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Formulation and Evaluation of Ibuprofen Fast Dissolving Tablets Employing Starch Malonate (Modified Starch) as a Superdisintegrant

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The goal of the study was to prepare a superdisintegrant named starch malonate followed by its evaluation for physicochemical properties. Prepared starch malonate was optimized in the preparation of fast dissolving tablets of ibuprofen by using 2^3 factorial designs.
Methods: Compatibility studies like FTIR, TLC and DSC were performed to check any interaction between starch malonate and ibuprofen. Fast dissolving tablets were compressed by direct compression method and subjected to various official tests like hardness, friability, drug content, dissolution etc. Wetting time and water absorption ratio were also performed. At last response surface plot and contour plot was plotted to check the effects of starch malonate, croscarmellose sodium and crospovidone (independent variables) on disintegration time and dissolution efficiency in 5 minutes (dependent variables). Stability studies were also performed to check the stability of prepared fast dissolving tablets of ibuprofen.
Results: Results of the studies showed that all the results are within acceptable limits and complying with the criteria of fast dissolving tablets. Drug content was found to be (100±5%), hardness of all tablets were found in between 3.8 -4 kg/cm^2, friability was found less than 0.15%. Optimized formulation has showed less wetting time, less disintegration time followed by enhanced

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drug release. Among all formulation, formulation F2 has shown least disintegration time and enhanced drug release (99.89%) as compared to other formulations. We can conclude that starch malonate can be used as a novel superdisintegrant.

Keywords: Fast dissolving tablets; Superdisintegrant; starch malonate; poorly soluble drugs.

1. INTRODUCTION

Drugs solubility is the important and critical step in the formulations of any dosage form. Bioavailability and stability of the dosage forms depends on the solubility of the drug. [1, 2]. Poorly soluble drug when formulated into oral dosage forms having low bioavailability because of its low solubility. Different dosage forms like oral solid dosage forms, liquid dosage forms, parenteral, rectal, nasal, buccal etc are available in market with their own advantages and disadvantages [3]. The oral route is the most common, stable, economical route compared to other dosage forms preferred by the major population [4]. Literature study has shown that conventional oral solid dosage forms (tablets or capsules) has shown the problem of swallowing, dysphasia (nausea), chocking and its difficult to administer to mentally ill, bed-ridden and unconscious patients [5]. To overcome these problems fast dissolving systems are in boom. They are named “fast dissolving systems” as they are characterized by their property to disintegrate within seconds as soon it comes in contact with saliva which results in fast release of drugs. Fast dissolving tablets and fast dissolving films are available under these systems. [6]. In market many conventional and parented technologies are available for the preparation of fast dissolving tablets. Researchers are still going on so that these fast dissolving tablets should be available for types of disease. In this competitive world, fast onset of action is first choice by every individual. If we consider patient comfort, fast dissolving tablets are first choice by doctors. They have already proved that fast dissolving tablets have high rate of acceptable for pediatrics, geriatrics, psychotic and bed-ridden patients. It is also easy to administer to patients who are travelling and forget to carry water [7]. Different methods are available for the preparation of fast dissolving tablet. But in among different methods, direct compression method in which superdisintegrant are added are the easy method, have less processing step and have low cost [8]. Superdisintegrant are the agents which help in the quick disintegration of tablets within seconds as it comes in contact with saliva. They are used in very low concentration [9]. Superdisintegrant helps to enhance the drug release of poorly soluble drugs have been already proved by literature survey [10]. In this current work our main aim is to prepare novel modified starch named starch malonate by esterification reaction which will be used as superdisintegrant in order to enhance the drug release of poorly soluble drug. Concentration of starch malonate alone or in combination with other known superdisintegrant (Croscarmellose sodium, Crospovidone) are optimized by using 2^3 factorial designs and fast dissolving tablets of Ibuprofen was prepared.

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen, Croscarmellose sodium, Crospovidone, starch and potato starch were purchased from Yarrow chemicals, Mumbai. Sodium hydroxide and Mannitol were obtained from Finar chemicals Ltd, Ahmadabad. Malonic acid was purchased from Liha Life sciencesHyderabad.Microcrystalline cellulose was procured from Qualigens fine chemicals, Mumbai. Magnesium stearate and Talc was purchased from molychem, Mumbai.

2.2 Methods

2.2.1 Preparation of a starch malonate

Initially, ten parts of malonic acid and ten parts of potato starch were dissolved in 25 parts of distilled water. Then, the pH of the solution was checked. If pH was not 3.5, the 10 Molar NaOH solution was added to make up to pH 3.5. This solution was then conditioned for 16 hrs. It was kept in the oven at 60º C until it got dried. The mass was washed with distilled water to remove the unreacted malonic acid. The product was held in an oven at 60°C until it got dried. The product obtained was ground and sieved (#120) [11].

2.2.2 Drug – Excipient compatibility studies

Drug excipient compatibility studies are the most important preformulation aspect as excipients

used in the formulation should not react with the drug used. Starch malonate compatibility was studied with the ibuprofen by performing FTIR and DSC studies.

2.2.3 Infrared spectroscopy

Mixture of ibuprofen with starch malonate was prepared in the ratio of 1:1. IR spectrum was recorded by using IR Spectroscopy, model: RXI, using KBr disc as reference [12].

2.2.4 Differential Scanning Calorimetry (DSC)

DSC thermograms of ibuprofen and their mixtures (1: 1) with starch malonate were recorded on Perkin Elmer Thermal Analyser. Samples (2- 5 mg) were sealed into aluminium pans and scanned at a heating rate of 100C min^{-1} over a temperature range of 30 – 350°C [13].

2.2.5 TLC STUDIES

Thin layer chromatography (TLC) study

Stationary Phase: Silica gel G (pre-coated TLC plates).

Mobile Phase: Toluene: n-Hexane: Ethyl Acetate: Glacial Acetic Acid (75:25:5)

Procedure: Mobile phase was prepared as per ratio given and kept in TLC chamber undisturbed for 24 hours in order to saturate the chamber. With the help of narrow capillary tube, pure drug, drug with excipient were spotted on the activated silica plate. The spotted plates were kept in the thin layer chromatography (TLC) chamber and allowed to run mobile phase. The plates were dried and kept in iodine chamber to develop the spots. Determine the retardation factor (Rf) by using the formula given below:

Retardation factor (R_F) = Distance travelled by sample / Distance travelled by solvent front.

2.2.6 Preparation of fast dissolving tablets of ibuprofen

Ibuprofen fast dissolving tablets composition formulas are given in below Table 1. Formula was optimized by using 2^3 factorial designs. First all the ingredients are weighed properly and then each ingredient was passed through mesh # 120 for uniformity in particle size. In a mortar pestle, an accurately weighed amount of starch malonate, crospovidone, croscarmellose sodium, and microcrystalline cellulose was added and triturated properly for uniform mixing and then drug (ibuprofen) was added to it. Talc and magnesium stearate were added to the powder mixture at last. [14]. Finally mixed blend was compressed by using an eight-station rotary press Karnavati Machinery Pvt, Ltd., Ahmadabad, India).

2.2.7 Evaluation of Ibuprofen fast dissolving tablets

Hardness test: Hardness of the prepared ibuprofen fast dissolving tablets were determined by Monsanto hardness tester and expressed in units of kg/cm² [15].

Uniformity of weight: Weight variation tells the variation in the individual weight of tablet from the average weight of 20 tablets. Randomly 20 tablets were selected from each formulation and weight variation test was performed [15].

Friability: Roche friabilator was used to determine the friability of fast dissolving tablets of ibuprofen. At 25 rpm tablets were rotated for 100 revolutions i.e for 4 minutes. Tablets were weighed before keeping in the friabilator and after friability test [15]. Tablets weight loss percentage was calculated by the given formula:

$$F = \frac{100 \text{ X W (initial)} - \text{W (final)}}{\text{W (initial)}}$$

Table 1. Formulae of Ibuprofen fast dissolving tablets employing starch malonate prepared by direct compression method

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Ibuprofen	200	200	200	200	200	200	200	200
Starch Malonate	….	30	…	30	….	30	….	30
Croscarmellose sodium	…	….	30	30	….	…..	30	30
Crospovidone	…	…	…..	….	30	30	30	30
Mannitol	180	130	130	100	130	100	100	70
Microcrystalline cellulose	200	220	220	220	220	220	220	220
Talc	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10
Total	600	600	600	600	600	600	600	600

Drug content uniformity: For content uniformity, ten tablets were weighed and powdered a quantity of powder equivalent to 10 mg of ibuprofen was extracted into 7.2 phosphate buffer and filtered. The ibuprofen content was determined by measuring the absorbance spectrophotometrically at 221 nm after appropriate dilution with 7.2 phosphate buffer [16]. The drug content was calculated as an average of three determinations.

Wetting Time: Five pieces of circular tissue paper were placed in Petri plate having 10 cm diameter. Ten ml of water containing a water-soluble dye (amaranth) was added to the petri dish. Carefully one tablet was kept in the petri plate in and the time taken by colored water to reach the upper surface of the tablet was noted as wetting time [17].

Water absorption ratio: The tissue paper was folded twice as per the diameter of the petri dish and 6 ml of water was added to the petri dish. A tablet was kept on the tissue paper and allowed to wet thoroughly and the wetted tablet was weighed. Water absorption ratio was calculated by using the given Equation:

$$R = \frac{100(\mathrm{W_d} - \mathrm{W_e})}{W_e}$$

Where,
W_d = Tablet weight after water absorption
W_e = Tablet weight before water absorption

***In – vitro* disintegration time:** A disintegration time study was performed using USP disintegration apparatus having pH 7.2 phosphate buffer as dissolution medium maintained at 37 ± 0.2°C. Time in seconds noted required for complete disintegration of the tablets with no palatable mass left in the apparatus [17].

