



Formulation And Evaluation of Cimetidine Fast Dissolving Tablets Using Synthetic Super Disintegrants

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ABSTRACT

Objective: The main aim of the present research work was to formulate fast dissolving tablets of Cimetidine by direct compression method and to evaluate the effect of synthetic super disintegrating agent on drug release pattern.

Methods: The fast dissolving tablets were prepared by using croscopovidone, croscarmellose sodium, sodium starch glycolate as superdisintegrants (2, 4 and 6 %w/w), mannitol 20 % and microcrystalline cellulose (44, 46 and 48 % w/w) as a directly compressible vehicle. All the prepared tablets were evaluated for hardness, friability, drug content uniformity, weight variation, disintegrating time, wetting time and *in vitro* drug release studies.

Results: All the prepared fast dissolving tablets formulations were within the Pharmacopoeial standards limits. Based on *in vitro* drug release studies (>90 % within 30 min), the optimised formulations were optimised tested for the short term stability (at 40 °C/75% RH for 3 mo) and drug excipient interaction (fourier transform infrared spectroscopy).

Conclusion: Hence, formulation prepared with 6 % w/w of crosspovidine and 44 % w/w of microcrystalline cellulose as emerged as the overall best formulation (>90 % within 30 min) compared to marketed product (>70 % within 30 min). Short-term stability studies on the formulations indicated that there are no significant changes in drug content and *in vitro* drug release ($p < 0.05$).

Keywords Cimetidine, Croscarmellose sodium, Crosspovidine, Sodium starch Glycolate, Fast dissolving tablets

INTRODUCTION

Oral routes of drug administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance. As solid formulations do not require any sterile conditions they are less expensive [1]. Cimetidine is a propanimidamide and histamine H₂-receptor antagonist with antacid activity. As a competitive inhibitor of histamine H₂-receptors located on



the basolateral membrane of the parietal cell, Cimetidine reduces basal and nocturnal gastric acid secretion, resulting in a reduction in gastric volume, acidity, and amount of gastric acid released in response to various stimuli. The drug is 40-45 % absorbed orally but it undergoes minimal metabolism on first pass through the liver. Cimetidine is metabolized in the liver to Cimetidine S-oxide (S-Cimetidine). They also inhibit gastric acid secretion stimulated by food, betazole, pentagastrin, caffeine, insulin and physiological vagal reflex. Cimetidine is used in the treatment of peptic ulcer disease and gastroesophageal reflux disease [2-4]. Thus, Cimetidine is better option for the development of immediate release tablets [5, 6]. The purpose of the present research work was to develop and characterize immediate release tablets of Cimetidine using various synthetic superdisintegrants such as crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG) with mannitol to release the medicament and mask bitter taste [7-9]. Fasting dissolving tablets (FDTs) helps in immediate release of medicament, leading to an increase in bioavailability of the drug and quick onset of pharmacological action can take place [10-14].

MATERIALS AND METHODS

Materials

Cimetidine, crospovidone, croscarmellose sodium and sodium starch glycolate were purchased from Yarrow chem. product, Mumbai, India. Mannitol was purchased from Fisher scientific laboratory, Andhra Pradesh, India. Microcrystalline cellulose was purchased from Chemica-biochemica reagents, Mumbai, India. All other reagents and chemicals were of analytical grade.

Table 1: Formulation of Cimetidine fast dissolving tablets

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Cimetidine	20	20	20	20	20	20	20	20	20
2.	Sodium starch glycolate	4	8	12	-	-	-	-	-	-
3.	Croscarmellose sodium	-	-	-	4	8	12	-	-	-
4.	Crospovidone	-	-	-	-	-	-	4	8	12
5.	Mannitol	20	20	20	20	20	20	20	20	20
6.	Microcrystalline cellulose	51	47	43	51	47	43	51	47	43
7.	Magnesium stearate	5	5	5	5	5	5	5	5	5
	Total weight	100	100	100	100	100	100	100	100	100

Methods

Preparation of Cimetidine FDTs

Each tablet containing 20 mg Cimetidine were prepared by using direct compression method with 50 tablets for batch. The compositions of various formulations of the tablets with F1 to F9 were listed in table 1. For preparation of powder blend, pure drug Cimetidine and superdisintegrants SSG, CCS and CP were passed through sieve No. 40 # and mixed well for 10 min in a glass motor and pestle. To the above add



microcrystalline cellulose after passing through sieve No. 40 # and blended thoroughly for 5 min to make powdered blend. This powder was lubricated with sufficient amount of magnesium stearate after passing through sieve No. 80 # [15]. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets of 100 mg weight on 12 station tablet compression machine (Rimek tablet MINI press, karnavathi engineering Pvt. Ltd. Gujarat, India) using 8 mm flat round punches with 2-4 kg/cm² hardness.

Evaluations

Evaluation of pre-compression parameters

Pre-compression parameters such as angle of repose, bulk density and tap density, Carr's compressibility index and Hausner's ratio were determined [16, 17].

Angle of repose

It was determined by funnel method. The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powder was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose (θ) was calculated by measuring the height (h) and radius® of the heap of granules, using Eq. 1.

$$\theta = \tan^{-1} \left[\frac{h}{r} \right] \dots\dots\dots \text{Eq. 1}$$

Bulk density

The bulk density was determined by pouring the blend into a graduated cylinder of density apparatus. The bulk volume (V₀) and the weight of powder (M) were determined. The bulk density (ρ_0) can be calculated using the formula given in Eq. 2.

$$\text{Bulk density}(\rho_0) = \frac{M}{V_0} \dots\dots\dots \text{Eq. 2}$$

Tapped density

The bulk density apparatus was allowed to tap for a fixed time. The minimum volume required in the cylinder (V_f) and weight of the blend (M) were obtained. The tapped density (ρ_f) can be calculated using the formula given in Eq. 3.

$$\text{Tapped density} = \frac{M}{V_f} \dots\dots\dots \text{Eq. 3}$$



Carr's compressibility index

The flow ability of powder can be evaluated by comparing the bulk density and tapped density of powder and the rate at which it packed down. The Carr's compressibility index is calculated by using the Eq. 4.

$$\% \text{ compressibility index} = \frac{\rho_t - \rho_0}{\rho_t} \times 100 \quad \text{Eq. 4}$$

Hausner's ratio

It is an indirect index of easy of powder flow. It is calculated by using Eq.5.

