

Original Article

DESIGN, OPTIMIZATION AND EVALUATION OF CETRIZINE DIHYDROCHLORIDE FAST DISSOLVING FILMS EMPLOYING STARCH TARTRATE–A NOVEL SUPERDISINTEGRANT

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ABSTRACT

Objective: The aim of the current research is optimization, preparation and evaluation of starch tartrate (novel super disintegrant) and preparation of fast dissolving oral films of cetirizine dihydrochloride by employing starch tartrate.

Methods: To check the drug excipient compatibility studies of the selected drug (Cetirizine dihydrochloride) and the prepared excipient i. e starch tartrate, different studies like FTIR (Fourier-transform infrared spectroscopy), DSC (Differential scanning calorimetry) and thin-layer chromatography (TLC) were carried out to find out whether there is any interaction between cetirizine dihydrochloride and starch tartrate. The solvent casting method was used for the preparation of fast dissolving films. The prepared films were then evaluated for thickness, folding endurance, content uniformity, tensile strength, percent elongation, *in vitro* disintegration time and *in-vitro* dissolution studies. Response surface plots and contour plots were also plotted to know the individual and combined effect of starch tartrate (A), croscarmellose sodium (B) and crospovidone (C) on disintegration time and drug dissolution efficiency in 10 min (dependent variables).

Results: Films of all the formulations are of good quality, smooth and elegant by appearance. Drug content (100±5%), thickness (0.059 mm to 0.061 mm), the weight of films varies from 51.33 to 58.06 mg, folding endurance (52 to 67 times), tensile strength (10.25 to 12.08 N/mm²). Fast dissolving films were found to disintegrate between 34 to 69 sec. Percent dissolved in 5 min were found to be more in F1 formulation which confirms that starch tartrate was effective at 1%.

Conclusion: From the research conducted, it was proved that starch tartrate can be used in the formulation of fast dissolving films of cetirizine dihydrochloride. The disintegration time of the films was increased with increase in concentration of super disintegrant.

Keywords: Fast dissolving Films, Superdisintegrant, Starch tartrate, Cetirizine dihydrochloride Dissolution efficiency, Disintegration time

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INTRODUCTION

Among different routes of drug delivery, oral route is the preferred route for systemic effects because of their advantages like convenient, drug withdrawal, low cost and stability [1]. Fast dissolving systems are the current trend going on in the market with their advantages over conventional tablets or liquid dosage forms. Fast dissolving systems are preferred choice for all age patients, including pediatrics, geriatrics, psychotic patients and unconscious patients. Fast dissolving systems are dosage forms that delivers drug with 5 to 10 min [2]. Fast dissolving systems was developed in the late 1970s to over the conventional solid oral dosage forms [3]. Fast dissolving films are solid dosage forms developed on the transdermal patches technology [4]. These orally disintegrating films contains drug in the form of the thin patch. After placing the thin patches on the patient's tongue or mucosa, as the patches comes in contact with the saliva, it gets dissolved and the drug get dissolved within 5 min to get the therapeutic effect [5]. Fast dissolving films mainly consist of water-soluble (hydrophilic) polymers that dissolve rapidly and drug reaches to the systemic circulation through mucosal absorption [6]. Fast dissolving films are easily accepted by the patients due to their ease of administration, portability and accurate dose. The texture of the films and its robustness depends on the polymers used. As per pharmacopeia, general time of fast dissolving films is 5-20 min [7]. Some of the incidents has reported with fast-dissolving tablets that patients are chewing or swallowing the tablets after giving the proper instruction also. These incidents are not possible with fast dissolving films and they are new approaches under fast dissolving systems so that 90% of the drug will reach to systemic circulation bypassing hepatic metabolism. Solvent casting methods are the commonly used method for the preparation of fast dissolving films [8]. Cetirizine dihydrochloride belongs to antihistaminic drugs used to get relief from symptoms like running nose, watery eyes, itching, and hives. It belongs

to BCS class III drugs having high solubility but low permeability. So by preparing fast dissolving films of cetirizine dihydrochloride, we can enhance the solubility which results in fast dissolution of the drug. In this research a novel super disintegrant was synthesized and optimized it as a super disintegrant in the formulation of fast dissolving films of cetirizine dihydrochloride.

MATERIALS AND METHODS

Cetirizine dihydrochloride, HPMC E5 LV, cross caramallose sodium, crospovidone, polyethylene glycol (PEG) 6000, aspartame and citric acid was procured from Yarrow chemicals, Mumbai. Tartaric acid, potato starch, and sodium hydroxide were procured from Finar chemicals Ltd, Ahmedabad. Distilled water was prepared in laboratory.

Preparation of starch tartrate (a novel super disintegrant)

Potato starch and tartaric acid were used for the preparation of starch tartrate by esterification reaction [9]. A procedure involved in the preparation of starch tartrate is given below in fig. 1.

Characterization of starch tartrate

The novel super disintegrant starch tartrate prepared was evaluated for the following parameters as given in fig. 2.

Solubility

Starch tartrate was checked for its solubility in distilled water and in prepared buffers of pH 1.2, 4.5 and 7.4 (aqueous solvents) and in acetone, petroleum ether, alcohol, chloroform and dichloromethane (organic solvents) [10].

pH

Starch tartrate 1% slurry was prepared by dissolving 1 part in 100 ml of distilled water and then checked for its pH using pH meter [10].

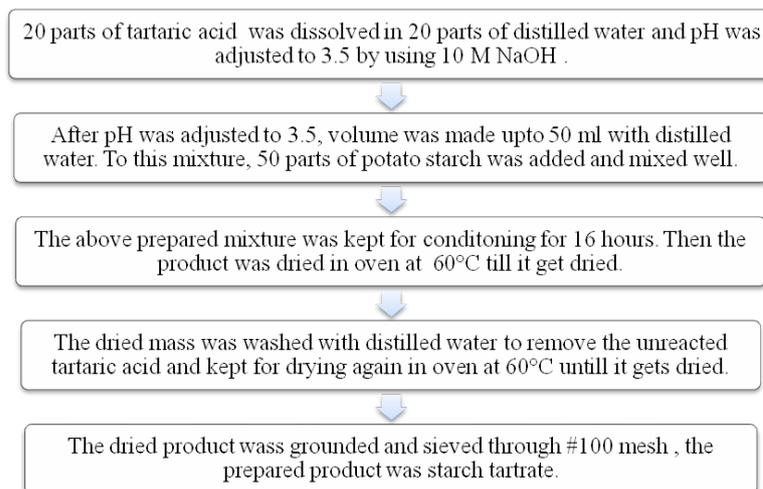


Fig. 1: Procedure for the preparation of starch tartrate

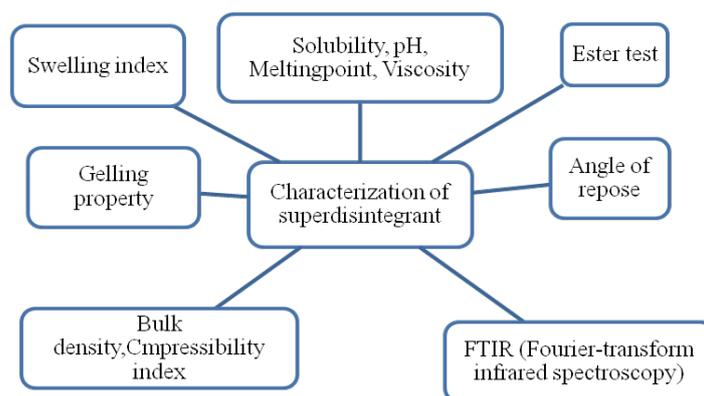


Fig. 2: Characterization parameters of starch tartrate

Melting point

The melting point apparatus was used to determine the melting point of prepared starch tartrate [10].