***In – vitro* dissolution studies:** The *in- vitro* dissolution studies of ibuprofen fast dissolving tablets were performed using 8 stage dissolution test apparatus (Electrolab TDT-08L) fitted with paddles (50 rpm) at 37 ± 0.50C, using pH 7.2 phosphate buffer (900 ml) as a dissolution media. At defined time intervals, 5 ml samples were withdrawn, filtered through a 0.45µ membrane filter, diluted and assayed at 221 nm using schimadzu UV/Visible double beam spectrophotometer. Cumulative percentage release was measured using standard absorbance from the calibration curve. *In vitro* dissolution experiments were conducted in triplicate (n = 3) [18].

2.8 Stability Studies

Stability studies for the formulation F2 was conducted as per ICH guidelines. The F2 formulation was packed in a screw capped bottle and stored for 6 months at accelerated storage condition (40^0C ± 2^0C and 75% RH). The formulation was evaluated for drug content and drug dissolution after storage for 6 months.

3. RESULTS AND DISCUSSION

The prepared new superdisintegrant starch malonate was found as slightly crystalline free flowing fine powder.

The starch malonate prepared was found to be fine, free flowing slightly crystalline powder. It was insoluble in aqueous solvents and insoluble in organic solvents tested (methanol, petroleum ether, dichloromethane, and chloroform). The pH of 1% w/v aqueous dispersion was checked and it was 3.15. In melting point study, it was found that starch malonate got charred at 270º C which indicates that it can be used in wet granulation method as it can resist temperature. Viscosity of 1% w/v aqueous dispersion was checked and found 1.022cps. Starch malonate exhibited good swelling in water. The swelling index was 83.95%. All micrometric properties indicated good flow and compressibility needed for solid dosage form manufacturing. The density of starch malonate was found to be 1.008 g/cc. The angle of repose and compressibility index showed good flow properties of starch malonate.

The evaluation results for all the tests performed (solubility, pH, swelling index, density) are given in Table 2.

Drug – Excipient compatibility studies: FTIR spectrum of starch malonate and potato starch showed in Fig. 1 and Fig. 2. The ester peak (1699.95 cm^{-1}) found only in Fig. 2 FTIR Spectra of starch malonate and is absent in potato FTIR spectrum. We can conclude that starch malonate formed due to reaction of Malonic acid with potato starch.

Fig. 3 shows the starch malonate X-ray diffraction pattern. Presence of small peaks indicates that starch malonate is slight crystalline in nature.

Table 2. Evaluation of starch malonate for its physical and micromeritics properties

Parameters	Observation
Solubility	Aqueous solvent : Insoluble organic solvents: Insoluble
pH (1% w/v aqueous dispersion)	3.15
Melting Point	Charred at 270º C
Viscosity (1% w/v aqueous dispersion)	1.022cps
Swelling index	83.95%
Gelling property	No gelling at 100˚C but formed a clear solution. Whereas in the case of starch, it was gelatinized and formed gel.
Particle Size	5.78±2.304 µm (120 mesh)
Density	1.008 g/cc
Bulk Density	0.718 g/cc
Angle of Repose	14.6±0.05
Compressibility Index	23.02±0.03%

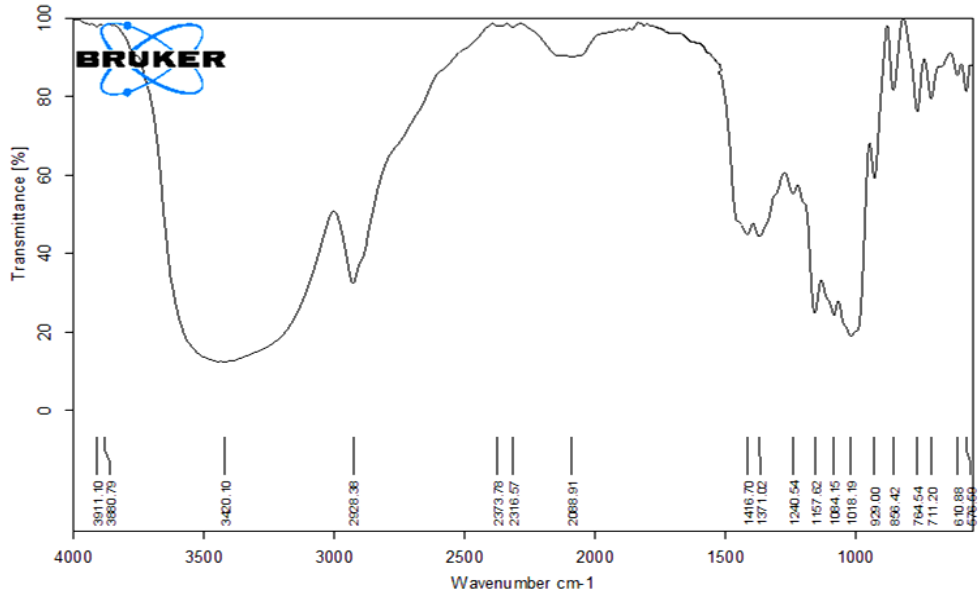


Fig. 1. FTIR spectra of potato starch

Figs. 4 and 5 shows the scanning electron microscopic (SEM) image of potato starch and starch malonate. The morphological structure of starch malonate was found slightly crystalline form when compared with potato starch which is amorphous in nature.

Compatibility of starch malonate with ibuprofen was evaluated by conducting Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), thin layer chromatography (TLC). Fig. 6 and Fig. 7 showed FTIR spectra of Ibuprofen and ibuprofen with starch malonate FTIR spectra. The characteristic peak of carboxylic group (-OH and C=O) present in FTIR spectra of ibuprofen plus starch malonate. This indicates that no interaction between starch malonate and drug selected (ibuprofen).

The DSC thermograms of ibuprofen and ibuprofen – starch malonate exhibited endothermic peaks at 78.48 ^{0}C and 77.53 ^{0}C respectively. These melting peaks of ibuprofen and ibuprofen – starch malonate correspond to the melting points of ibuprofen (75-78^{0}C). The peaks observed in the DSC thermograms of ibuprofen and ibuprofen – starch malonate mixtures correspond to the melting points of the respective drug indicating no interactions between the selected drug and starch malonate. Fig. 8 and Fig. 9 shows the DSC thermograms of ibuprofen and ibuprofen–starch malonate.

Table 3. Shows the peaks present in Ibuprofen and ibuprofen and starch malonate

Functional group		Characteristic peak Present in ibuprofen	Characteristic peak Present in Ibuprofen plus starch malonate
-	OH	2923.39 cm^{-1}	2921.64 cm^{-1}
-	C=O	1720.93cm^{-1}	1720.13 cm^{-1}
-	C-H	2871.45	2871.68
-	C-O-H	1419.42	1419.77