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_0} \quad \text{Eq. 5}$$

Compatibility studies

The compatibility studies were performed using fourier transform infrared spectroscopy (FTIR), differential scanning calorimetric studies (DSC), X-ray diffraction studies (XRD) and scanning electron microscope (SEM).

Evaluation of post-compression parameters

Post-compression parameters such as weight variation, thickness, hardness, friability, water absorption ratio, wetting time, disintegration test, in vitro dispersion time, content uniformity and in vitro dissolution study were determined.

Weight variation

Randomly 20 tablets were taken from each batch and their weight was determined individually and collectively on a digital weighing balance. The average weight of the tablet was determined from the collective weights [18].

Thickness

Randomly 10 tablets from each formulation were taken and their thickness was measured using a Vernier callipers and the reading was recorded in millimetres [19].

Hardness

Three tablets were randomly picked from each formulation batch and the mean and standard values were calculated [19]. Hardness of the tablet was determined using the Monsanto hardness tester and expressed in kg/cm².

Friability

A sample of whole tablets corresponding to about 6.5 g was weighed and the initial weight was recorded (Wo) and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions [15]. Then



tablets were removed from the friabilator, dusted off the fines and again weighed and the final weight was recorded (W_f). Percentage friability was calculated by using the formula given in Eq. 6.

$$\%Friability = \left[\frac{W_o - W_f}{W_o} \right] \times 100 \quad \text{Eq. 6}$$

Wetting time and water absorption ratio

A piece of tissue paper folded twice and placed in small petri dish containing 10 ml of water. Initially tablet was weighed (W_b), placed on the paper and time for complete wetting was measured as wetting time [19]. The wetted tablet was weighted (W_a). Water absorption ratio, R , was calculated using the formula given in Eq. 7.

$$R = \left[\frac{W_a - W_b}{W_b} \right] \times 100 \quad \text{Eq. 7}$$

Disintegration test

The disintegration time was performed using USP disintegration test apparatus with 0.1 N HCl medium at $37 \pm 0.5^\circ\text{C}$. A tablet was placed in each of six tubes of apparatus and one disc was added to each tube. The time was recorded when all the fragments of the disintegrated tablet (6 tablets) passed through the screen of the basket [18].

Content uniformity

The drug content was determined by taking 10 dosage units at random and powdered. The blend equivalent to 20 mg of Cimetidine was weighed and dissolved in 100 ml of 0.1 N HCl solution, stirred for 15 min and filtered. Absorbance was measured at 265 nm using a UV-Visible double beam spectrophotometer (Cary 60, Agilent technologies, Germany) [5].

In vitro dissolution studies

In vitro dissolution studies of Cimetidine were performed in USP XXIII dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl (pH-1.2), at $37 \pm 0.5^\circ\text{C}$ with 50 rpm speed. A sample of 5 ml solution was withdrawn from the dissolution apparatus at 5, 10, 15, 30, 45 and 60 min respectively and replaced with 5 ml of fresh dissolution medium. The samples were filtered through Whatmann filter paper (No. 41, Ash less circles 150 mm) and measured after suitable dilutions using spectrophotometrically at 265 nm. All the dissolution tests were carried out in triplicates. Cumulative percentage of drug release was drug release was calculated using an equation obtained from a standard curve [5].

Statistical analysis



All the values are expressed as mean $\pm$ standard deviation (SD). The t-test was used to study the significance difference between the control and test at 0.05% of level of significance. All the values are represented in three determinents. The value less than 0.05 was taken as no significance difference.

RESULTS AND DISCUSSION

In the present investigation, FDT of Cimetidine were prepared by using synthetic superdisintegrants such as crosspovidone, cross carmellose sodium and sodium starch glycolate.

Identification of pure drug

Physical characterization studies stated that Cimetidine is white to pale yellow crystalline powder with bitter taste. The melting point of Cimetidine was found to be in the range of 162–164 °C when tested using capillary method in melting point apparatus in triplicate, which complies with the standard values in the official monograph as per USP-NF. It was found that Cimetidine is practically insoluble in water, but soluble in organic solvents like acetone, glacial acetic acid.

Identification of the drug was done from absorption maxima, IR and DCS studies. Absorption maxima of 265 nm confirmed that the drug was pure Cimetidine as it was previously mentioned in associated literature [5]. The spectra were recorded for pure drug Cimetidine shown in fig. 1.

