--	--

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation. d. f-Degree of freedom, *S. S-Sum of Square, *M. S. S-Mean Sum of Square, P>0.05 indicates non-significance, P<0.05 Indicates Significance, ANOVA-Analysis of Variance.

Table 5.3: ANOVA of water absorption ratio of aceclofenac fast dissolving tablets formulated by employing starch glutamate

Source of variation	d. f	Sum of squares	Mean S. S	Variance ratio	Result
Replicates	2	0.109	0.05	2.461	P>0.05
Treatments	7	199.79	28.54	1288.97	P<0.05
Starch glutamate (A)	1	35.09	35.09	1584.71	P<0.05
Croscarmellose sodium (B)	1	12.56	12.56	567.09	P<0.05
Starch glutamate x croscarmellose sodium (AB)	1	32.06	32.06	1448.00	P<0.05
Crospovidone (C)	1	19.91	19.91	899.20	P<0.05
Starch glutamate x crospovidone (AC)	1	30.92	30.92	1396.27	P<0.05
Croscarmellose sodium x crospovidone (BC)	1	31.14	31.14	1406.54	P<0.05
Starch glutamate x croscarmellose sodium x crospovidone (ABC)	1	38.10	38.10	1720.75	P<0.05
Error	14	0.31	0.02	--	--
Total	23	--	--	--	--

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation. d. f-Degree of freedom, *S. S-Sum of Square, *M. S. S-Mean Sum of Square, P>0.05 indicates non-significance, P<0.05 Indicates Significance, ANOVA-Analysis of Variance.

Table 5.4: ANOVA of dissolution efficiency in 5 min of aceclofenac fast dissolving tablets formulated by employing starch glutamate

Source of variation	d. f	Sum of squares	Mean S. S	Variance ratio	Result
Replicates	2	0.61	0.31	0.788	P>0.05
Treatments	7	22364.00	3194.86	8252.40	P<0.05
Starch glutamate (A)	1	6134.40	6134.40	15845.32	P<0.05
Croscarmellose sodium (B)	1	948.78	948.78	2450.73	P<0.05
Starch glutamate x croscarmellose sodium (AB)	1	341.26	341.26	881.48	P<0.05
Crospovidone (C)	1	976.65	976.65	2522.71	P<0.05
Starch glutamate x crospovidone (AC)	1	396.09	396.09	1023.12	P<0.05
Croscarmellose sodium x crospovidone (BC)	1	7729.27	7729.27	19964.91	P<0.05
Starch glutamate x croscarmellose sodium x crospovidone (ABC)	1	5837.52	5837.52	15078.47	P<0.05
Error	14	5.42	0.39	--	--
Total	23	--	--	--	--

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation. d. f-Degree of freedom, *S. S-Sum of Square, *M. S. S-Mean Sum of Square, P>0.05 indicates non-significance, P<0.05 Indicates Significance, ANOVA-Analysis of Variance.

Factorial design

Independent variables, i.e. superdisintegrants like starch glutamate (A), croscarmellose sodium (B) and crospovidone (C) whereas response variables (dependent variables) i.e. percent dissolved in 5 min and dissolution efficiency in 5 min has been co-related by using a polynomial regression algorithm. Polynomial equation of percent dissolved in 5 min and dissolution efficiency in 5 min was given as equation 1 and 2 respectively.

$$\text{Percent dissolved in 5 min} = +79.9+16.92A+6.91B+6.44C-3.42AB-3.08AC-119.09BC+15.93ABC \quad (R^2 = 1.000) \quad \text{--Eq 1}$$

$$\text{Dissolution efficiency in 5 min} = +76.40+15.98A+6.30B+6.37C-3.77AB-4.05AC-17.93BC+15.60ABC \quad (R^2 = 1.000) \quad \text{--Eq 2}$$