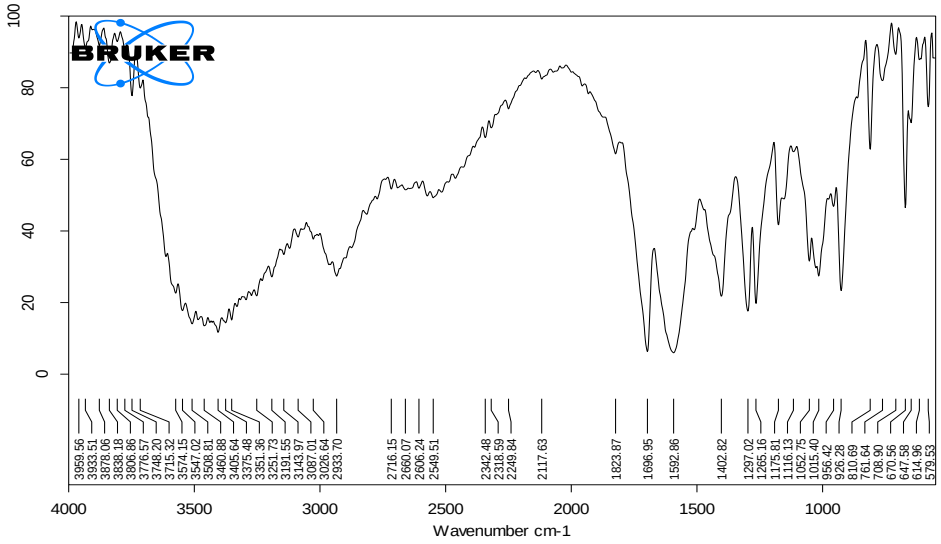


Fig. 2. FTIR Spectra of starch malonate

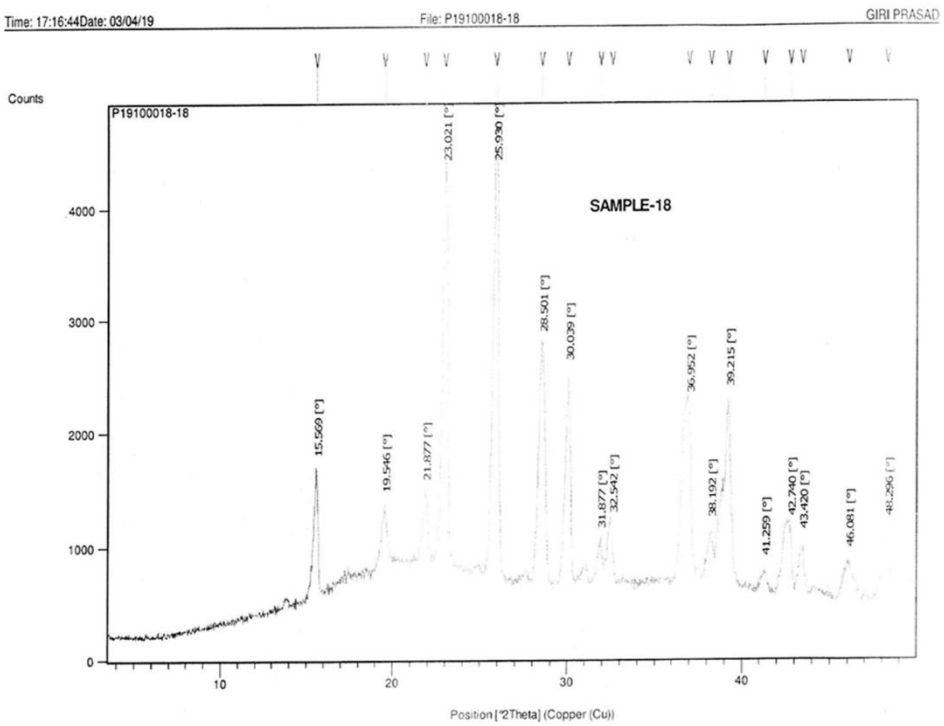


Fig. 3. X –Ray diffraction of starch malonate

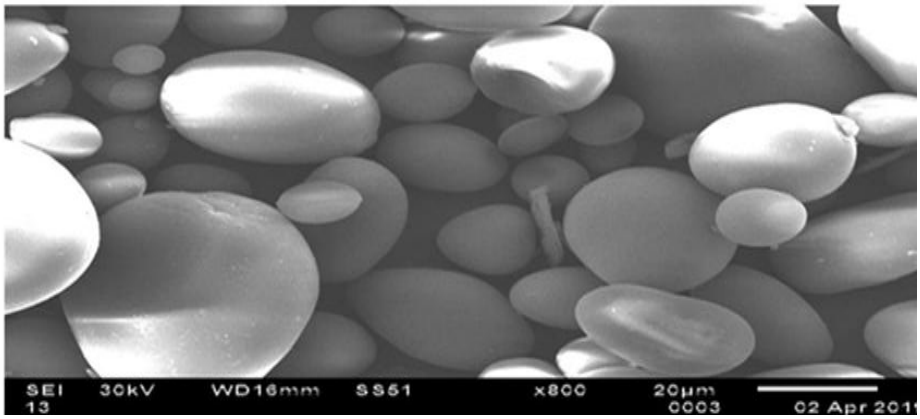


Fig. 4. SEM image of potato starch and starch malonate

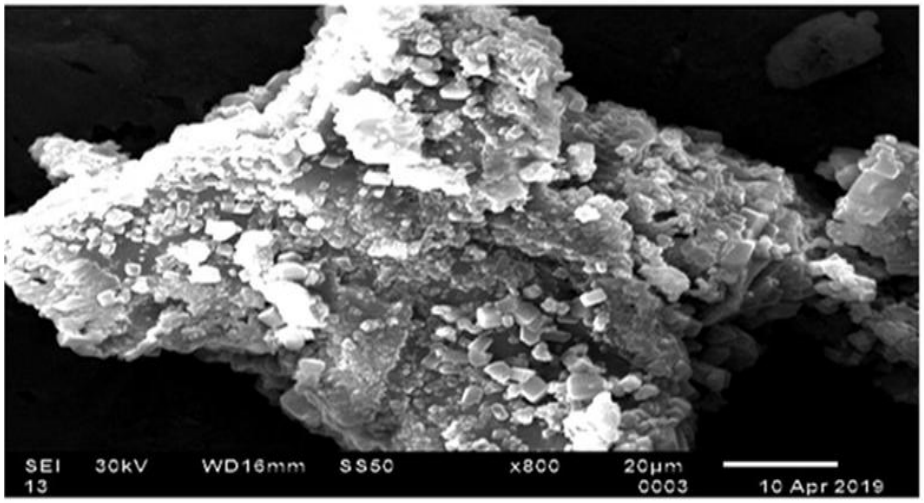


Fig. 5 SEM image of starch malonate

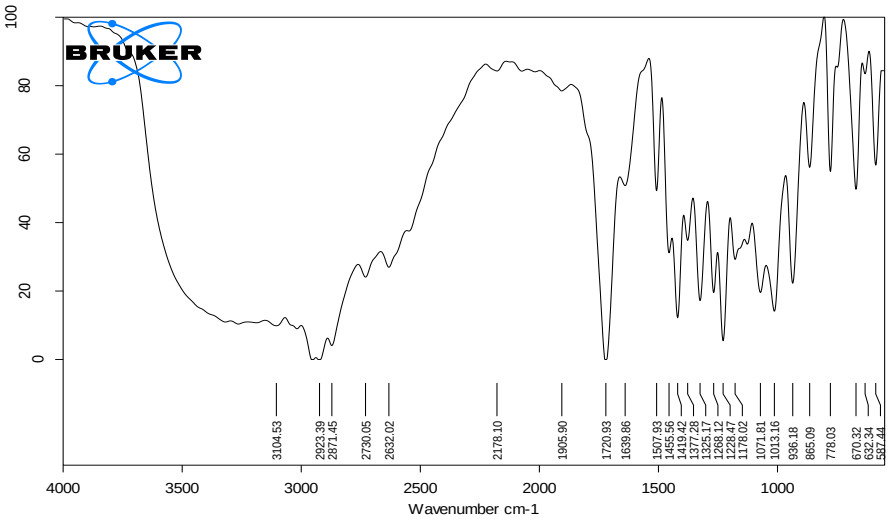


Fig. 6. FTIR Spectra of ibuprofen pure drug

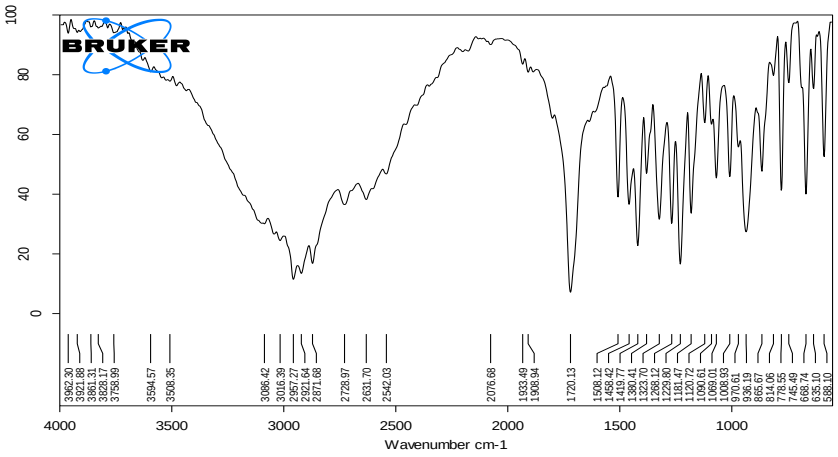


Fig. 7. FTIR Spectra of Ibuprofen plus starch malonate

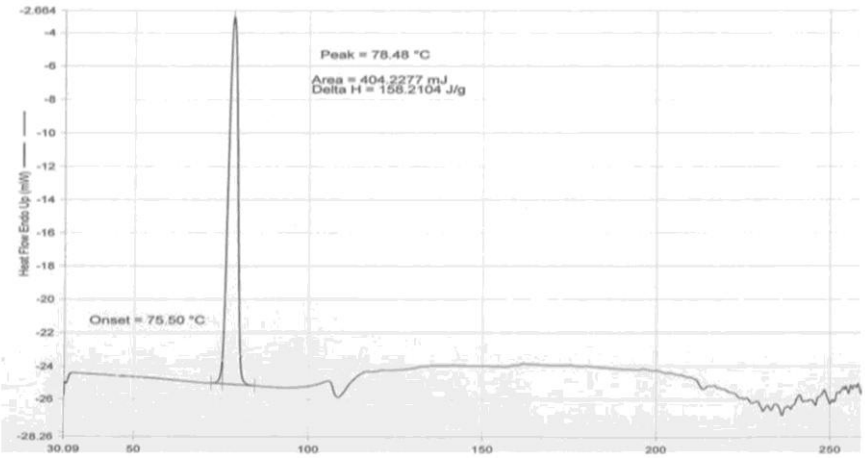


Fig. 8. DSC Thermogram of Ibuprofen API

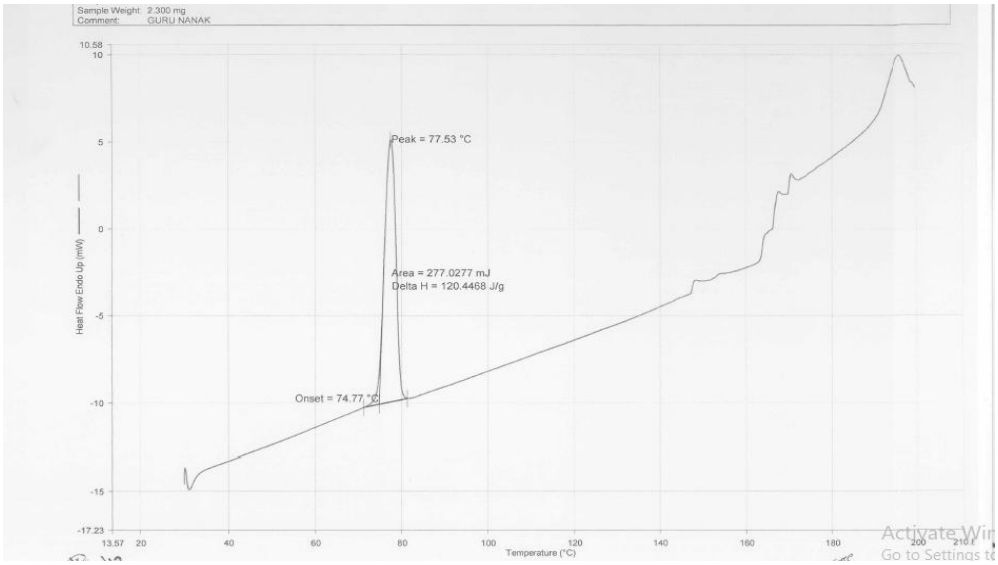


Fig. 9. DSC Thermogram of Ibuprofen API with Starch malonate

Thin layer chromatography was performed to check the interaction between drug and excipient. Stationary Phase used was Pre-coated TLC plates (Silica gel G)