Viscosity

Viscosity was measured by preparing 1% dispersion of starch tartrate in distilled water then dispersion was checked for its viscosity by Ostwald viscometer [10].

Swelling index

Two graduated test tubes (10 ml) were taken in which distilled water and liquid paraffin was filled up to the mark. Accurately weighed 200 mg of the starch tartrate was added in both the test tubes containing distilled water and liquid paraffin and mixed well. Then, the test tubes were kept aside for 12 h and after 12 h volume of sediment was recorded [10]. The formula used for the calculation of swelling index is as given below.

$$S.I(\%) = \frac{\text{Volume of sediment in distilled water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100$$

Test for gelling property

Gelation property was checked by heating the 7% dispersion of starch tartrate and potato starch in a water bath for 30 min at 100 °C [10].

Particle size

Starch tartrate particle size was determined by using eyepiece micrometer [10].

Density

Starch tartrate density was checked by the liquid displacement process using benzene as liquid [10].

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) of starch tartrate was determined by transferring the accurately weighed amount of sample in a clean and dry 50 ml measuring cylinder. After transferring the sample in a measuring cylinder, volume of packing was noted down. The tapped volume of packing was recorded after tapping the cylinder containing sample 50 times on a plane surface [10]. The formula used for the calculation of loose bulk density (LBD) and tapped bulk density (TBD) is given below.

$$LBD = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$TBD = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

Percentage compressibility index

The formula used to calculate Carr's compressibility index of the powder blend is given below:

$$\% \text{ Carr's Index} = \frac{(\text{Tapped bulk density} - \text{Loose bulk density})}{\text{Tapped bulk density}} \times 100$$

Angle of repose

Fixed funnel method was used for the determination of angle of repose [10]. Equation used to measure angle of repose is as given below:

$$\tan \theta = \frac{h}{r}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

Where θ = angle of repose; h = height of pile; r = radius of pile.

FTIR (Fourier-transform infrared spectroscopy)

IR Spectra of potato starch and starch tartrate was recorded by preparing samples of starch tartrate and potato starch on KBr (potassium bromide) discs. They are scanned in the range of 500 to 4000 cm^{-1} [11].

X-Ray diffraction

X-ray diffractometer was used to obtain the X-ray diffraction pattern of starch tartrate prepared at room temperature [11].

Drug-excipients compatibility studies

Cetirizine dihydrochloride compatibility was evaluated with prepared super disintegrant (starch tartrate) by performing DSC (Differential scanning calorimetry), TLC (thin layer chromatography) and FTIR (Fourier-transform infrared spectroscopy) studies.

Differential scanning calorimetry (DSC)

Drug (cetirizine dihydrochloride) and starch tartrate (novel super disintegrant) was mixed in 1:1 ratio for the sample to record the DSC (Differential scanning calorimetry) thermograms. Equipment used was Perkin Elmer thermal analyser. 2-5 mg of samples was sealed in an aluminum pan and scanned under the temperature range of 30–350 $^{\circ}\text{C}$.

FTIR (Fourier-transform infrared spectroscopy)

Starch tartrate and cetirizine was mixed in 1:1 ratio and by using potassium bromide discs samples was prepared. As a reference

potassium bromide discs was taken. Spectra were recorded by Perkin Elmer spectrophotometer.

TLC (thin layer chromatography) study

TLC (thin layer chromatography) study was carried out with cetirizine and their mixture with starch tartrate (1:1) as follows:

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

Mobile Phase: Ammonia: Methanol: Methylene chloride (1: 10: 90 v/v/v)

Procedure:

The mobile phase was prepared and taken in a TLC chamber. The chamber was allowed to saturate with solvent vapor for 24 h. Standard (pure drug) and test (cetirizine with starch tartrate mixtures) samples were spotted on activated silica plates using narrow capillary tubes. The spotted plates were kept in the TLC chamber and allowed to run the mobile phase. The plates were dried and kept in iodine chamber to develop the spots. The R_f values of standard and test samples were determined by the following formula.

R_f (retardation factor) = Distance traveled by sample/Distance travelled by solvent front.

Preparation of cetirizine fast dissolving films

Oral fast-dissolving films of cetirizine dihydrochloride were prepared by solvent casting method. Formula was optimized by 2^3 factorial designs. In one beaker, cetirizine dihydrochloride (5 mg) was dissolved in 1 ml of the distilled water. In another beaker film forming polymer i.e HPMC E5 LV, starch tartrate along with plasticizer PEG 6000, citric acid and aspartame was dissolved in specific amount of water. The drug and distilled water mixture was added to the film forming solution. The semisolid mixture was sonicated to remove air bubbles. Then, the final solution was casted into a petridish having area of 38.46 cm^2 and kept for drying in vacuum drying oven at 50 $^{\circ}\text{C}$. After drying, the patches were carefully removed from the petridish and sized into 2 cm diameter size [12]. (area of 2x2 cm^2).

Table 1: Formulae of cetirizine dihydrochloride fast dissolving films employing starch tartrate as per 2^3 factorial designs

Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
Cetirizine dihydrochloride	5	5	5	5	5	5	5	5
HPMC ES LV	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2
Starch tartrate	3.3	6.6	3.3	6.6	3.3	6.6	3.3	6.6
Croscarmellose sodium	---	---	3.3	3.3	---	---	3.3	3.3
Crospovidone	---	---	---	---	3.3	3.3	3.3	3.3
PEG(6000)	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Aspartame	0.52	0.52	0.52	0.52	0.52	0.52	0.52	0.52
Citric acid	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Distilled water(ml)	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04

Evaluation of cetirizine dihydrochloride fast dissolving films

Visual inspection

Prepared fast dissolving films of cetirizine dihydrochloride was checked visually for transparency and air bubbles [13].

Weight

Fast dissolving films of cetirizine dihydrochloride were weighed individually on analytical weighing balance and their weight was noted down [13].

Thickness

The thickness of the prepared fast dissolving films was determined by means of micrometer screw gauge. In between the jaws of the screw gauge, films of 2 cm were placed and its thickness was measured in different five positions [13].

Folding endurance

Folding endurance of the prepared fast dissolving films of cetirizine dihydrochloride was determined manually. Prepared film strip of

2x2 cm was folded at one place repeatedly till it get broken. Number of times the strip folded at the same place without broke tells the exact value of folding endurance [13].