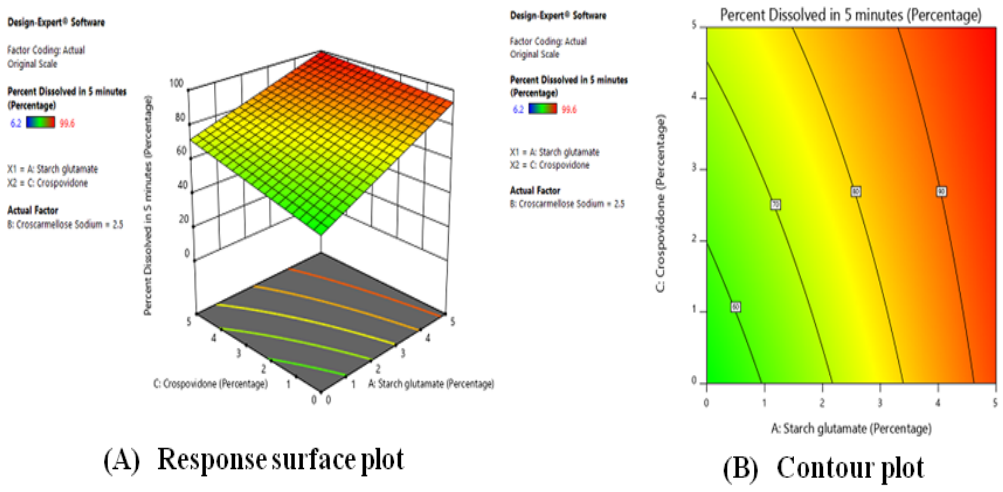
The interaction between the superdisintegrants starch glutamate (A), croscarmellose sodium (B), and crospovidone (C) and their effect on percent dissolved in 5 min and dissolution efficiency in 5 min given in the following table 6.

The response surface plots and contour plots indicate the relationship between the concentration of superdisintegrants on the percent dissolved in 5 min and dissolution efficiency in 5 min. Table 7 describes the relationship between the concentration of superdisintegrant on the percent dissolved in 5 min and dissolution efficiency in 5 min.

Table 6: Interactions between superdisintegrants and their effect on percent dissolved in 5 min and dissolution efficiency in 5 min

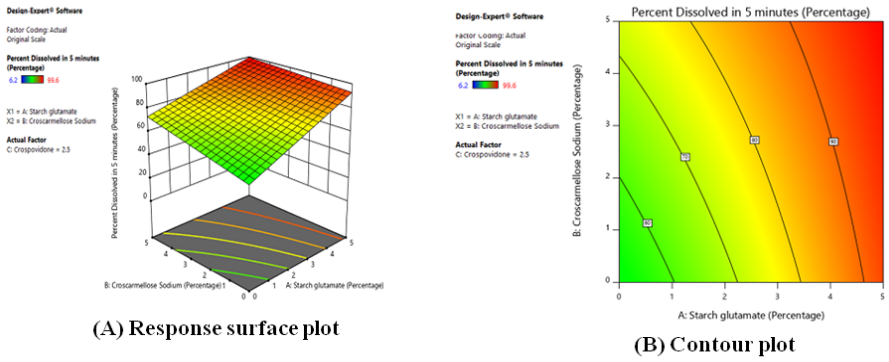
Interactions between superdisintegrants	Effect on	
	Percent dissolved in 5 min	Dissolution efficiency in 5 min
Starch glutamate X croscarmellose sodium (AB)	-	-
Starch glutamate X crospovidone (AC)	-	-
Croscarmellose sodium X crospovidone (BC)	-	-
Starch glutamate (A)	+	+
Croscarmellose sodium (B)	+	+
Crospvidone (C)	+	+
Starch glutamate X croscarmellose Sodium X crospovidone (ABC)	+	+

'-'which means negative effect; '+' which means a positive effect, contour plots and surface response plots were drawn based on the interaction effects on percent dissolved in 5 min and dissolution efficiency in 5 min. Contour plots and surface plots were given in fig. 12.1-12.6.



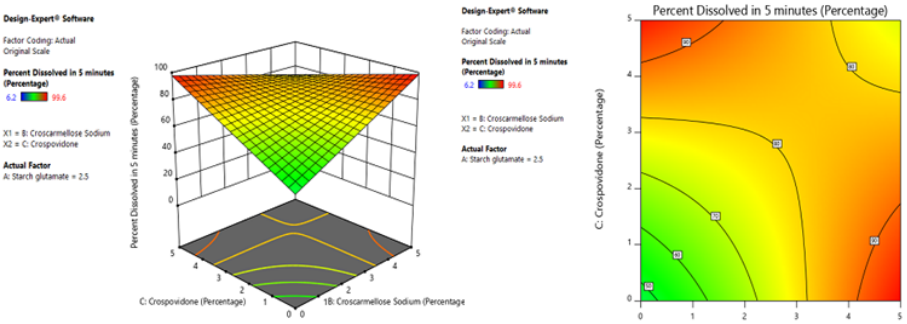
(A) Response surface plot (B) Contour plot

Fig. 12.1: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of starch glutamate and croscarmellose sodium on percent dissolved in 5 min)