Mobile Phase n-Hexane**:** Ethyl Acetate: Glacial Acetic Acid
(75:25:5)

In this study, single spots were observed for a pure drug (ibuprofen) as well as their mixture with starch malonate (1:1). The R_f values of pure drug and their mixture were found to be close. R_f values of pure drug and their mixture were close, which indicate no interactions between the drug and starch malonate.

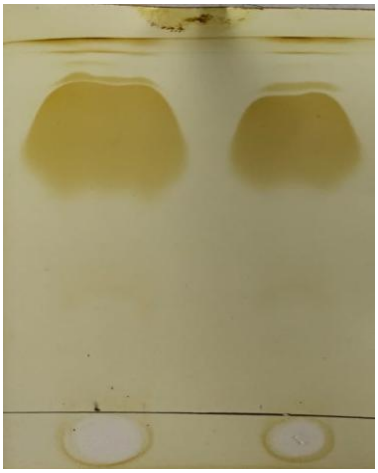


Fig. 10. TLC plate (A) Ibuprofen pure drug (B) Ibuprofen and starch malonate

Hardness of all ibuprofen fast dissolving tablets found to be in the range of 3.7-4.0 kg/cm$^{2.}$

Hardness of tablets determines its capability to withstand physical stress during handling and transportation.

Percentage friability was determined by performing friability of the randomly selected tablets from each formulation. Weight loss of the friability was found to be less than 0.15% of all formulations. As per IP, percent friability below 1% is an indication of good mechanical resistance of the tablets. Thus, it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage and manufacturing processes.

Drug content of randomly selected tablets from each formulation was determined and it was found within 100 ±5% of the labeled amount. Drug content test signifies the all the prepare tablets are having accurate amount of drug and uniform Hence, it can be concluded that all the formulations are having an accurate amount of drug and it should fulfill the official criteria as per IP.

The disintegration time of all the formulated tablets was found to be in the range of 24± 0.02 to 3200± 0.02 seconds, given in the table 3. The water absorption ratio was in between 65.0±0.22-172±0.13. The wetting time found between 20±0.015-202±0.011 seconds. Results of water absorption ratio and wetting time of all formulations are given in Table 4 and wetting time of ibuprofen fast dissolving tablet are shown in Fig. 11. Formulation F2 showed less wetting time i.e. 20±0.0015s as compared to other formulations.

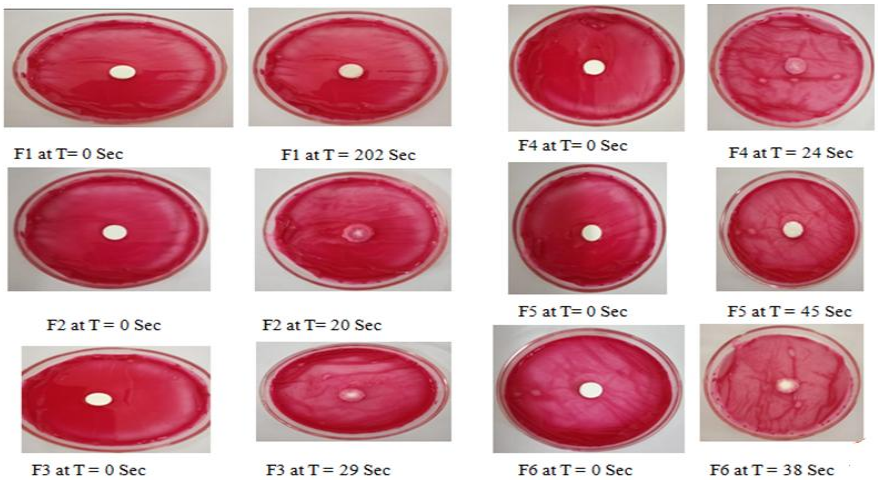


Fig. 11a. Wetting Time of Ibuprofen Fast Dissolving Tablets Formulated by Direct Compression Employing Starch Malonate (A New Superdisintegrant) of formulation F1-F6

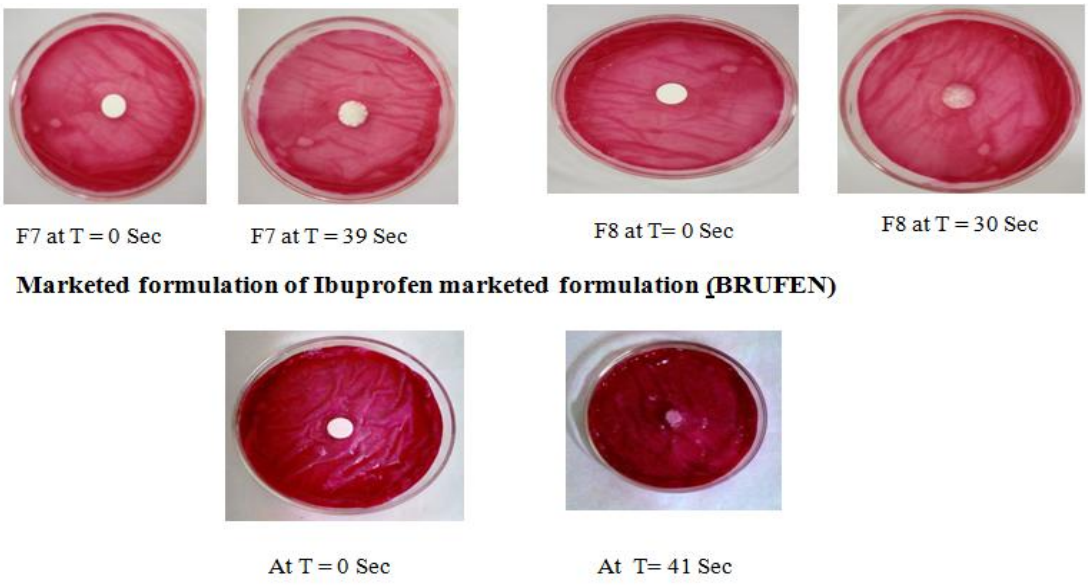


Fig. 11b. Wetting Time of Ibuprofen Fast Dissolving Tablets Formulated by Direct Compression Employing Starch Malonate (A New Superdisintegrant) of formulation F7-F8

Percentage drug release of the prepared fast dissolving tablets was determined by performing *in vitro* dissolution test using USP type II paddle apparatus. Wetting time of the disintegrant determines the dissolution rate of tablets means if wetting time of the tablets is within seconds, tablets are having enhanced drug release within 5 minutes. From the *in vitro* dissolution carried out, it was found that formulation F2 containing starch malonate alone as disintegrant has showed less disintegration as compared to other formulations. In compare to other formulations, F2 has showed lest wetting time and enhanced drug release which showed that selection of starch malonate as disintegrant is the correct selection for fast dissolving tablets of poorly soluble drugs. From the study result we can see that formulation F1 showed longer disintegration time and wetting time as it does not contain any superdisintegrant which helps in the swelling and wetting of tablet fast. Dissolution profile of formulations F1-F8 is shown in Fig.12. PD5 (percent dissolved in 5 minutes) and DE5 (dissolution efficiency in 5 minutes) was found more in formulation F2 as compared to other optimized and marketed formulation. From the PD5 and DE5 it can be concluded that starch malonate is effective as novel superdisintegrant for enhancing the drug release of poorly soluble drugs. Table 5 gives the information regarding number of folds increases in DE5%. Thus from the results it was concluded that starch malonate (new superdisintegrant) can be used as superdisintegrant in the formulation of fast dissolving tablets of poorly soluble drugs.

ANOVA were done to evaluate the effect of three factors (Starch malonate, Crospovidone, Croscarmellose sodium) alone or in combination by 2^3 factorial designs.

ANOVA of disintegrating time (Table 7), ANOVA of percent dissolved in 5 min (Table 8), ANOVA of wetting time (Table 9), ANOVA of water absorption ratio(Table 10) and ANOVA of dissolution efficiency in 5 min (Table 11) indicated that the individual and combined effect of three factors (Croscarmellose sodium, starch malonate, Crospovidone). ANOVA results indicates that effect were significant ($P<0.05$) on disintegration time, percent dissolved in 5 min, wetting time, water absorption ratio and dissolution efficiency in 5 min.

On comparison with the marketed formulation, the optimized F2 formulation gave release of 99.89% in 5 min fulfilling the official specification based on the disintegration time, percent drug dissolved in 5 min, wetting time, water absorption ratio and dissolution efficiency in 5 min.