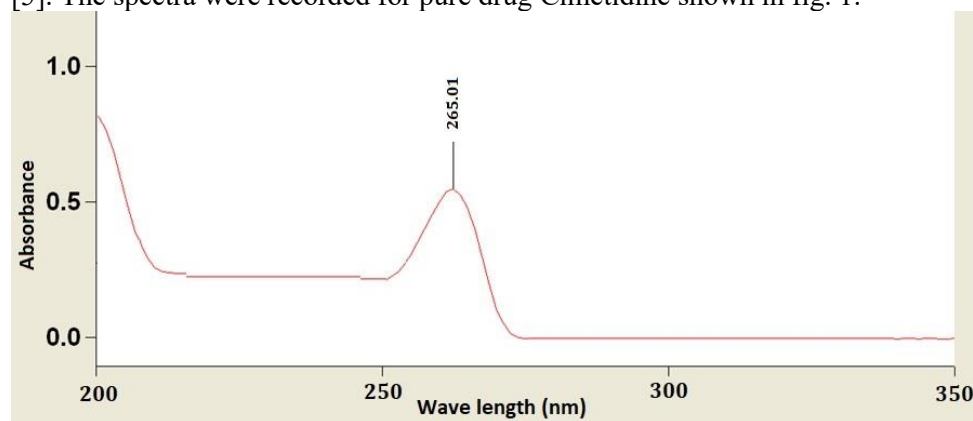
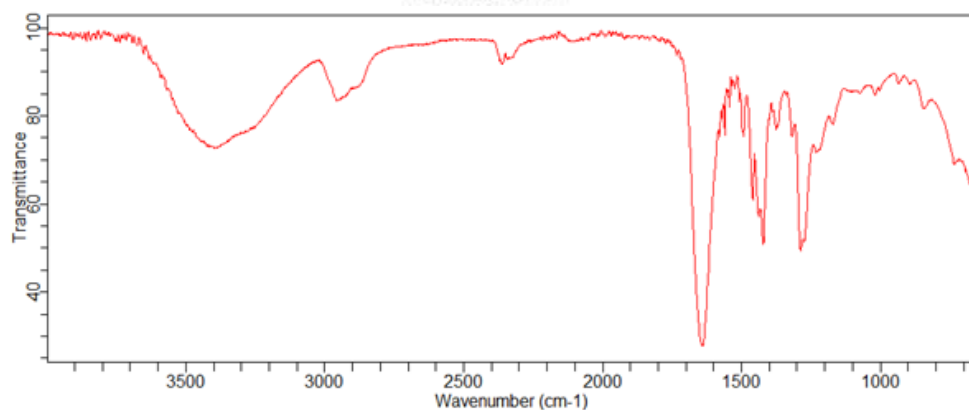
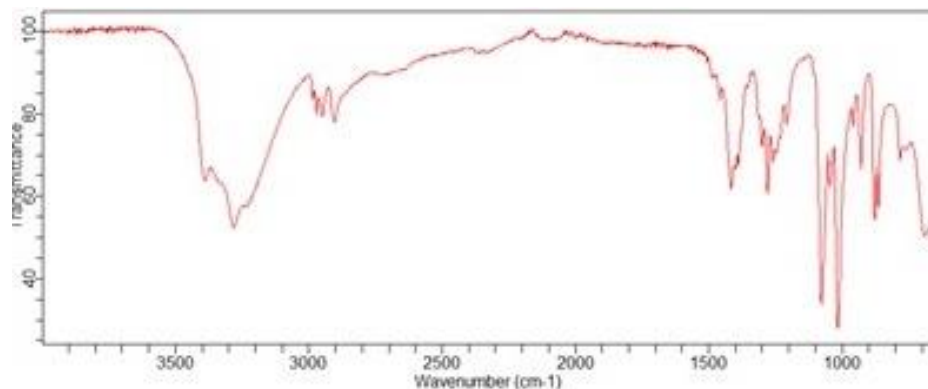
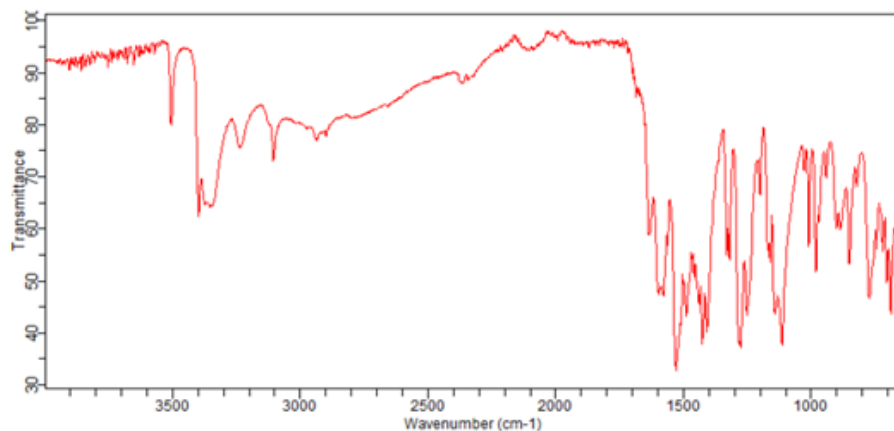