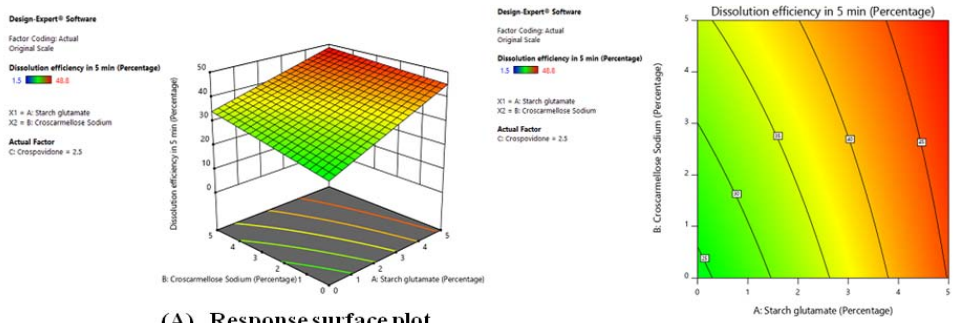
(A) Response surface plot (B) Contour plot

Fig. 12.2: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of starch glutamate and crospovidone on percent dissolved in 5 min)



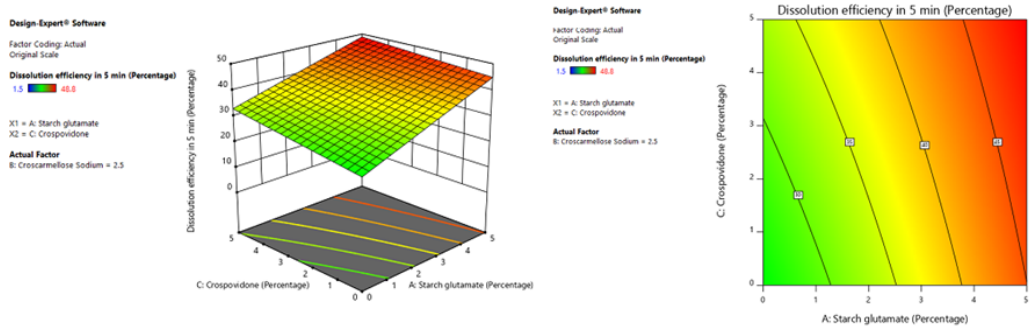
(A) Response surface plot (B) Contour plot

Fig. 12.3: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of crospovidone and croscarmellose sodium on percent dissolved in 5 min)



(A) Response surface plot (B) Contour plot

Fig. 12.4: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of starch glutamate and croscarmellose sodium on dissolution efficiency in 5 min)



(A) Response surface plot (B) Contour plot

Fig.12.5: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of starch glutamate and crospovidone on dissolution efficiency in 5 min)

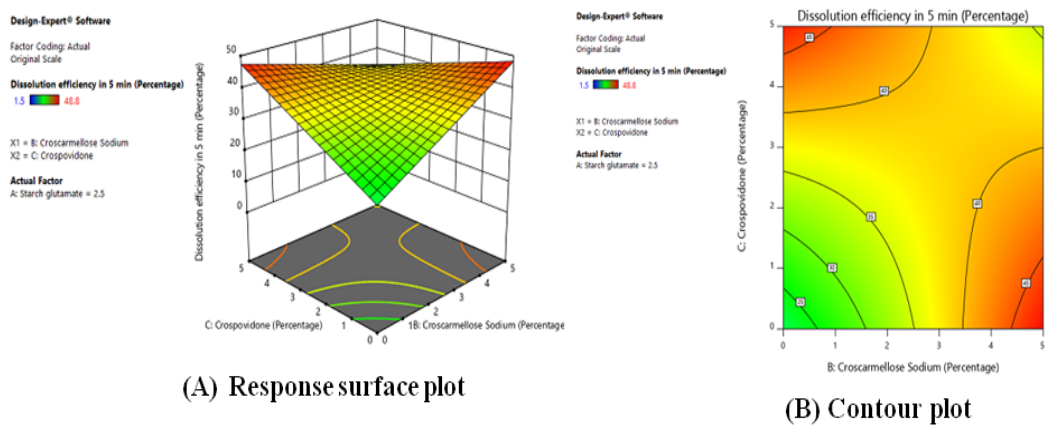


Fig. 12.6: (A) Response surface plot (B) Contour plot of aceclofenac fast dissolving tablets (Effect of crospovidone and croscarmellose sodium on dissolution efficiency in 5 min)

Table 7: Relation between concentrations of superdisintegrant on percent dissolved in 5 min and dissolution efficiency in 5 min

Interactions between superdisintegrants	Relation established		Suitable concentration range
	On percent dissolved in 5 min	On dissolution efficiency in 5 min	
Starch glutamate **X** croscarmellose sodium (AB)	Linear	Linear	4-5%
Starch glutamate **X** crospovidone (AC)	Linear	Linear	4-5%
Croscarmellose sodium **X** crospovidone (BC)	Non-linear	Linear	4-5%

Optimal formula

The formulation F8, which was formulated employing 5% concentration of starch glutamate, 5% concentration of croscarmellose sodium and 5% concentration of crospovidone showed more percent dissolved in 5 min and dissolution efficiency in 5 min. Formulation F2 containing a single superdisintegrant i.e. starch glutamate in the concentration range of 5% is also comparable to the formulation F8. Therefore, F2 can be considered as an optimized formulation which was more economical.