The optimized formulation F2 showed enhanced drug release with least disintegration time found to be comparable with marketed formulation. The starch malonate can be used a novel superdisintegrant

Table 4. Physical properties: hardness, friability, drug content of ibuprofen fast dissolving tablets prepared by direct compression method

Formulation	Hardness (Kg/Cm^2) n± S.D	Friability (%) n± S.D	Drug Content (mg/tab) n± S.D	Disintegration Time (sec) n ± S.D	Wetting Time (sec) n ± S.D	Water Absorption Ratio (%) n ± S.D
F1	4.0 ± 0.04	0.14±0.015	198.14 ± 0.71	3200± 0.02	202± 0.011	65.0 ± 0.22
F2	4.0 ± 0.02	0.10±0.014	199.33± 0.79	24± 0.02	20± 0.015	170 ± 0.014
F3	3.9 ± 0.01	0.13±0.010	199.21 ± 0.63	30± 0.02	29± 0.10	130± 0.24
F4	3.9 ± 0.02	0.11±0.014	197.18 ± 0.55	43± 0.01	24± 0.08	172± 0.22
F5	3.8 ± 0.04	0.15±0.013	199.30 ± 0.56	47± 0.03	85± 0.011	66.0± 0.017
F6	3.8 ± 0.02	0.10±0.009	198.20 ± 0.18	42± 0.02	38± 0.14	159± 0.013
F7	3.7 ± 0.04	0.12±0.010	199.16 ± 0.57	41± 0.01	45± 0.10	141± 0.10
F8	4.0 ± 0.03	0.13±0.015	199.22 ± 0.11	33± 0.02	39± 0.05	166± 0.14
Marketed formulation	4.0± 0.01	0.12± 0.010	199.28± 0.11	41 ± 0.02	49 ± 0.19	60± 0.17

**SD Standard Deviation from mean, n=3*

Table 5. Ibuprofen Percent Dissolved from Fast Dissolving Tablets Employing Starch Malonate (n ± S.D)

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	Marketed formulation
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	3.98 ± 0.08	99.89 ± 0.10	83.89 ± 0.13	99.99 ± 0.14	42.77 ± 0.13	98.7 ± 0.12	83.89 ± 0.10	75.67 ±0.13	90.1 ± 0.19
10	4.19 ± 0.11		89.6 4± 0.11		52.63 ± 0.11	99.21 ± 0.10	90.48 ± 0.09	84.71 ±0.10	95.68 ± 0.11
15	17.76 ± 0.09				53.46 ± 0.12		94.58 ± 0.12	91.29± 0.13	99.31 ± 0.31
30	17.93 ± 0.10				77.31 ± 0.09				
45	26.4 ± 0.13				79.78 ± 0.13				
60	29.36 ± 0.10				88.83 ± 0.11				

Table 6. Dissolution parameters of ibuprofen fast dissolving tablets formulated employing starch malonate

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	Marketed formulation (BRUFEN)
PD_5	1 3.98 ±0.08	99.89 ±0.05	83.89 ±0.09	99.99 ±0.02	42.77 ±0.04	98.70 ±0.07	83.89 ±0.02	75.67 ±0.08	90.1 ± 0.19
DE_5%	1.6 ±0.08	94.7 ±0.09	76.0± 0.02	94.2 ±0.08	35.6 ±0.06	93.7 ±0.10	79.1 ±0.03	68.3 ±0.08	85.2 ± 0.33
No. of folds increase in DE_5%	---	59.18 ±0.05	47.5 ±0.08	58.87 ±0.02	22.25 ±0.12	58.56 ±0.09	49.44 ±0.07	42.69 ±0.05	

**SD standard deviation from mean, n=3, PD5--percent dissolved in 5 min., DE5%-dissolution efficiency in 5 min*

Table 7. ANOVA of disintegration time of ibuprofen fast dissolving tablets formulated employing starch malonate

Source of variance	Degree of freedom	Sum square	Mean sum square (sum quare/d.f)	Variation ratio(f) (mss/mss error)	f ratio	Significant/non significant
Replicates	2	8918.5	4459.25	1.878341582	2.77	P>0.05
Treatments	7	25328313	3618330.429	1524.126367	4.66	P<0.05
Starch malonate (A)	1	3648840	3648840	1536.97772	4.66	P<0.05
Croscarmellose sodium (B)	1	3627038	358.8267	0.151146294	4.66	P<0.05
Starch malonate x Croscarmellose sodium (AB)	1	3670708	3670708	1546.189039	4.66	P<0.05
Crospovidone ©	1	3548166	3548166	1494.57145	4.66	P<0.05
Starch malonate x Crospovidone (AC)	1	3591361	3591361	1512.766206	4.66	P<0.05
Croscarmellose sodium x Crospovidone (BC)	1	3557400	3557400	1498.461029	4.66	P<0.05
Starch malonate x croscarmellose sodium x Crospovidone (ABC)	1	3684801	3684801	1552.125344	4.66	P<0.05
Error	14	33236.5	2374.035714			
Total	23	25370468				

*P<0.05 indicate significance; p>0.05 indicate non-significance; d. f – Degree of Freedom * S.S – Sum of Square * M.S.S – Mean Sum of Squares*
All the values are expressed as mean ±SD, where n=3, SD: Standard Deviation; ANOVA-Analysis of Variance

Table 8. ANOVA of percent dissolved of ibuprofen fast dissolving tablets formulated employing starch malonate

Source of variance	Degree of freedom	sum square	mean sum square (sum square/d.f)	variation ratio(f) (mss/mss error)	f ratio	P VALUE Significance
Replicates	2	0	0	0	2.77	P>0.05
Treatments	7	24095.73	3442.247143	688449.4286	2.77	P<0.05
starch malonate(A)	1	9564.034	9094.827	1818965.4	4.6	P<0.05
Croscarmellose sodium(B)	1	3601.99	5421.02	1084204	4.6	P<0.05
Starch malonate X Croscarmellose sodium (AB)	1	7786.804	7482.189	1496437.8	4.6	P<0.05
Crospovidone(C)	1	66.46682	491.596	98319.2	4.6	P<0.05
Starch malonate X Crospovidone (AC)	1	1545.936	82.88167	16576.334	4.6	P<0.05
Croscarmellose X Crospovidone (BC)	1	14439.33	20.64615	4129.23	4.6	P<0.05
Starch malonate X Croscarmellose sodium X Crospovidone (ABC)	1	91.18202	73.22027	14644.054	4.6	P<0.05
Error	14	0.07	0.005			
Total	23	153978.5	6694.717391			

*P<0.05 indicate significance; p>0.05 indicate non-significance; d. f – Degree of Freedom * S.S – Sum of Square * M.S.S – Mean Sum of Squares*
All the values are expressed as mean ±SD, where n=3, SD: Standard Deviation; ANOVA-Analysis of Variance

Table 9. ANOVA of wetting time of ibuprofen fast dissolving tablets formulated employing starch malonate

Source of variance	degree of freedom	sum square	mean sum square(sum square/d.f)	variation ratio(f)(mss/mss error)	f ratio	significant/ non significant
Replicates	2	4.745	2.3725	0.9422695	2.77	P>0.05
Treatments	7	78006.62	11143.80286	4425.9075	4.66	P<0.05
Starch malonate (A)	1	88938.38	88938.38	35323.045	4.66	P<0.05
Croscarmellose sodium (B)	1	16485.04	358.8267	142.51273	4.66	P<0.05
Starch malonate x Croscarmellose sodium (AB)	1	17876.04	1901.04	755.02298	4.66	P<0.05
Crospovidone (C)	1	1785.375	640.6667	254.44919	4.66	P<0.05
Starch malonate x Crospovidone (AC)	1	6834.375	549.1267	218.09287	4.66	P<0.05
Croscarmellose sodium x Crospovidone (BC)	1	6240.375	47.60167	18.905628	4.66	P<0.05
Starch malonate x Croscarmellose sodium x Crospovidone (ABC)	1	7245.375	135.375	53.765957	4.66	P<0.05
Error	14	35.25	2.517857143		4.66	P<0.05
Total	23	78046.62				
		4.745	2.3725	0.9422695		

P<0.05 indicate significance; p>0.05 indicate non-significance
*d. f – Degree of Freedom * S.S – Sum of Square * M.S.S – Mean Sum of Squares*
All the values are expressed as mean ±SD, where n=3,
SD: Standard Deviation
ANOVA-Analysis of Variance

Table 10. ANOVA of water absorption ratio of ibuprofen fast dissolving tablets formulated employing starch malonate

Source of variance	degree of freedom	sum square	mean sum square(sum square/d.f)	variation ratio(f)(mss/mss error)	f ratio	significant/non significant
Replicates	2	0.225	0.1125	0.013762069	2.77	P>0.05
Treatments	7	41564.93	5937.847143	726.3738914	4.66	P<0.05
Starch malonate (A)	1	26070.04	5884.402	719.8359736	4.66	P<0.05
Croscarmellose sodium (B)	1	8626.042	358.8267	43.89509197	4.66	P<0.05
Starch malonate x Croscarmellose sodium (AB)	1	6435.375	1901.04	232.5532789	4.66	P<0.05
Crospovidone ©	1	12.04167	640.6667	78.37243916	4.66	P<0.05
Starch malonate x Crospovidone (AC)	1	301.0417	549.1267	67.17439643	4.66	P<0.05
Croscarmellose sodium x Crospovidone (BC)	1	108.375	47.60167	5.823088645	4.66	P<0.05
Starch malonate x Croscarmellose sodium x Crospovidone (ABC)	1	12.04167	135.375	16.5603565	4.66	P<0.05
Error	14	114.445	8.174642857		-	-
Total	23	78046.62			-	-