Content uniformity

For the determination of the content uniformity, blank and sample solution was prepared. Sample solution was prepared by dissolving the film having 2 cm diameter in a beaker containing 10 ml 0.1 N HCl and the contents were dissolved by placing the beaker on a magnetic stirrer so that films gets dissolved. Then, the contents of the beaker were transferred to a 10 ml volumetric flask and its absorbance was noted at 231 nm. A blank solution was prepared in a similar manner by preparing blank polymer film solution [14]. The experiment was performed in triplicate and the average value was calculated.

Tensile strength

Elasticity and strength of the prepared fast dissolving thin film were determined by tensile strength. Tensile strength is the maximum stress applied to a point at which the film specimen can break [15].

It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below: Where,

Tensile strength= Load at failure × 100/Film thickness× film width.

Percent elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample [16]. Generally, the elongation of film increases as the plasticizer content increases.

% Elongation: [Final length-Initial length]×100/Initial length

In vitro disintegration time

Disintegration time is the time when the films starts to break or disintegrate. Prepared film disintegration time was determined by using USP disintegration apparatus. Films was placed in the tubes of the container containing 0.1 N HCl as a medium and disc was placed over it [16].

In vitro dissolution studies

Dissolution rate of the prepared fast films of cetrizine dihydrochloride was determined using USP type I dissolution apparatus. 900 ml of 0.1 N HCl was taken as dissolution medium. The study was performed at 37±0.5 ° C with the paddle speed of 50 rpm. At specified time intervals, 5 ml of the sample solution was taken and replaced with fresh dissolution medium [17]. The absorbance of the filtrate was recorded at 231 nm. The dissolution release studies was performed in triplicate.

Response surface plot study

Fast dissolving films was optimized by 2³ factorial designs and the individual and combined effect of 3 factors at two levels was determined by response surface plot study. Effect of factor A (Starch tartrate), factor B (Croscarmellose sodium) and factor C

(Crospovidone) was evaluated at 2 different level i.e. disintegration time and dissolution efficiency in 10 min.

A polynomial regression algorithm was used to rotate the independent variables to the response variables. The general first order model and equation they could be constructed from 2ⁿexperimental design is indicated in the following equation.

$$Y = \beta_0 + \beta_1A + \beta_2B + \beta_3C + \beta_{12}AB + \beta_{13}AC + \beta_{23}BC + \beta_{123}ABC$$

Where 'y' is the measured response, β_0 is the arithmetic mean response of 10 min, $\beta_1, \beta_2, \beta_3, \beta_{12}, \beta_{13}, \beta_{23}, \beta_{123}$ are the coefficient for the corresponding factors and A, B, C, AB, AC, BC, and ABC are the percentages of starch tartrate, croscarmellose sodium, and crospovidone and interaction terms respectively. The coefficients were calculated accordingly to the general formula given in equation.

$$\beta = \sum XY/2^n$$

Where β is coefficient, X is the corresponding variable (A,B,C) and Y is the response value (disintegration time and dissolution efficiency in 10 min) n is the level. The two levels of three factors employed in the experimental design are indicated in table 2 and transformed design for analysis of responses of cetrizine dihydrochloride fast dissolving films is shown in table 3.

Stability studies

Stability studies were carried out to see the effect of the influence of environmental factors like temperature, humidity, light with respect to time on the drug product. To check the quality of the prepared fast dissolving films, stability study of F1 formulation was carried out. Films of F1 formulation was packed in screw-capped HDPE (high-density polyethylene) bottles and stored at 40 °C±2 °C and 75% RH for 6 mo. After 6 mo, the stored film was evaluated for drug content and dissolution study as per the method discussed before.

Table 2: Levels of the three factors used in experimental design

S. No.	Factors/Ingredients	Code	Level L1	Level L2
1	Starch tartrate	A	1	2
2	Croscarmellose sodium	B	0	1
3	Crospovidone	C	0	1

Factor A (starch tartrate), Factor B (croscarmellose sodium), Factor C (crospovidone)

Table 3: Transformed design for analysis of the response of cetrizine dihydrochloride fast dissolving films

S. No.	Formula code	A (%)	B (%)	C (%)
1	F1	1	0	0
2	F2	2	0	0
3	F3	1	1	0
4	F4	2	1	0
5	F5	1	0	1
6	F6	2	0	1
7	F7	1	1	1
8	F8	2	1	1

Table 4: Physical and micromeritics properties of the starch tartrate (novel super disintegrant)

Parameters	Observation
Solubility	Insoluble in all aqueous and organic solvents tested
Melting Point	Charred at 250 °C
Viscosity(1% w/v aqueous dispersion)	1.035cps
Swelling index	72%
Gelling property	No gelling and the swollen particles of starch tartrate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
Moisture absorption	4.9%
Particle Size	150 µm (80/120 mesh)
Density	0.670 g/cc
Bulk Density	0.570 g/cc
Angle of Repose	19.95 °
Compressibility Index	16.7%

The FTIR (Fourier-transform infrared spectroscopy) spectrum of potato starch and starch tartrate is given in fig. 3 and fig. 4. So from FTIR spectrum, it was concluded that starch tartrate (Ester) was formed when starch was allowed to react with tartaric acid.

RESULTS AND DISCUSSION

Starch tartrate was found to be free-flowing crystalline, fine and smooth in texture. The physical and micropolitics properties of the starch tartrate are summarized in table 4. Starch tartrate was found to be insoluble in all aqueous and non-aqueous solvents, exhibiting good swelling in water. The swelling index was found to be 72%.

Starch tartrate was found to have good flow and compressibility as required for solid dosage forms. Starch tartrate density was found to

be 0.670 g/cc. Starch tartrate was found to have good flow property confirmed by an angle of repose and compressibility index.

The X-ray diffraction pattern of starch tartrate showed that it is crystalline in nature. The fig. 5 showed the X-ray diffraction pattern of novel prepared super disintegrant starch tartrate. The disappearance of pink colour in the ester test confirmed the presence of ester, i.e., starch tartrate. As the starch tartrate was crystalline, smooth, free-flowing powder and it had got all the characteristics of super disintegrants it was concluded that starch tartrate can be used as a novel super disintegrant in the formulation of fast dissolving systems.