Pharmacokinetics studies

Pharmacokinetic studies revealed that the optimized formulation (F2) of aceclofenac fast dissolving tablets reached peak plasma concentration in less time (1 sec) and with increased absorption and relative bioavailability (182.77) when compared to pure drug. These results were in agreement with the results obtained by Dahiya *et al.* [21]. Summary of pharmacokinetic parameters was shown in table 8.

Stability studies

Stability studies indicated that the optimized formulation (F2) of aceclofenac fast dissolving tablets employing starch glutamate was stable at accelerated conditions and found comparable with the aceclofenac tablets prepared by Sanjay S. Patel *et al.* [22]. Various physical properties of the optimized formulation were shown in table 9 and the dissolution profile of optimized formulation F2, before and after storage of six months was shown in fig. 13.

Table 8: Summary on pharmacokinetic parameters

Pharmacokinetic parameter	Pure aceclofenac (A)	Optimized aceclofenac fast dissolving tablet formulation F2 employing starch glutamate (B)
C_{max} (µg/ml)	1.58	8.7
T_{max} (h)	4.0	1.0
$AUC_{0\text{-}7h}$ (µg. h/ml)	9.072	31.825
$AUC_{0\text{-}\infty}$ (µg. h/ml)	18.687	34.155
BA (%)	100	182.77
K_a (h^{-1})	0.695	0.728
K_{el} (h^{-1})	0.1144	0.4711
MRT (h)	0.98	0.96

Table 9: Physical properties of optimized aceclofenac fast dissolving tablets before and after storage during the stability studies

Formulation	Hardness (kg/cm^2) n±SD	Friability (%) n±SD	Drug content (mg/tab) n±SD	Wetting time (sec) n±SD	Water absorption ratio (%) n±SD	Disintegration time (sec) n±SD
Aceclofenac (F2) (before stability)	3.9±0.02	0.12±0.011	99.1±0.53	8±1.00	9.81±0.10	23.0±1.00
Aceclofenac (F2) (after stability)	3.9±0.01	0.13±0.010	99.0±0.32	8±1.01	9.80±0.01	22.0±1.02

All the values are expressed as mean±SD, where n=3, SD: Standard Deviation.

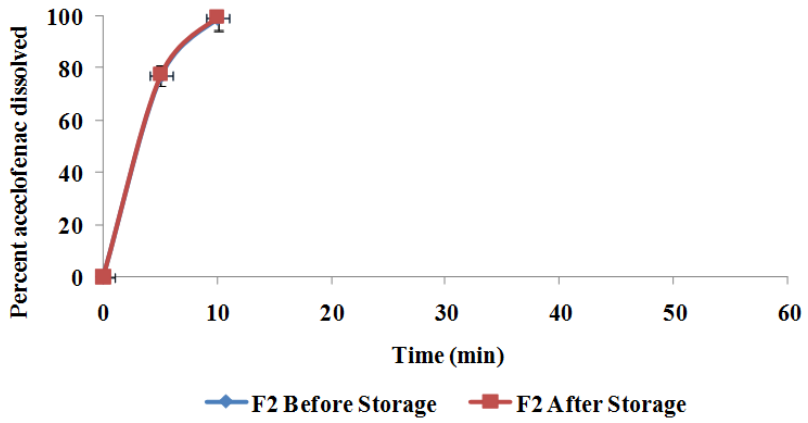


Fig. 13: Dissolution profiles of aceclofenac fast dissolving tablets F2 before and after storage for 6 mo during the stability study

CONCLUSION

The novel superdisintegrant i.e. starch glutamate which was synthesized from esterification of potato starch and glutamic acid is found to be best and is used as a superdisintegrnat for the preparation of fast dissolving tablets. Optimized aceclofenac fast dissolving tablets were prepared by using a 5% concentration of starch glutamate were subjected to *in vitro* and *in vivo* studies and stability studies showed the best drug release and increased relative bioavailability. Based on the above studies, the superdisintegrant nature of starch glutamate was proved.