Fig. 1: Spectrometric graph of Cimetidine pure drug



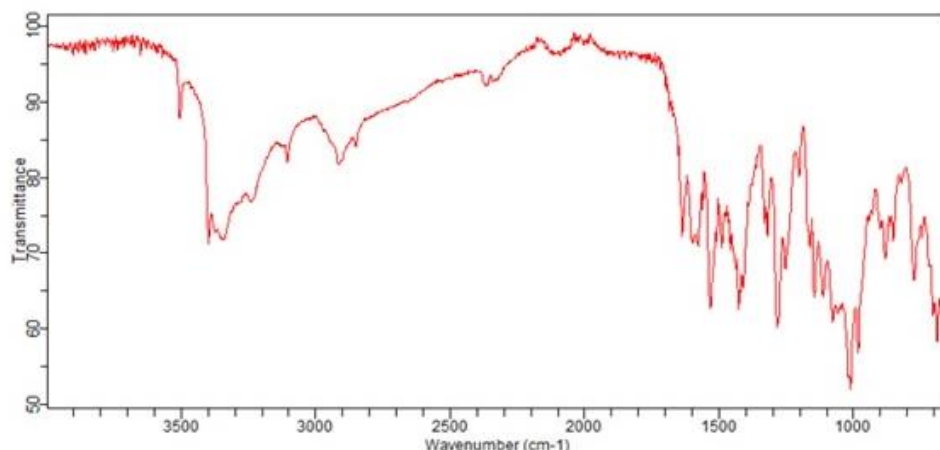


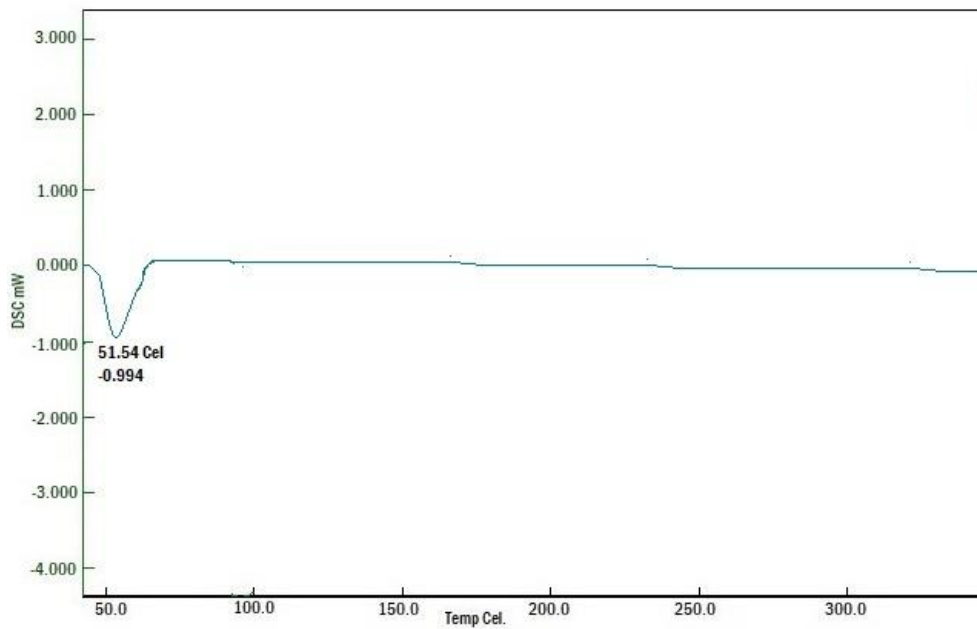
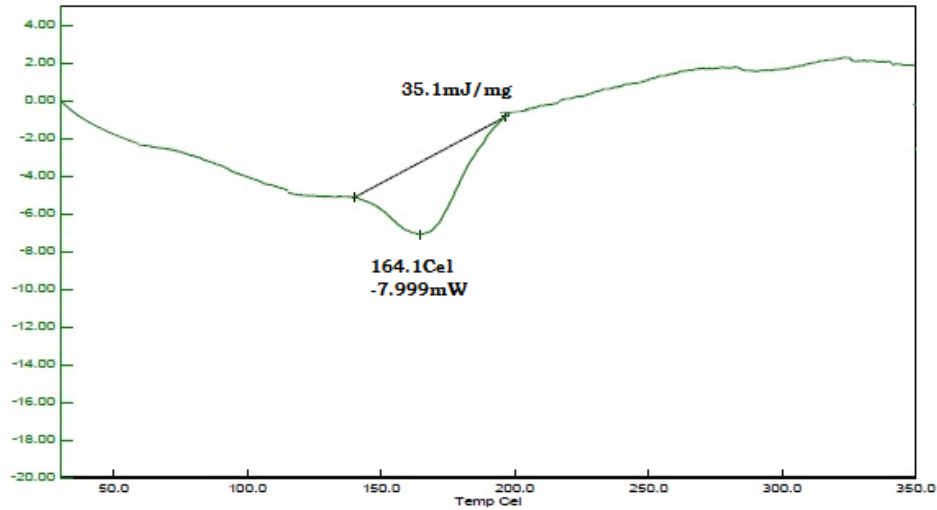
Fig. 2: FTIR Spectrum of a) Cimetidine, b) Mannitol, c) Crosspovidone and d) Optimised formulation F8 containing 8 % of crosspovidone

Fourier transform infrared spectroscopy

Drug polymer interaction was studied by FTIR analysis. The FTIR spectra of the pure drug Cimetidine, mannitol, crosspovidone and optimised formulation F8 were shown in the fig. 2. The FTIR spectrum of pure drug showed a characteristic peak of alcohol (OH) stretching vibration at 3400 cm^{-1} and alkynes stretching vibration at 3300 cm^{-1} . An asymmetric stretching peak at 2100 cm^{-1} and symmetric stretching peak at 1600 cm^{-1} indicating the drug was pure. The FTIR spectrum of mannitol showed absorption band nearly at 3300 cm^{-1} (N-H), 2800 cm^{-1} (C-H) and 1400 cm^{-1} (C=C) stretching vibration. The FTIR spectrum of crosspovidone showed absorption band nearly at 3400 cm^{-1} (OH), 2900 cm^{-1} (C=O) and 1300 cm^{-1} (C=C) stretching vibration. The same peaks were reported in the optimised formulation F8 containing 8% of crosspovidone and mannitol. There was no change or shifting of characteristic peaks of Cimetidine tablets, suggested that there was no significant drug polymer interaction which indicates the stable nature of drug inside the formulation.

Differential scanning calorimetric studies

The DSC thermograph of pure Cimetidine, mannitol, crosspovidone and optimised formulations F8 shown in fig. 3. The DSC thermograph of Cimetidine showed a sharp endothermic peak at 163.8 $^{\circ}\text{C}$ due to melting point of the drug with the enthalpy value of 34.1 mJ/mg . This shows that the drug considered for the research is in pure form. The melting peak of optimised formulation F8 was shifted to 164.1 $^{\circ}\text{C}$ with 16.49 mJ/mg enthalpy value. The change in melting endotherm of drug may be due to mixing process which lowers purity of each component, it could be concluded that drug was in amorphous state.