P<0.05 indicate significance; p>0.05 indicate non-significance
*d. f – Degree of Freedom * S.S – Sum of Square * M.S.S – Mean Sum of Squares*
All the values are expressed as mean ±SD, where n=3,
SD: Standard Deviation
ANOVA-Analysis of Variance

Table 11. ANOVA of Dissolution efficiency of Ibuprofen Fast Dissolving Tablets Formulated Employing Starch Malonate

Source of variance	degree of freedom	sum square	mean sum square(sum square/d.f)	variation ratio(f)(mss/mss error)	f ratio	significant/non significant
Replicates	2	0.211	0.1055	0.772085729	2.77	P<0.05
Treatments	7	23163.88	3309.125714	24217.33403	4.66	P<0.05
No superdisintegrant	1	110717.8	145115.7	1062007.214	4.66	P<0.05
Starch malonate (A)	1	13915.35	9094.827	66559.1103	4.66	P<0.05
Croscarmellose sodium (B)	1	3190.12	5421.02	39672.91166	4.66	P<0.05
Starch malonate x Croscarmellose sodium (AB)	1	11859.26	7482.189	54757.26398	4.66	P<0.05
Crospovidone ©	1	38.76042	491.596	3597.670674	4.66	P<0.05
Starch malonate x Crospovidone (AC)	1	335.2538	82.88167	606.5569158	4.66	P<0.05
Croscarmellose sodium x Crospovidone (BC)	1	1171.804	20.64615	151.0957135	4.66	P<0.05
Starch malonate x Croscarmellose sodium x Crospovidone (ABC)	1	290.5104	73.22027	535.8514271	4.66	P<0.05
Error	14	1.913	0.136642857			
Total	23	23166	1007.217391			

P<0.05 indicate significance; p>0.05 indicate non-significance
*d. f – Degree of Freedom * S.S – Sum of Square * M.S.S – Mean Sum of Squares*
All the values are expressed as mean ±SD, where n=3,
SD: Standard Deviation
ANOVA-Analysis of Variance

3.1 Design Expert Study (Response Surface plot study)

Response surface plots and contour plots were plotted using design Expert 7.11 version. polynomial regression algorithm equation was developed to co-relate the independent variables (starch malonate (A), Croscarmellose sodium (B) and Crospovidone (C)) with dependent variables (disintegration time and dissolution efficiency in 5 minutes).

Below are the equations 1 and 2 representing polynomial equation for disintegration time and dissolution efficiency in 5 minutes.

Disintegration time in 5 minutes =+432.50 +397.00 A-395.75 B - 391.75 C +398.25AB + 393.75AC+392.00BC--399.00ABC (R2= 1.000)

Dissolution efficiency in 5 minutes= +67.90+19.83A+11.50B+1.27C-17.98AB-8.00AC-6.97BC+0.75ABC (R2=1.000)

Effect of starch malonate (A), Croscarmellose sodium (B) and Crospovidone (C) and their interaction on disintegration time and dissolution efficiency in 5 minutes are given in below Table 12.

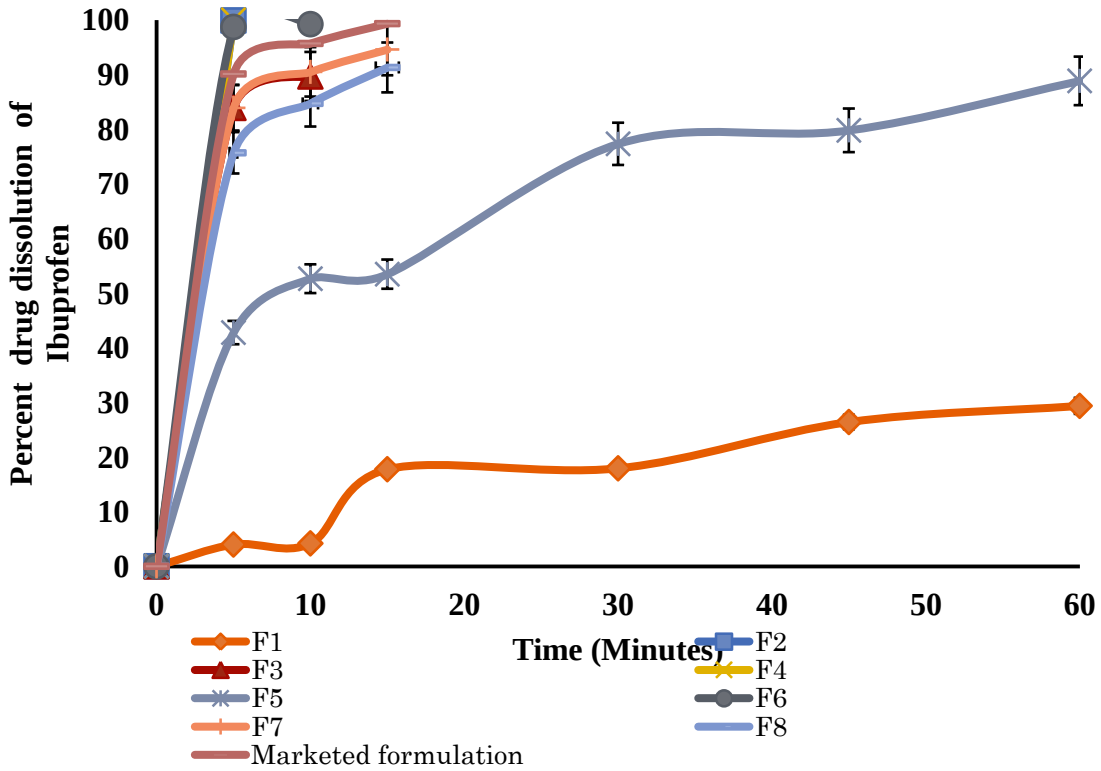


Fig. 12. Dissolution profiles of ibuprofen fast dissolving tablets prepared employing starch malonate of formulation F1- F8

Table 12. Interaction on disintegration time and dissolution efficiency in 5 minutes

Parameters	Effect of disintegration time	Effect on dissolution efficiency in 5 minutes
A	+	+
B	-	+
C	-	+
AB	+	–
AC	+	–
BC	+	–
ABC	–	+

+ means positive effect, (-) means negative effect

3.2 Effect of Different Superdisintegrant on Disintegration Time

Starch malonate (A) in combination with Croscarmellose Sodium (B) has showed a linear relation on disintegration time. When the concentration of starch malonate and Croscarmellose increases, disintegration time of tablet decreases. Tablets will disintegrate more rapidly.

Starch malonate (A) in combination with Crospovidone (C) has showed a linear relation on disintegration time. When the concentration of starch malonate and Crospovidone (C) increases, disintegration time of tablet decreases. Tablets will disintegrate more rapidly.

Croscarmellose Sodium (B) in combination with Crospovidone (C) has showed a linear relation on disintegration time. When the concentration of Croscarmellose Sodium and Crospovidone increases, disintegration time of tablet decreases. Tablets will disintegrate more rapidly. Fig. 13, Fig. 14 and Fig. 15 showed the response and contour plot of effect of different superdisintegrant on disintegration time of Ibuprofen fast dissolving tablets employed starch malonate.

Starch malonate (A) in combination with Croscarmellose Sodium (B) and Crospovidone (C) has showed a non-linear relation on disintegration time. When the concentration of starch malonate, Croscarmellose and Crospovidone increases, disintegration time of tablet increases.

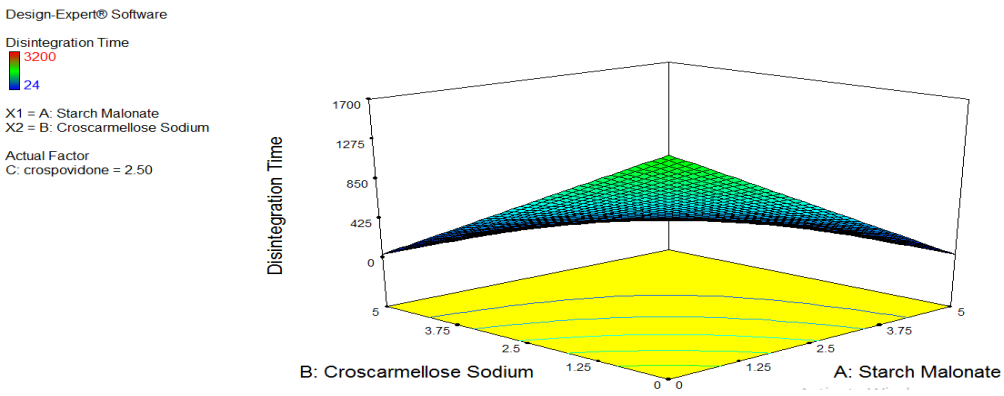
3.3 Effect of Different Superdisintegrant on Dissolution Efficiency in 5 Minutes

Effect of combination AB (Starch malonate with Croscarmellose Sodium), AC (Starch malonate with Crospovidone) and BC (Croscarmellose Sodium with Crospovidone) was found to be non-linear on dissolution efficiency in 5 minutes. In combination these superdisintegrant are not showing good drug release profile. Starch malonate with Croscarmellose Sodium and Crospovidone has showed linear relation means when concentration will increases it will enhance the dissolution efficiency in 5 minutes. Fig. 16, Fig. 17 and Fig. 18 showed the response and contour plot of effect of different superdisintegrant on disintegration time of Ibuprofen fast dissolving tablets employed starch malonate.