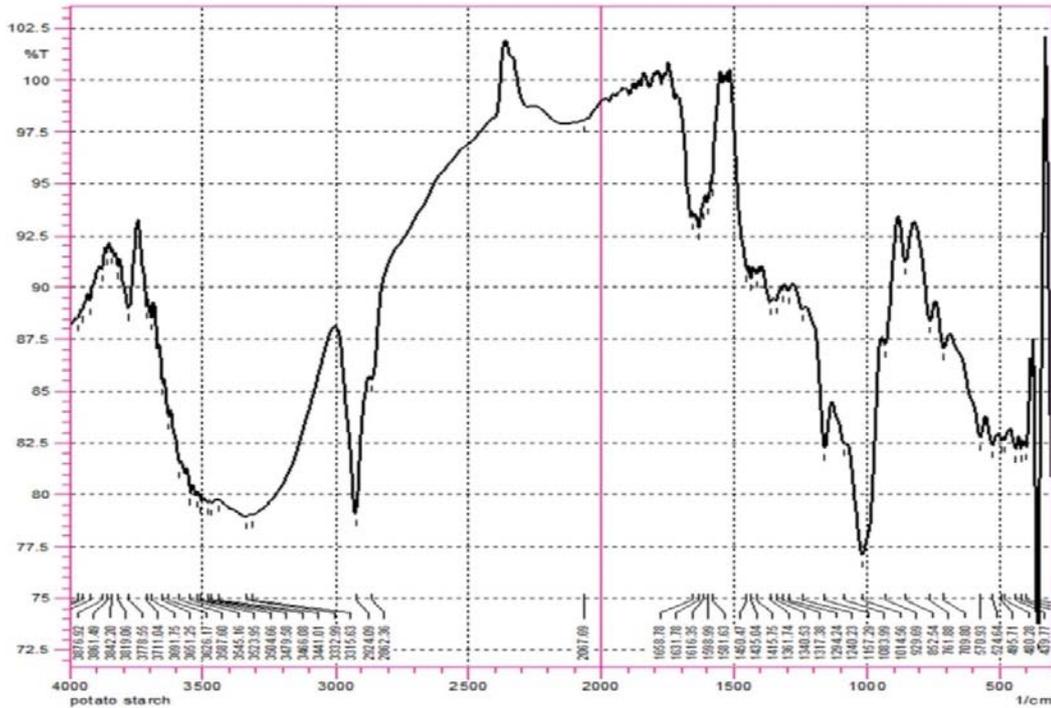


Fig. 3: FTIR (Fourier-transform infrared spectroscopy) spectra of potato starch

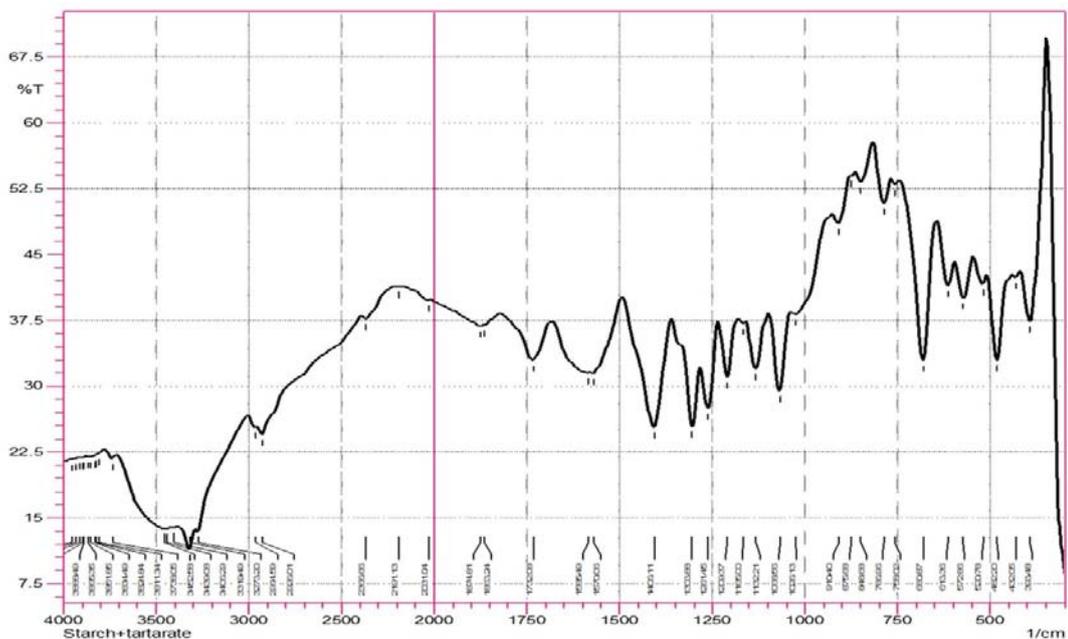


Fig. 4: FTIR (Fourier-transform infrared spectroscopy) spectra of starch tartrate

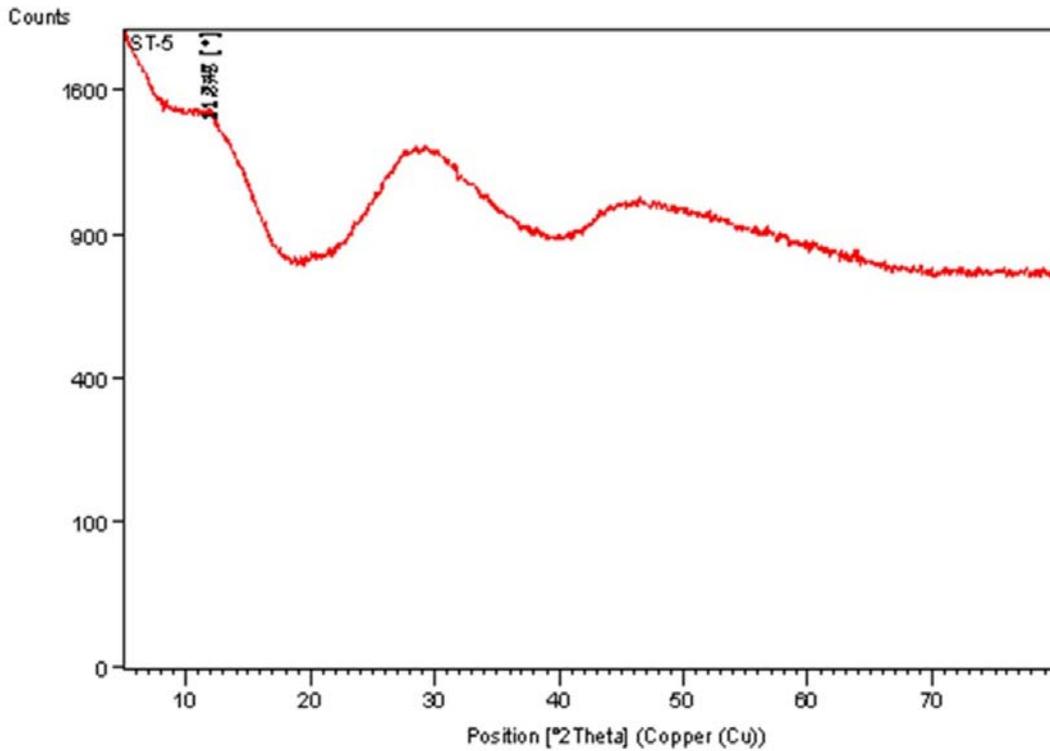


Fig. 5: X-ray diffraction pattern of starch tartrate

The compatibility of starch tartrate with the cetirizine dihydrochloride was evaluated by DSC (Differential scanning calorimetry), FTIR (Fourier-transform infrared spectroscopy) and TLC (Thin layer chromatography)

studies. The DSC (Differential scanning calorimetry) thermograms of cetirizine dihydrochloride and cetirizine dihydrochloride with starch tartrate are shown in fig. 6 and fig. 7.