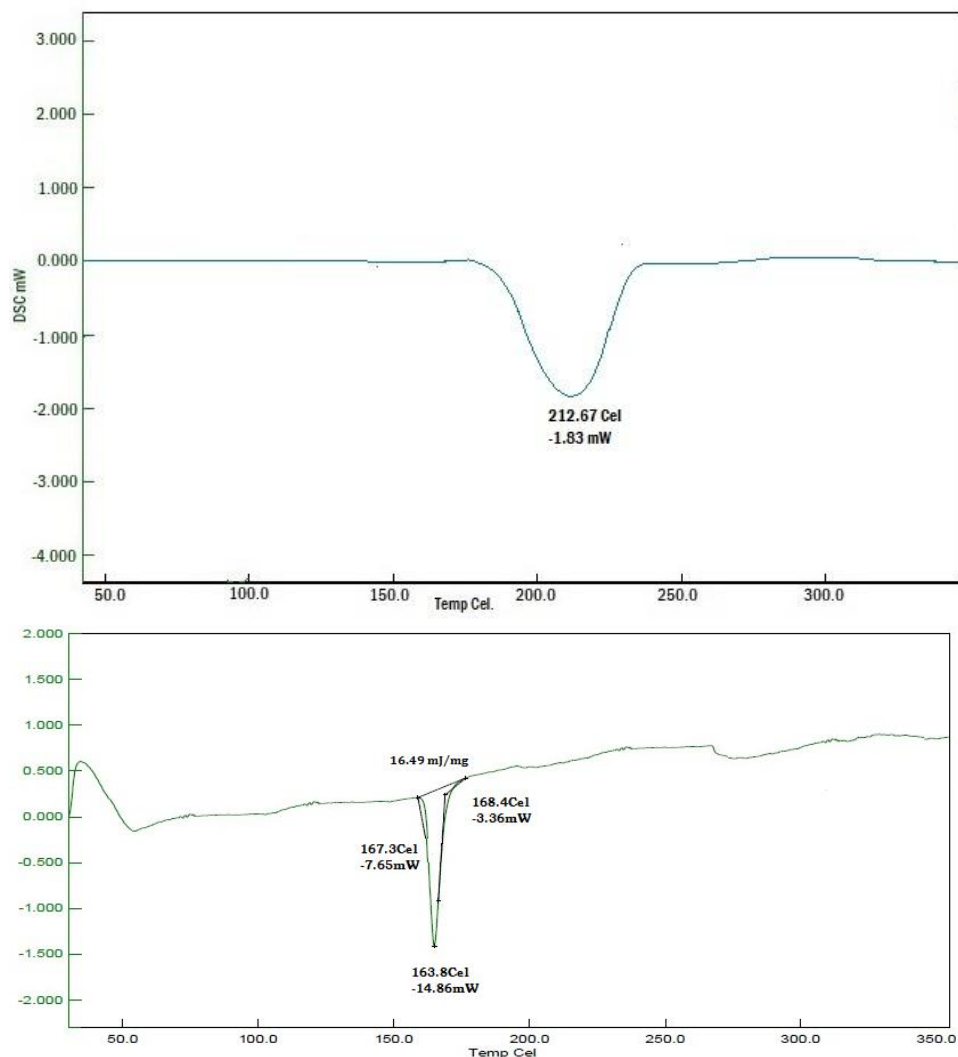


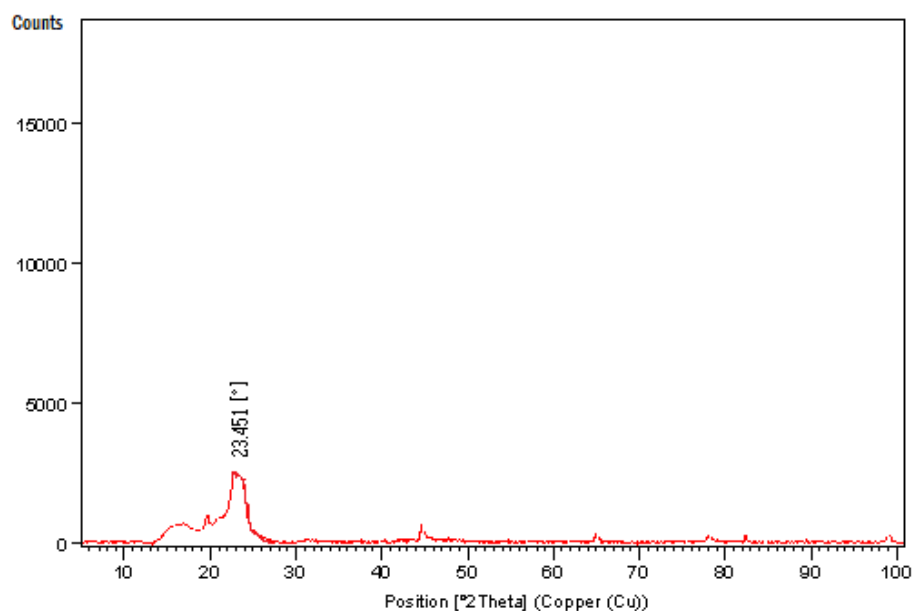
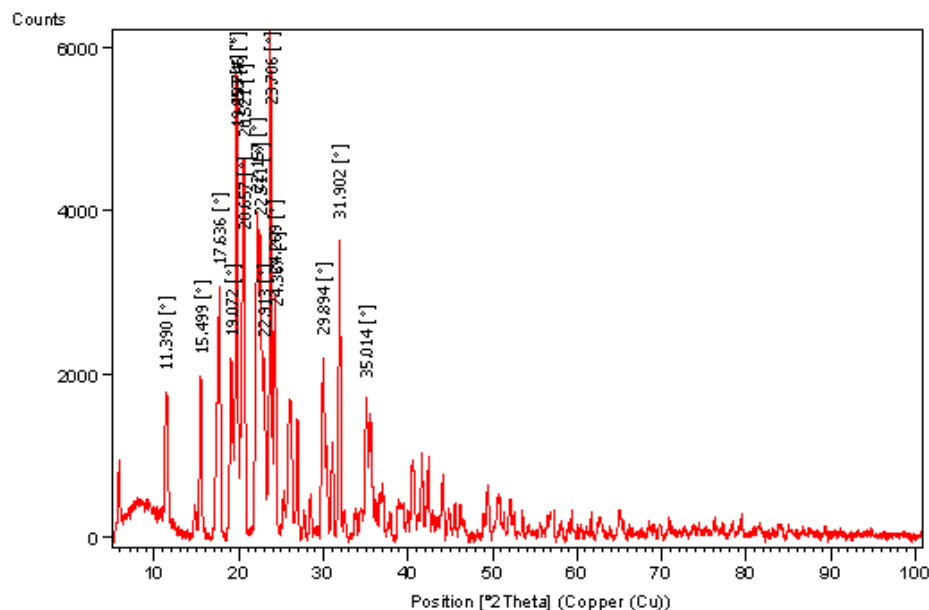
Fig. 3: DSC thermogram of a) Cimetidine, b) Mannitol, c) Crosspovidone and d) Optimised formulation F8 containing 8 % of crosspovidone

XRD studies

The XRD pattern of Cimetidine, mannitol, crosspovidone, optimised formulations F8 were shown in fig. 4. The XRD pattern of Cimetidine showed characteristic sharp intensity diffraction peaks at 2θ equivalent to 11.39° , 15.49° , 17.63° , 20.65° , 23.70° and 31.9° which reflects the crystalline nature of drug. The XRD diffractogram of the optimised formulation F8 with 8 % CP showed reduction in peak intensity when compared to the Cimetidine which was negligible. The results showed that the formulation F8 converted the drug which is a strong crystal habit into a totally amorphous one and was supported by DSC. As a result



of amorphisation and substantial increase in surface area, drug particles acquired high internal energy necessary for their enhancing the dissolution of tablets.