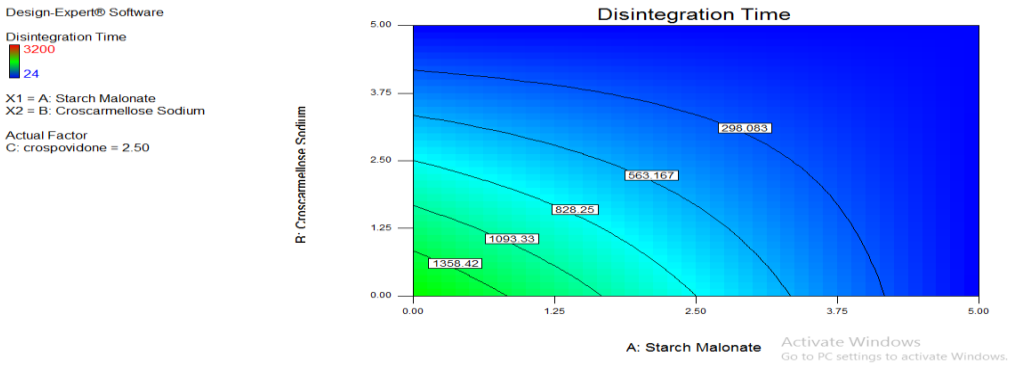
After storing period of 6 months, no physical changes was observed in the formulation. Drug content and dissolution profile was evaluated. Drug content was not found different after stability testing. The drug dissolution profiles of the fast-dissolving tablets before and after storage are given in Table 13. Drug content and drug dissolution rate of the fast dissolving tablets formulated employing starch malonate were quite stable.

Table 13. Drug Dissolution profile of optimized formulation F2 before and after storage for 6 months for stability studies

Optimized formulation	Percent Drug Dissolution
Formulation F2 (Before stability)	98.52 ± 0.11
Formulation F2 (After stability)	95.74 ± 0.13

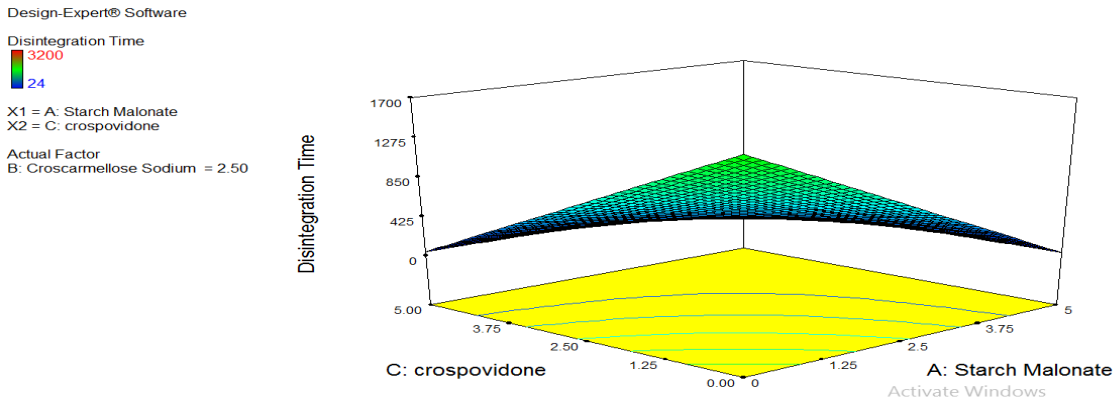


Response plot

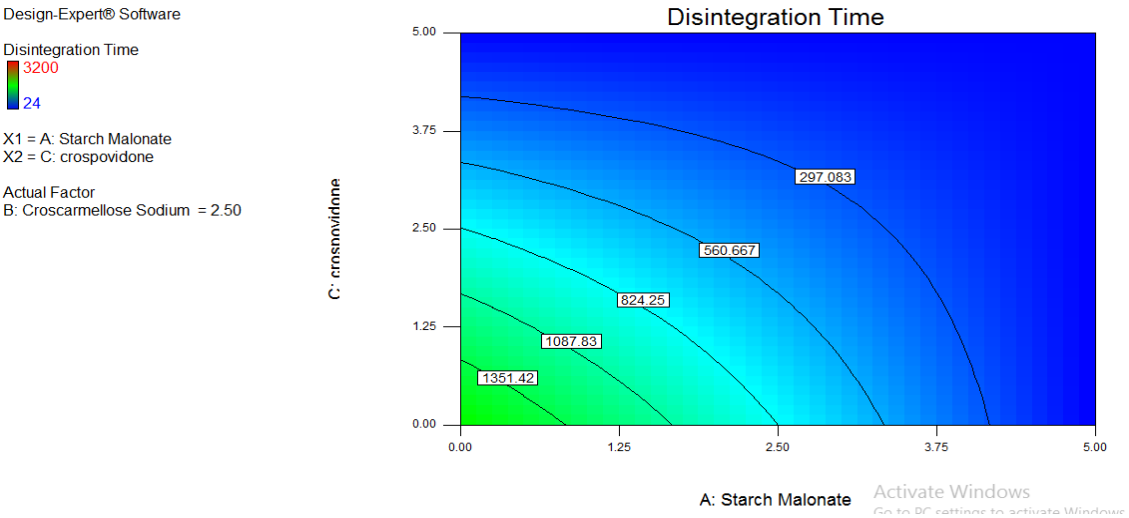


Contour plot

Fig. 13. Response plot and contour plot of Effect of starch malonate and croscarmellose sodium on disintegration time

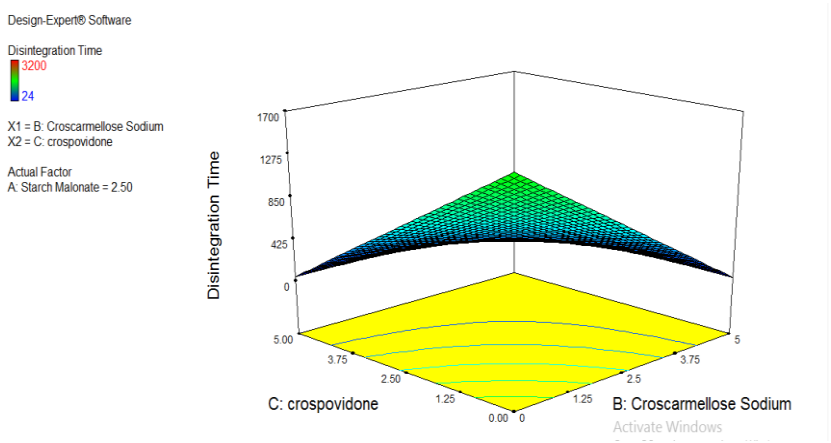


Response plot

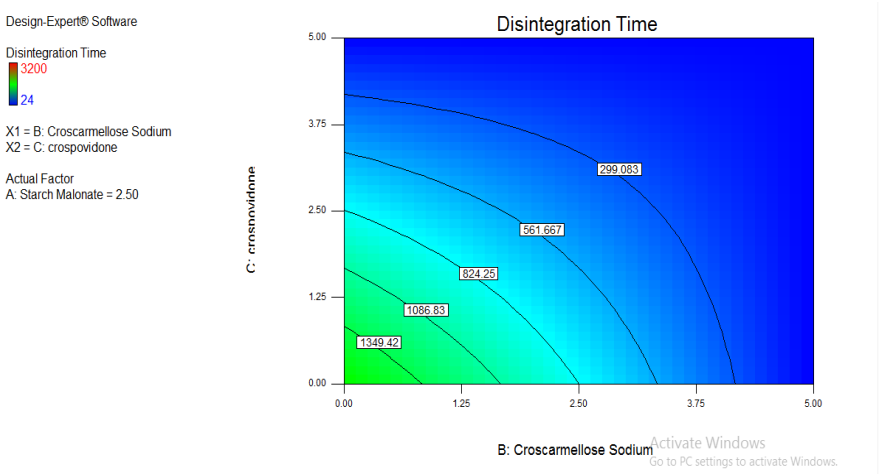


Contour plot

Fig. 14. Response plot and contour plot of Effect of starch malonate and Crospovidone on disintegration time

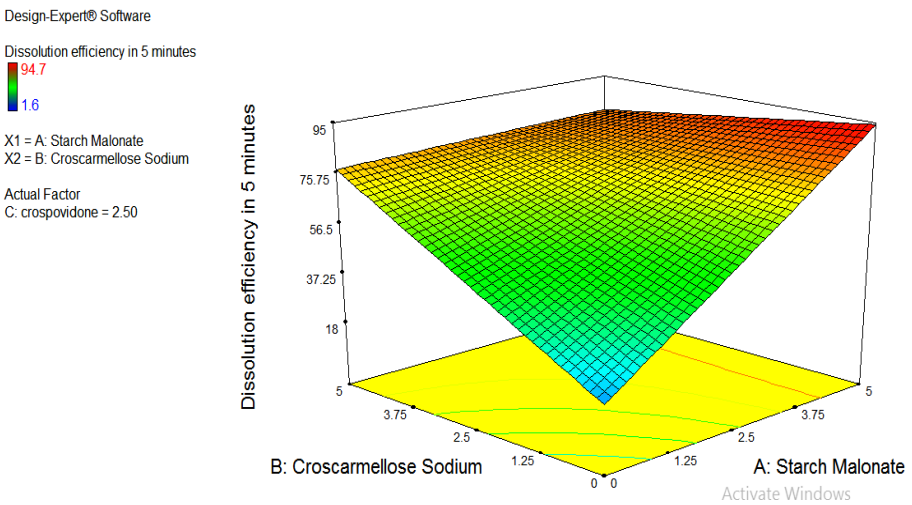


Response plot



Contour plot

Fig. 15. Response plot and contour plot of Effect of croscarmellose sodium and Crospovidone on disintegration time