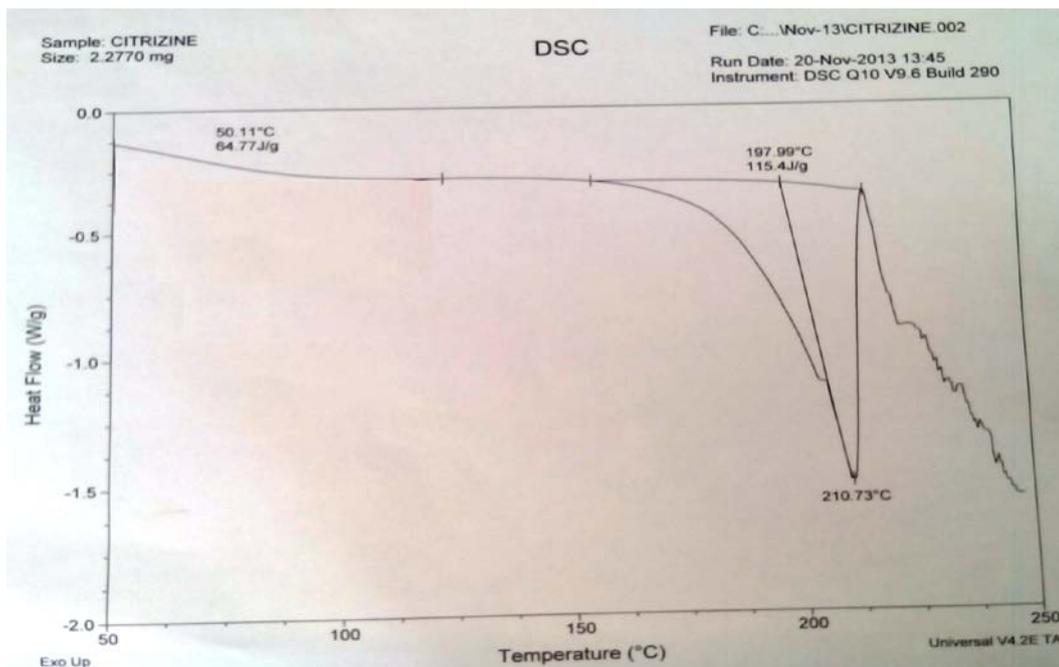


Fig. 6: DSC (Differential scanning calorimetry) thermogram of cetirizine dihydrochloride pure drug

The DSC thermogram of cetirizine dihydrochloride and cetirizine dihydrochloride-starch tartrate exhibited exothermic at 210.63 °C and 209.65 °C respectively. These melting peaks of cetirizine dihydrochloride and cetirizine dihydrochloride-starch tartrate

correspond to the melting point of cetirizine dihydrochloride. DSC studies tell that there is no drug interaction with prepared super disintegrant and the selected drug cetirizine dihydrochloride.

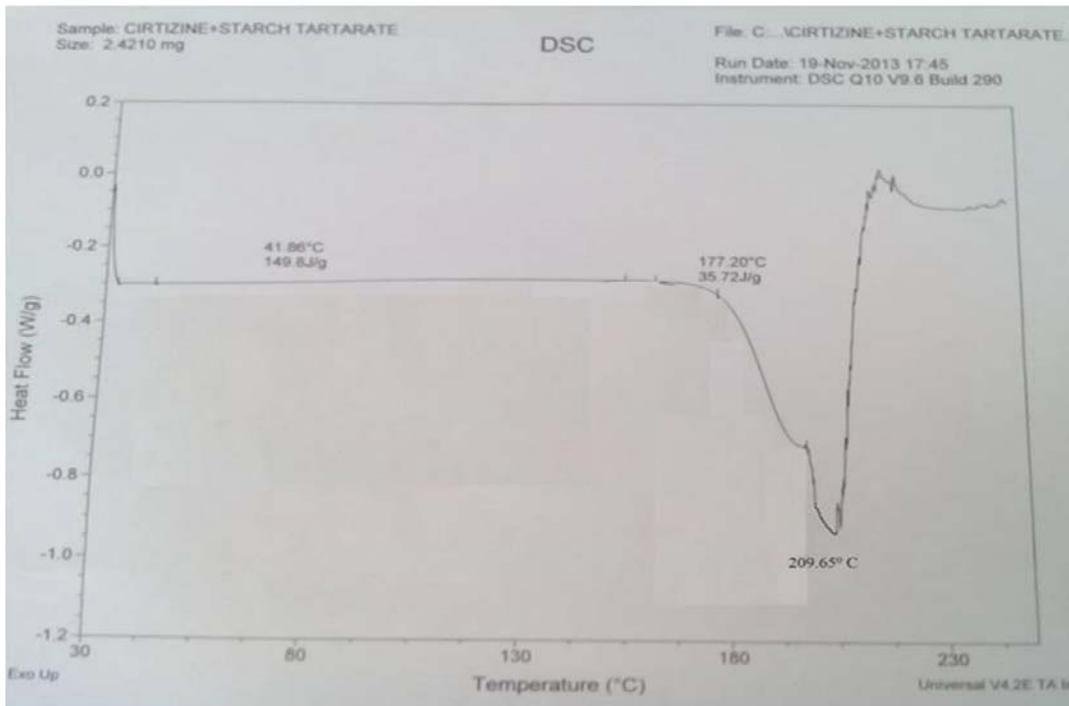


Fig. 7: DSC (Differential scanning calorimetry) thermogram of cetirizine dihydrochloride with starch tartrate

The characteristic FTIR bands of cetirizine dihydrochloride (C=O group) at 1737 cm^{-1} , and 2939.52 cm^{-1} , 2420 cm^{-1} (H stretching) were all observed in FTIR spectra of both cetirizine dihydrochloride and cetirizine dihydrochloride-starch tartrate. The FTIR (Fourier-transform infrared spectroscopy) spectra of

cetirizine dihydrochloride and cetirizine dihydrochloride-starch tartrate mixture are shown in fig. 8 and fig. 9. FTIR (Fourier-transform infrared spectroscopy) spectra observations also indicated no interaction between starch tartrate and cetirizine dihydrochloride.