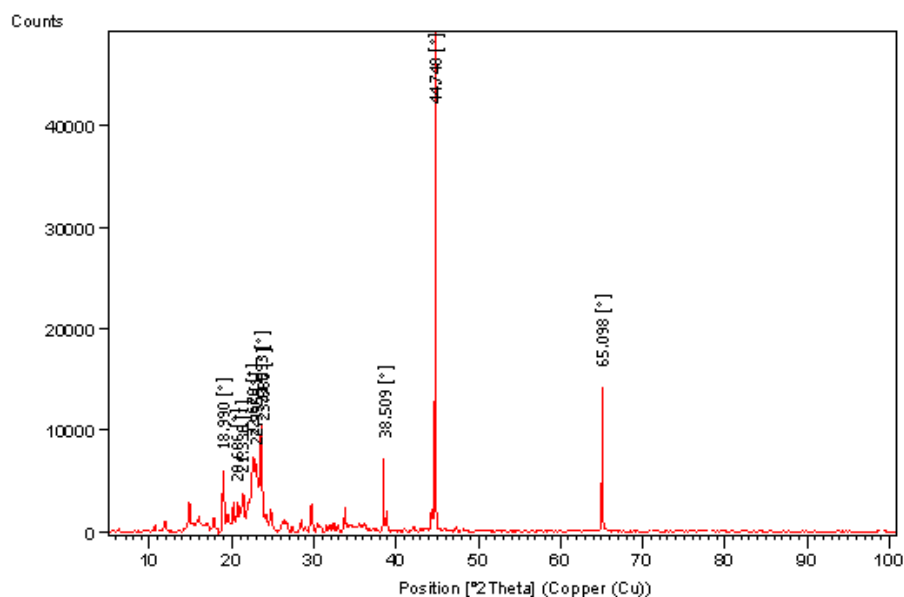
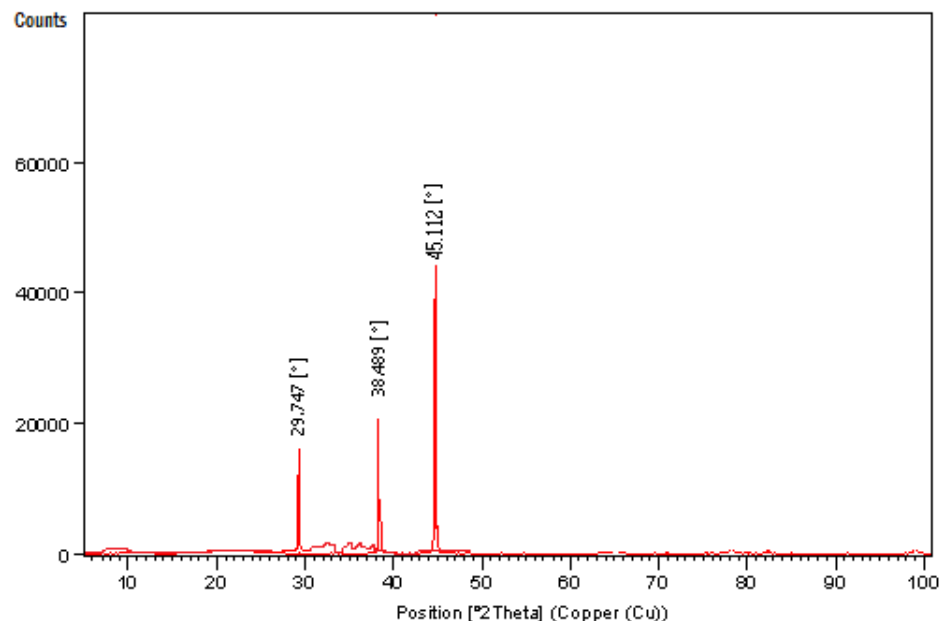


Fig. 4: XRD studies of a) Cimetine, b)Mannitol, c) Crosspovidone and d) Optimised formulation F8 containing 8% of crosspovidone

SEM analysis

The SEM analysis of Cimetine, mannitol, crosspovidone, optimised formulations F8 shown in fig. 5. The microphotograph of Cimetine showed shaped crystalline structure. In the optimised formulations FR4



and FR8, the crystallinity of the drug was lost that indicate the molecular mixing of the drug with CCS and fenugreek seed mucilage powder.

Evaluation of pre-compression studies

Direct compression technique was used for the preparation of the FDT. Flow characteristics of the material being compressed are important parameters and hence studies were undertaken for the evaluation of flow characteristics of the lubricated blend used in the present study. The results of flow properties of the prepared lubricated blends are shown in table 2. As the angle of repose values were within the range of 21.08° to 27.15° for F1 to F9 formulations respectively, which indicates excellent to good flow properties. The compressibility index of all the formulations were within the range of 11.17–14.56 % respectively, with good compressibility index as all the values are within 15 % results in good to excellent flow properties and which describes the frictional and cohesive interactions of the polymers in the formulation. Hausner's ratio of all the formulations was in the range of 1.12 to 1.24 which indicated good flow characteristics for the prepared lubricated blends, as all the values are <1.25 indicating the polymers with low interparticle friction.