ABBREVIATIONS

FTIR-Fourier Transform Infrared Spectra, DSC-Differential Scanning Calorimetry, SEM-Scanning Electron Microscopy, HPLC-High Performance Liquid Chromatography, ICH-International Conference On Harmonisation, WHO-World Health Organization.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Aher Smita S, Saudagar RB, Shinde Mayuri S. Review: fast dissolving tablet. Int J Curr Pharm Res 2018;10:5-12.
2. Prashant Bhide, Reeshwa Nachinolkar. Formulation development and characterisation of meclizine hydrochloride fast dissolving tablets using solid dispersion technique. Int J Appl Pharm 2018;10:141-6.
3. Sanket Kumar, Shiv KR Garg. Fast dissolving tablets (FDTS): current status, new market opportunities, recent advances in manufacturing technologies and future prospects. Int J Pharm Pharm Sci 2014;6:22-35.
4. GB Preethi, Sayan Banerjee, HN Shivkumar, M Ravikumar. Formulation of fast dissolving tablets of doxazosin mesylate drug by direct compression method. Int J Appl Pharm 2017;9:22-8.
5. Kalindi Chauhan, Rakesh Solanki, Shivani Sharma. A review on fast dissolving tablet. Int J Appl Pharm 2018;10:1-7.
6. GV Radha, K Tridev Sastri, P Prathyusha, P Bhanu, Jampala Rajkumar. Formulation and evaluation of aceclofenac prinosomes loaded orabase for management of dental pain. Int J Appl Pharm 2018;10:204-10.
7. Nazia Khanam, MD Irshad Alam, Quazi MD Aamer, Iqbal MD Yusuf Ali, Aquil-UR-Rehman Siddiqui. A review on optimization of drug delivery system with experimental designs. Int J Appl Pharm 2018;10:7-12.
8. R Santhosh Kumar, T Naga Satya Yagnesh. Synthesis, characterisation and evaluation of starch xanthane as a superdisintegrant in the formulation of fast dissolving tablets. Int J Appl Pharm 2018;10:249-58.
9. Prashant Bhide, Reeshwa Nachinolkar. Formulation of fast-dissolving tablets of doxazosin mesylate drug by direct compression method. Int J Appl Pharm 2017;9:22-8.
10. Chatwal GR, Anand SK. Instrumental methods of chemical analysis. 5th Edition. Himalaya Publishing House; 2009. p. 2.49-2.51.
11. The United States Pharmacopoeia 29, National Formulary 24, Asian Edition. Rockville, MD: United States Pharmacopoeia Convention, Inc; 2006. p. 1890.
12. Jain C, Naruka P. Formulation and evaluation of fast dissolving tablet of valsartan. Int J Pharm Pharm Sci 2009;1:219-26.
13. Hiremath JG, Shastry CS, Srinath MS. Pharmaceutical approaches of taste masking in oral dosage forms. Indian Drugs 2004;41:253-7.
14. Rasha Khalid Dhahir, Myasar Al-Kotaji. Formulation of orally disintegrating tablets of cinnarzine by using direct compression method. Int J Appl Pharm 2019;11:117-23.
15. Roy A. Orodispersible tablet: a review. Asian J Pharm Chem Res 2016;2:19-26.
16. Babji Movva, D Laxman Kumar, K Mohan Ravi Kumar. Formulation and evaluation of fast dissolving tablets of ranitidine hydrochloride by hole technology. Asian J Pharm Clin Res 2013;6:143-7.
17. S Jaya, V Amala. Formulation and *in vitro* evaluation of oral disintegrating tablets of amlodipine besylate. Int J Appl Pharm 2019;11:49-54.
18. Caretensen JT. Guidelines for drug stability: principles and practices. Third Edition. Marcel Dekkar; 2005. p. 252-5.
19. Jahan Nur Rahman Hazarika, Pulak Deb. Formulation evaluation and optimization of immediate release tablet of aceclofenac by direct compression method. Int J Curr Pharm Res 2017;9:118-22.
20. S Gopinadh, C Umamaheswara Reddy, KPR Chowdary. Factorial studies on enhancement of dissolution rate and formulation of aceclofenac tablets employing βCD and Kolliphor HS15. Int J Curr Pharm Res 2015;7:43-6.
21. Sunita Dahiya, Atul Kaushik, Kamla Pathak. Improved pharmacokinetics of aceclofenac immediate release tablets incorporating its inclusion complex with hydroxypropyl-β-cyclodextrin. Sci Pharm 2015;83:501-10.
22. Sanjay S Patel, Natvarlal M Patel. Development of directly compressible co-processed excipient for dispersible tablets using 3^2 full factorial design. Int J Pharm Pharm Sci 2009;1:125-48.