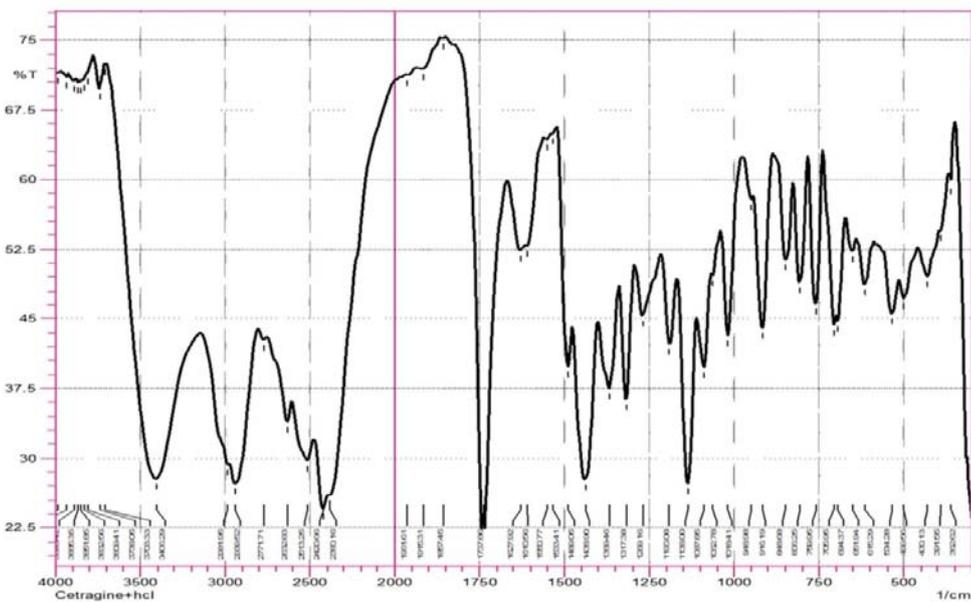


Fig. 8: FTIR (Fourier-transform infrared spectroscopy) spectra of pure drug cetirizine dihydrochloride

In the TLC (thin layer chromatography) plate, single spots were observed of pure drug and starch tartrate-cetirizine dihydrochloride mixture. TLC plate showing single spots of drug and starch tartrate-cetirizine dihydrochloride mixture is showing in below-given fig. 10. R_f value of both pure drug (cetirizine

dihydrochloride) and mixture containing cetirizine dihydrochloride-starch tartrate was closed to each other, given in table 5. Thus, from the TLC (thin layer chromatography) study, it was concluded that there is no interaction between cetirizine dihydrochloride and starch tartrate.



Fig. 9: FTIR (Fourier-transform infrared spectroscopy) spectra of cetirizine dihydrochloride with starch tartrate

Table 5: R_f value of the cetirizine dihydrochloride and their mixture (1:1) with starch tartrate

S. No.	Product	R _f value
1	Cetirizine dihydrochloride	0.74
2	Cetirizine dihydrochloride-starch tartrate	0.71

R_f: retardation factor

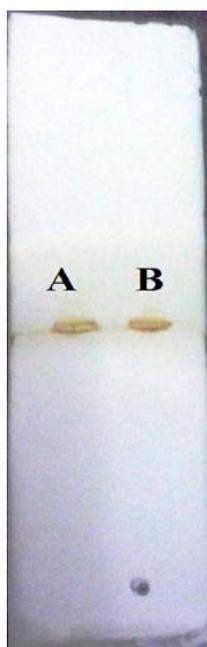


Fig. 10: TLC (thin layer chromatography) plate showing (A) Cetirizine dihydrochloride Pure Drug (B) Cetirizine dihydrochloride with starch tartrate

Thus, from the results of the studies carried out FTIR (Fourier-transform infrared spectroscopy), DSC (Differential scanning calorimetry) and TLC (thin layer chromatography), it was proved

that there is no interaction between the novel prepared super disintegrant starch tartrate and selected drug i. e cetirizine dihydrochloride. Hence, starch tartrate can be used as a super disintegrant in the design of fast dissolving systems.

All the prepared films were found elegant with a smooth texture. Films weight was found varying from 51.33 to 58.06 mg with thickness of 0.059 to 0.061 mm. Folding endurance of the fast-dissolving thin films was found 52 to 67 times from F1 to F8 formulations. Drug content uniformity of all the formulations was found within 100±5% of the labeled amount.

Fast dissolving films of cetirizine dihydrochloride having new super disintegrant starch tartrate was found to disintegrate between 34 to 69 sec. Tensile strength was found good between 10. 25±0.22 to 12.08±0.53 indicating prepared films have good strength and elasticity. The results of all physical evaluation tests carried out of cetirizine dihydrochloride fast dissolving oral films are given in below table 6.

In vitro dissolution test of prepared orally disintegrating films was carried out in USP (United States Pharmacopeia) type I paddle apparatus. The drug release from fast dissolving oral films of cetirizine dihydrochloride was found to be more in F1 formulation in 5 min as compared to other formulations. Dissolution profiles of all formulations F1 to F8 are shown in fig. 11. The PD₅ (percent dissolved in 5 min) was more in F1, which consists only 1% starch tartrate. The same was in the case of DE_{10%} (dissolution efficiency in 10 min). The PD₁₀ and DE_{10%} reveals that starch tartrate was effective at 1%. The PD₁₀ and DE_{10%} reveals that starch tartrate was effective at 1%. The K₁ also increased in all the formulations when compared to F1 formulation. The number of folds increases in DE_{10%} and the number of folds increases in K₁ (min⁻¹) were given in table 7, From the results it was concluded that starch tartrate (new super disintegrant) could be used as a super disintegrant in the formulation of fast dissolving films of Cetirizine dihydrochloride.

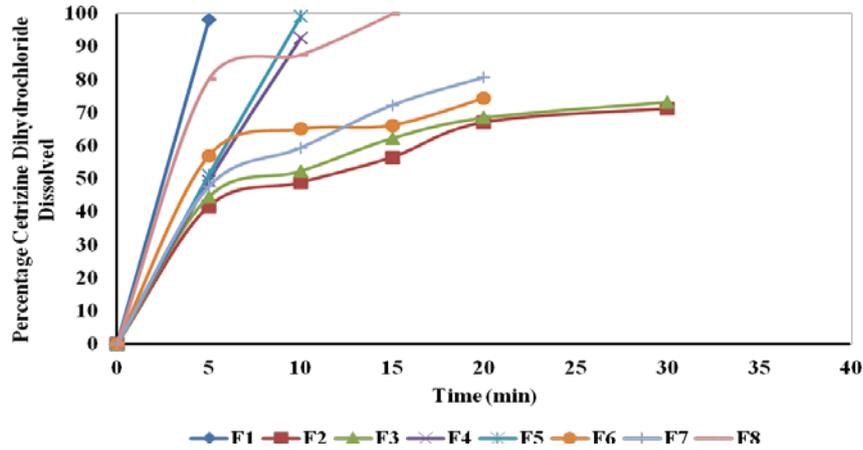


Fig. 11: Dissolution profiles of cetrizine dihydrochloride fast dissolving films prepared by solvent casting method (F₁-F₈)

Table 6: Physical properties: thickness, folding endurance, drug content and disintegration time of fast dissolving oral films of cetrizine dihydrochloride employing novel super disintegrant i.e. starch tartrate