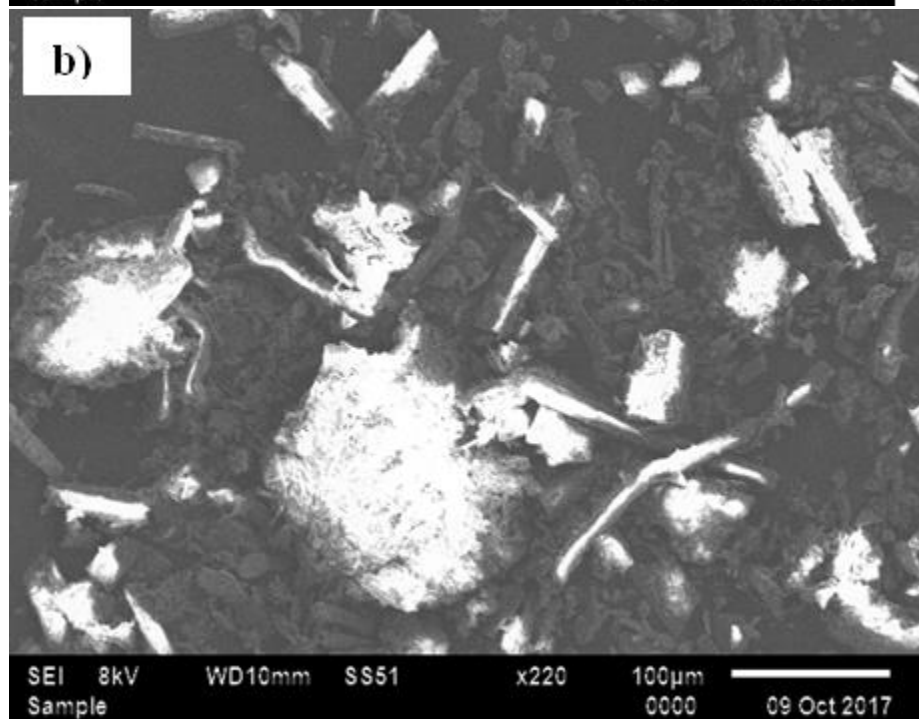
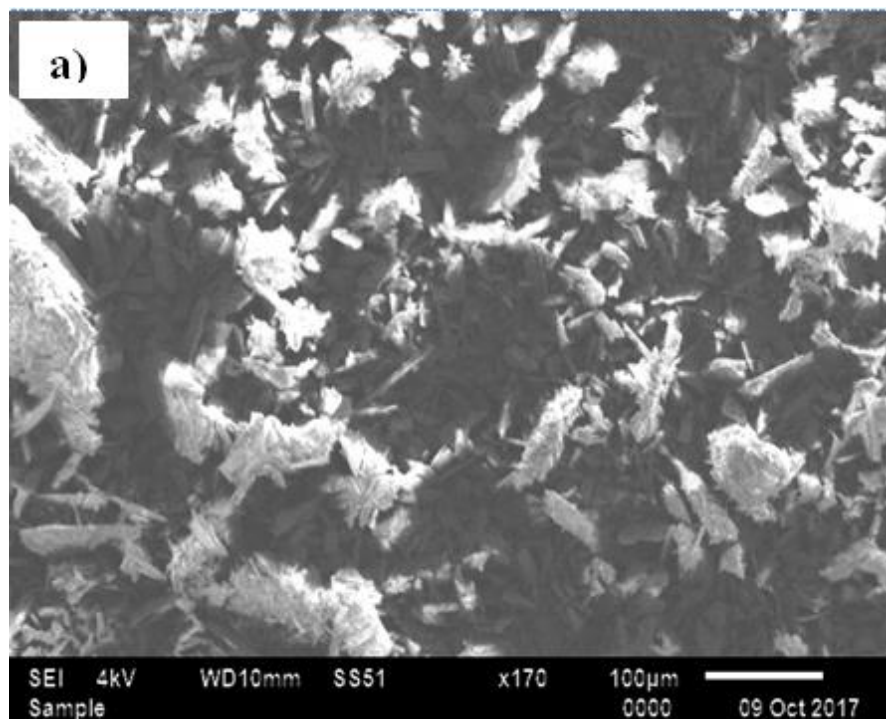
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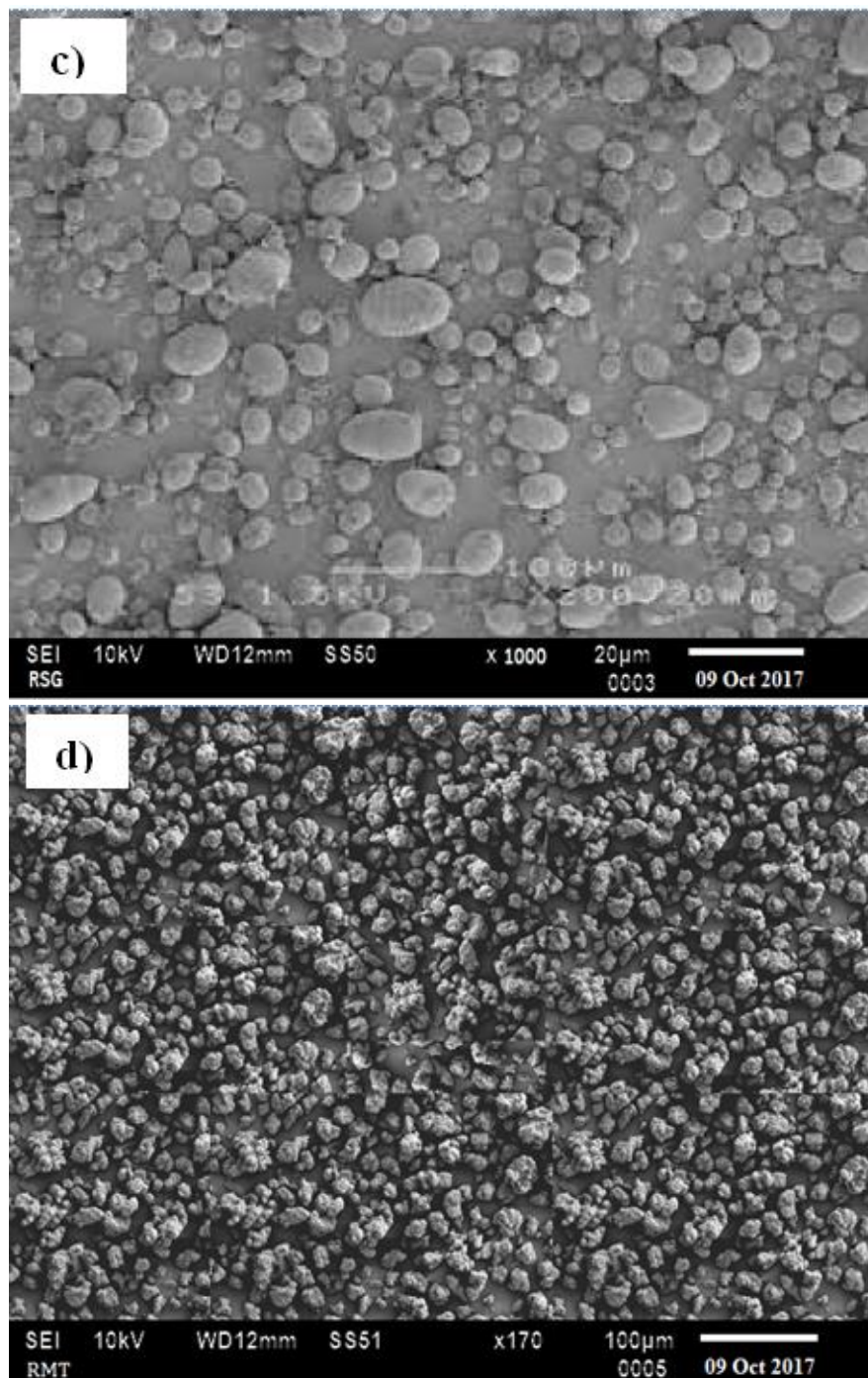