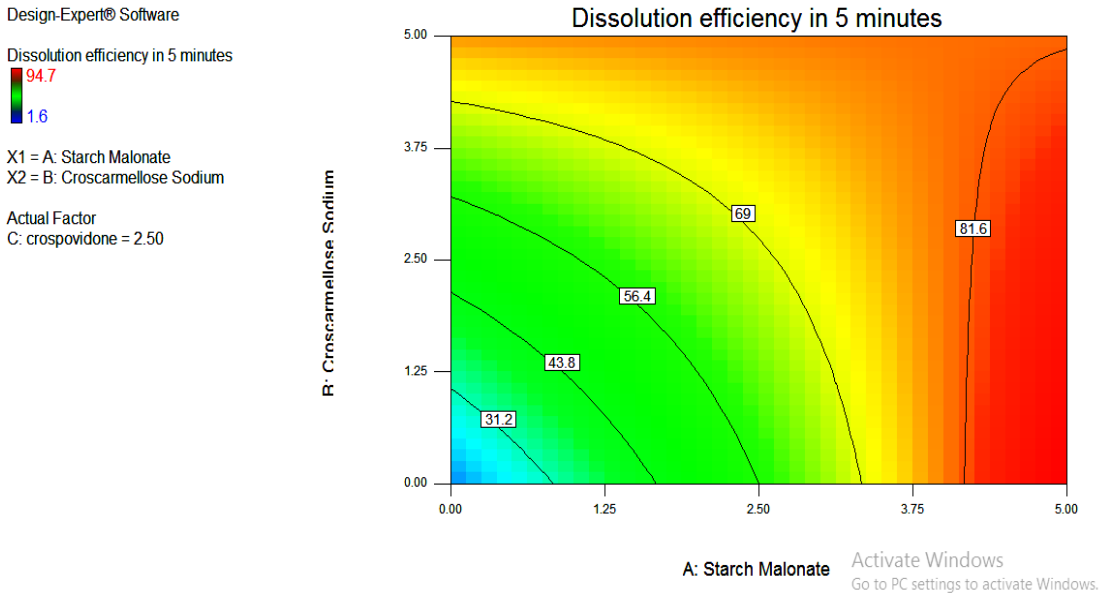


Fig. 16. Response plot and contour plot of Effect of starch malonate and croscarmellose sodium on dissolution efficiency in 5 minutes

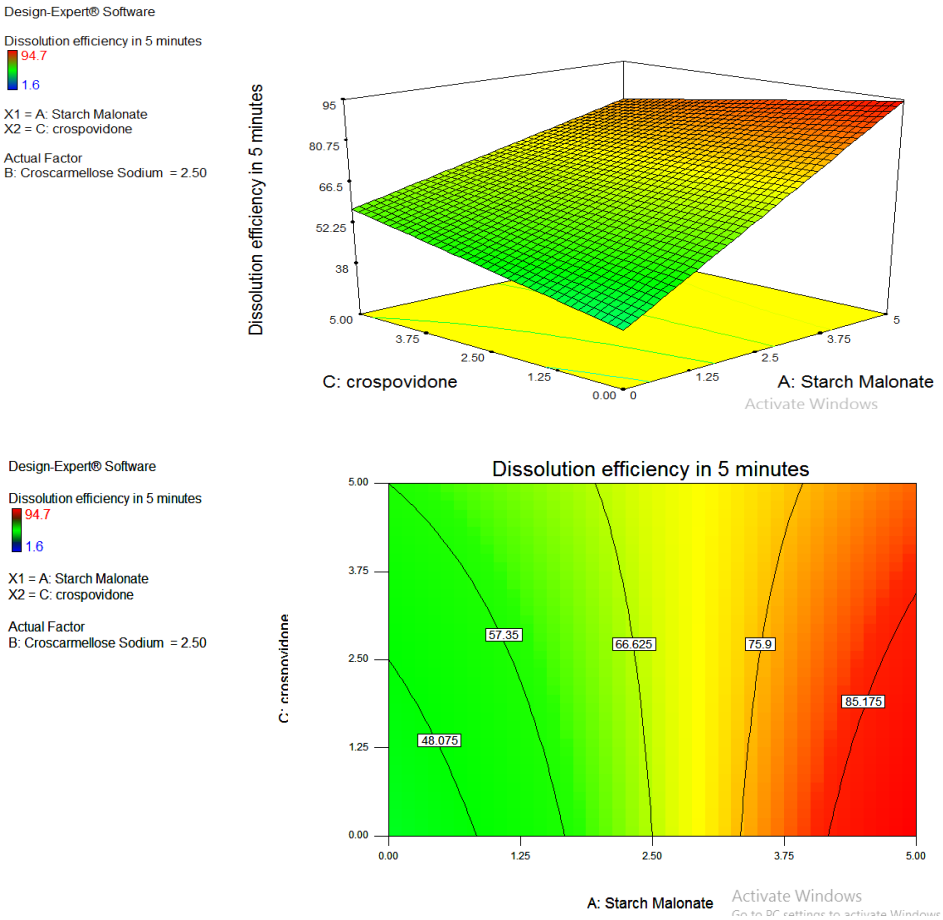


Fig. 17. Response plot and contour plot of Effect of starch malonate and crospovidone on dissolution efficiency in 5 minutes

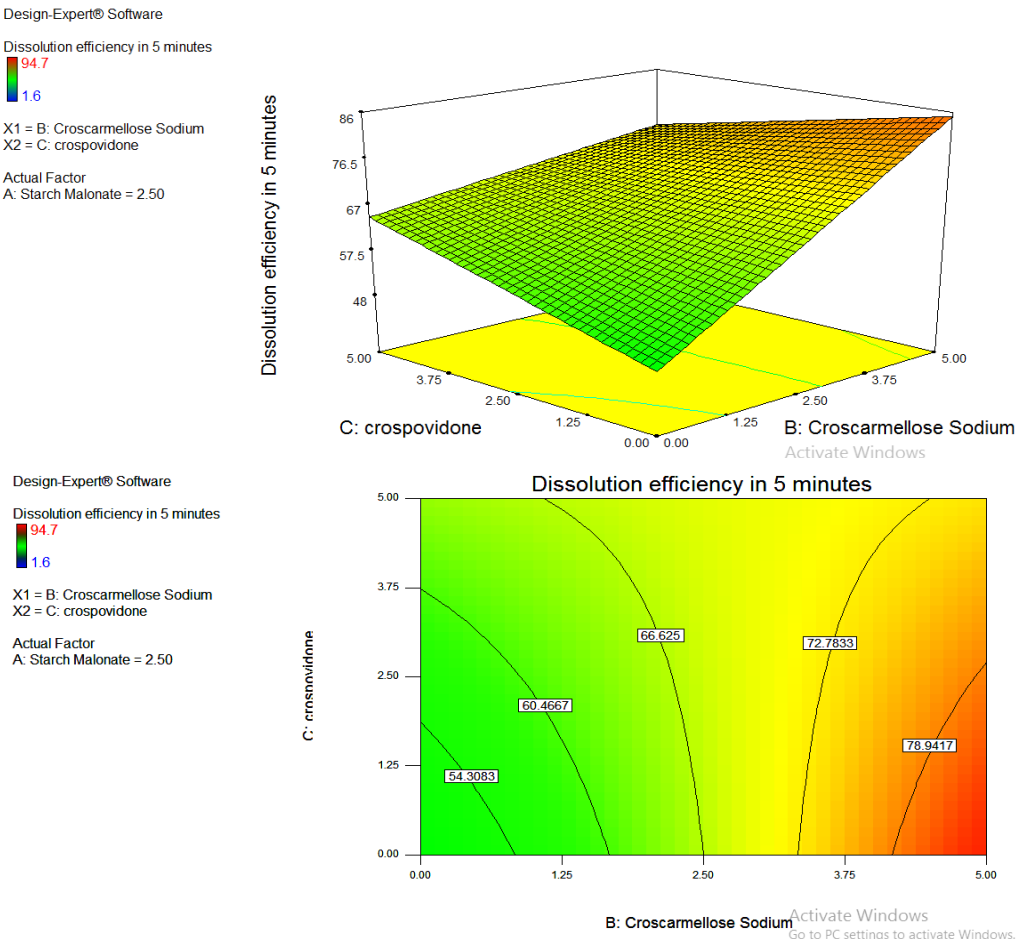


Fig. 18. Response plot and contour plot of Effect of croscarmellose sodium and Crospovidone on dissolution efficiency in 5 minutes

4. CONCLUSION

Fast dissolving tablets are designed to get fast relief from symptoms, which depend on the disintegration of the tablets. Starch malonate as disintegrant alone or in combination showed least disintegration time and enhanced dissolution. From the study, it was found that optimized formulation F2 having starch malonate alone has showed least disintegration time with enhanced drug release as compared to other formulations. Hence, starch malonate can be used as a novel superdisintegrant in the preparation of fast dissolving tablets of poorly soluble drugs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these product s as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVALS

We conducted our research after obtaining proper IEC approval.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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