Formulation code	Visual appearance	Weight (mg) (n±SD)	Thickness (mm) (n±SD)	Folding endurance (n±SD)	Tensile strength (N/mm ²) (n±SD)	Percent elongation (n±SD)	Drug content (n±SD)	Disintegration time (sec) (n±SD)
F1	Transparent	58.06±0.15	0.061±0.01	52±0.31	12.08±0.53	10.76±0.45	96.24±0.7	34±0.55
F2	Transparent	48.50±0.06	0.061±0.01	67±0.65	11.08±0.52	15.34±0.11	98.32±0.80	42±0.44
F3	Transparent	55.12±0.44	0.061±0.01	65±0.58	11.22±0.42	16.55±0.31	97.61±0.50	60±0.45
F4	Transparent	54.18±0.10	0.059±0.03	57±0.46	11.64±0.31	18.86±0.53	98.51±0.69	37±0.53
F5	Transparent	52.52±0.23	0.061±0.12	54±0.44	10.77±0.11	13.75±0.53	97.33±0.13	39±0.56
F6	Transparent	55.67±0.32	0.060±0.08	62±0.46	10.25±0.22	12.88±0.44	96.44±0.39	65±0.58
F7	Transparent	51.33±0.44	0.061±0.09	60±0.33	10.55±0.22	8.33±0.53	96.17±0.15	69±0.20
F8	Transparent	51.33±0.44	0.060±0.12	58±0.12	10.55±0.16	9.88±0.32	95.51±0.11	62±0.21

All results value are expressed in mean with±S. D, *SD Standard Deviation from mean, n=3

Table 7: Dissolution parameters of cetrizine dihydrochloride fast dissolving oral films prepared by solvent casting method employing starch tartrate

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
PD ₁₀	98.03±0.11	48.77±0.20	52.25±0.24	92.44±0.12	98.96±0.10	65.02±0.22	59.35±0.11	87.48±0.15
PD ₂₀	-	67.02±0.15	68.41±0.22	-	-	74.31±0.16	80.77±0.20	-
DE ₁₀ (%)	95±0.18	43±0.10	47.5±0.13	87.5±0.19	95±0.17	60±0.10	50.5±0.23	82.5±0.10
K (min ⁻¹)	0.081±0.09	0.055±0.17	0.057±0.18	0.046±0.21	0.034±0.20	0.066±0.14	0.025±0.17	0.034±0.19

All values are expressed in mean with±SDS. D-standard deviation, n=3, PD₁₀--percent dissolved in 10 min., PD₂₀-percent dissolved in 20 min DE₁₀%-dissolution efficiency in 1 min., K₁ =first order rate constant

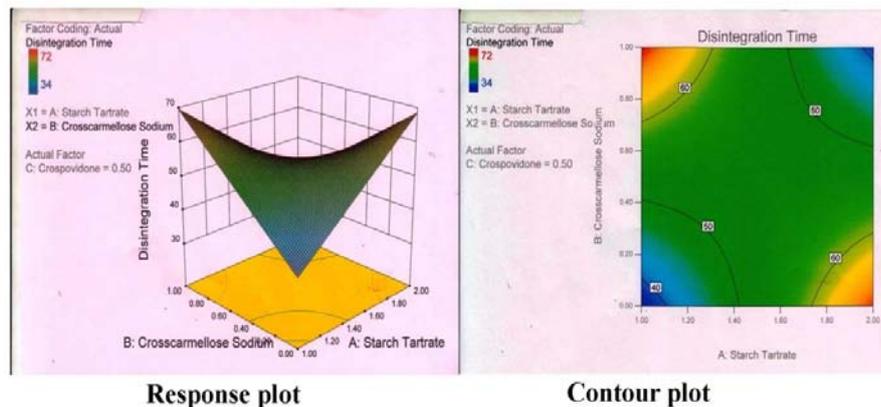


Fig. 12: Response plot and contour plot of cetrizine dihydrochloride fast dissolving film (Effect of starch tartrate and croscarmellose sodium on disintegration time)

Response surface plots study

The response surface plots and contour plots reveal that as the concentration of starch tartrate (A), croscarmellose sodium (B), crospovidone (C), increases disintegration time increased. By response surface plots we can see the effect of starch tartrate (A), croscarmellose sodium (B) on disintegration time and it was determined from contour plot that a less disintegration time can be obtained with starch tartrate (A) level range between 1 and 1.2% and croscarmellose sodium (B) level range from 0 to 0.2% as shown in fig. 12

The effects of croscarmellose sodium (B) and crospovidone (C) on disintegration time in 10 min are shown in fig. 13. The contour plots

were found to be almost non-linear indicating the nonlinear relationship between croscarmellose sodium (B) and crospovidone (C). It was determined from contour plot that less disintegration time less disintegration time can be obtained with croscarmellose sodium (B) level in between 0 to 0.2% and crospovidone (C) level range from 0.8 to 1.0%.

The effects of starch tartrate (A) and crospovidone (C) shown in fig. 14. It was determined from the contour plot less disintegration time can be obtained when the starch tartrate (A) level in between 1 and 1.2% and crospovidone (C) level between 0.8 to 1.0% of the total weight of the film.

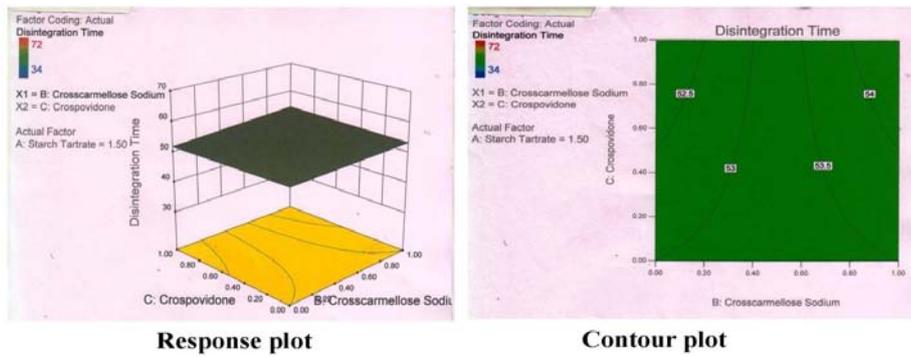


Fig. 13: Response plot and contour plot of cetrizine dihydrochloride fast dissolving film (Effect of croscarmellose sodium and crospovidone on disintegration time)

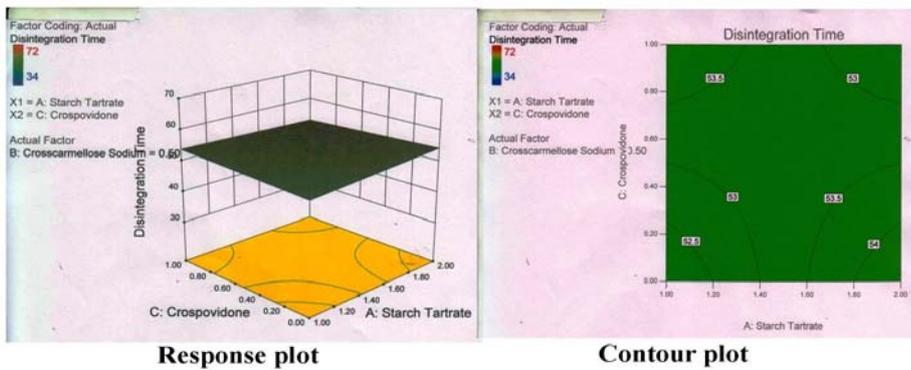


Fig. 14: Response plot and contour plot of cetrizine dihydrochloride fast dissolving film (Effect of starch tartrate and crospovidone on disintegration time)

The response surface plot and the contour plots revealed that as a concentration of starch tartrate (A), croscarmellose sodium (B) and crospovidone (C) increases, dissolution efficiency in 10-minute decreases. The effect of starch tartrate (A) and croscarmellose sodium (B) on dissolution efficiency in 10 min are

shown in fig. 15. The contour plots were found to be nonlinear to certain extent. It was determined from the contour plot that more dissolution efficiency in 10 min can be obtained with starch tartrate (A) level range between 1 and 1.2% and croscarmellose sodium (B) level range 0 to 0.2%.

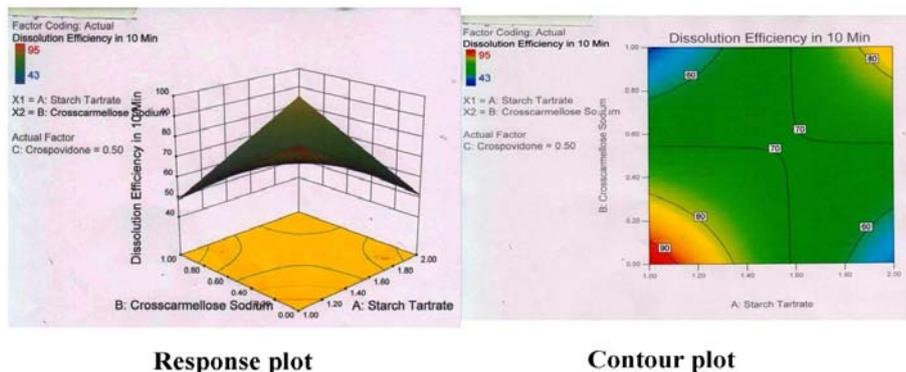


Fig. 15: Response plot and contour plot of cetrizine dihydrochloride fast dissolving film (Effect of starch tartrate and croscarmellose sodium on dissolution efficiency in 10 min)

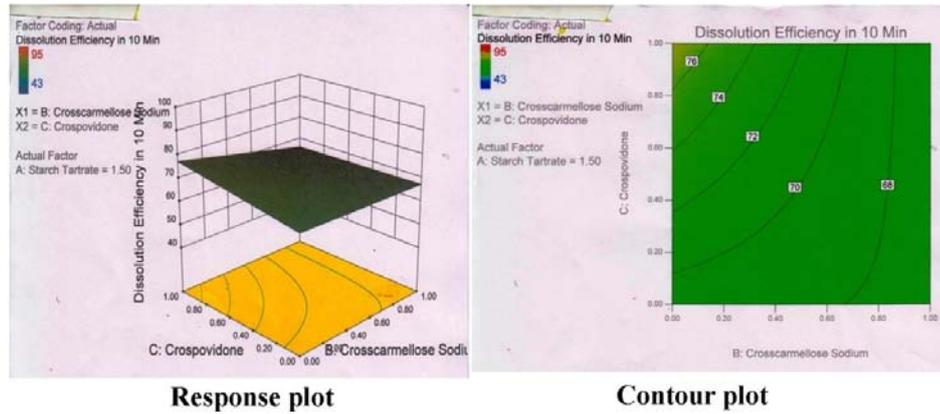


Fig. 16: Response plot and contour plot of cetirizine dihydrochloride fast dissolving film, (Effect of croscarmellose sodium and crospovidone on dissolution efficiency in 10 min)

The effects of croscarmellose sodium (B) and crospovidone (C) are shown in fig. 16. The contour plots were found to be almost nonlinear indicating the nonlinear relationship between croscarmellose sodium and crospovidone. It was found that more dissolution efficiency in 10 min can be obtained with croscarmellose sodium (B) level range between 0 and 0.2% and crospovidone (C) level range between 0.8 to 1.0%.

The effects of starch tartrate (A) and crospovidone (C) are shown in fig. 17. The contour plots were found to be nonlinear indicating the non-linear relationship between starch tartrate and crospovidone. It was determined from the contour plot more dissolution efficiency in 10 min can be obtained in starch tartrate (A) level range between 1 and 1.2% and crospovidone (C) level range between 0.8 and 1.0%.

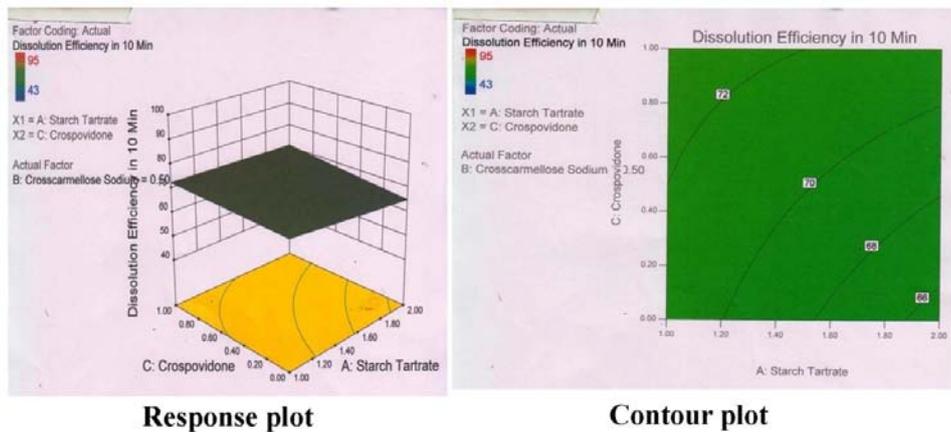


Fig. 17: Response plot and contour plot of cetirizine dihydrochloride fast dissolving film (Effect of starch tartrate and crospovidone on dissolution efficiency in 10 min)

Stability study

After 6 mo, no visible changes were observed in the oral fast dissolving films of cetirizine dihydrochloride. No significant difference was observed in the percent drug content before and after storage for 6 mo. The drug dissolution profiles of the oral fast

dissolving films before and after storage are given in table 8. The drug release characteristics of the formulation tested remained unaltered during the storage period. The results, thus, indicated that the drug content and drug dissolution rate of the oral fast dissolving films formulated employing starch tartarate were quite suitable.

Table 8: Dissolution profiles of cetirizine dihydrochloride oral fast dissolving films, F1 before and after storage for 6 mo during the stability testing

Time (min)	Before storage	After 6 mo
1	98.03±0.21	97.14±0.02

CONCLUSION

In the present investigation starch tartrate, a new super disintegrant was prepared and evaluated for its application as super disintegrant in the fast-dissolving dosage form. Fast dissolving films of cetirizine dihydrochloride was prepared employing starch tartrate according

to 2³ factorial designs. All these fast-dissolving films prepared were evaluated for drug content, weight, thickness, folding endurance, tensile strength, percent elongation, disintegration time and other dissolution characteristics like PD₁₀, PD₂₀, DE₁₀% and K₁. From the present investigation it was found that in from the fast-dissolving films formulated employing starch tartrate (1-1.2%), croscarmellose

sodium (0-0.2%) and crospovidone (0.8-1%) by solvent casting method was fast and it is within 10 min.

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AUTHOR CONTRIBUTIONS

All the authors contributed equally

CONFLICT OF INTERESTS

The authors confirm that the article content has no conflict of interest.

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