Fig. 5: SEM analysis of a) Cimetidine, b) Mannitol, c) Crosspovidone and d) Optimised formulation F8 containing 8 % of crosspovidone

Table 2: Pre-compression properties of prepared formulations

Formulation code	Angle of repose	Bulk density(gm/cm ³)	Tapped density(gm/cm ³)	Carr's index	Hausner's ratio
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F1	26.25±0.64	0.39±0.03	0.46±0.24	13.21	1.17
F2	25.41±0.48	0.39±0.12	0.47±0.19	12.02	1.20
F3	22.73±0.46	0.38±0.09	0.46±0.24	14.56	1.24
F4	26.76±0.32	0.37±0.17	0.45±0.12	11.55	1.18
F5	22.14±0.66	0.38±0.15	0.41±0.14	13.75	1.10
F6	21.84±0.89	0.40±0.16	0.45±0.16	11.17	1.12
F7	27.15±0.42	0.38±0.12	0.46±0.21	12.13	1.24
F8	22.21±0.36	0.37±0.16	0.47±0.18	13.17	1.12
F9	21.08±0.32	0.36±0.14	0.43±0.12	14.13	1.23

All the values are expressed as mean±SD where number of experiments (n=3).

Evaluation of post-compression parameters

Tableting characteristics of the Cimetidine FDTs

Prepared tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and assay and results are given in table 3 and 4.

All the prepared Cimetidine FDT are greater than 100 mg and are well within the range of 5 % and hence qualify the test for uniformity of weight. The thickness of all the formulations was in the range of 0.83 to 0.98 mm and hardness of all the formulations was in the range of 3 to 4 kg/cm². The percentage weight loss in the friability test was found to be less than 0.5 % for all the batches.

The wetting time of all the formulations was in the range of 37 to 45 sec. The water absorption ratio of all the formulations was in the range of 83.2 to 99.6 sec. The disintegration time of all the formulations was in the range of 85-120 sec. Assay was found to be in the range of 98.94 to 101.29 % of the stated amount of Cimetidine. Thus, Cimetidine FDT prepared with the selected superdisintegrants were regarded as good quality fulfilling the official and other requirements of tablets.

Table 3: Physicochemical properties of the Cimetidine FDT

S. No.	Weight variation (kg/cm ²)*	Thickness (mm)**	Hardness (kg/cm ²)**	Friability (%)***
F1	100.08±0.11	0.83±0.14	3-4	0.39
F2	101.07±0.12	0.98±0.16	3-4	0.42
F3	100.17±0.14	0.92±0.18	3-4	0.38
F4	100.97±0.13	0.91±0.24	3-4	0.45
F5	100.83±0.12	0.86±0.23	3-4	0.37
F6	101.01±0.11	0.92±0.15	3-4	0.35
F7	100.95±0.14	0.91±0.18	3-4	0.42
F8	100.21±0.12	0.89±0.22	3-4	0.40
F9	101.01±0.18	0.93±0.15	3-4	0.35

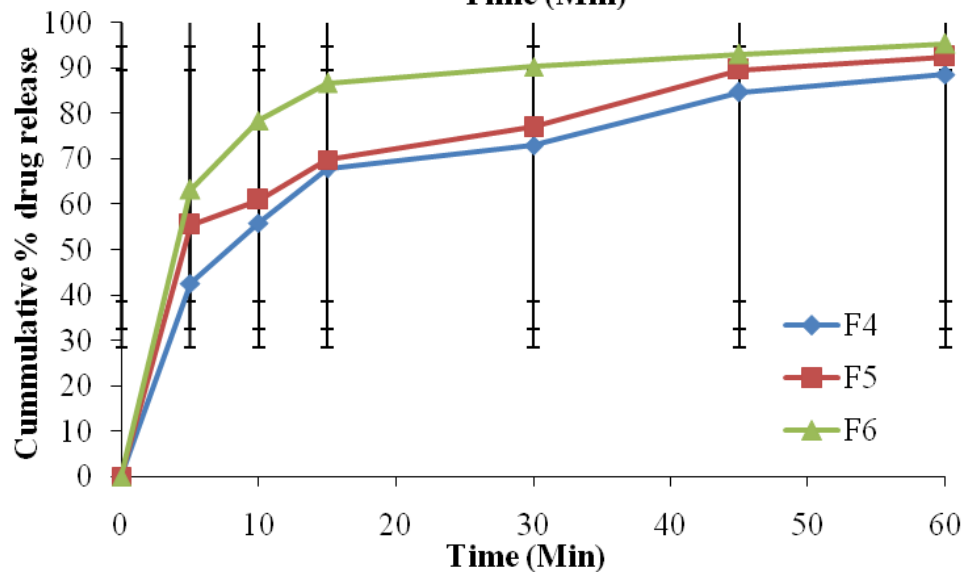
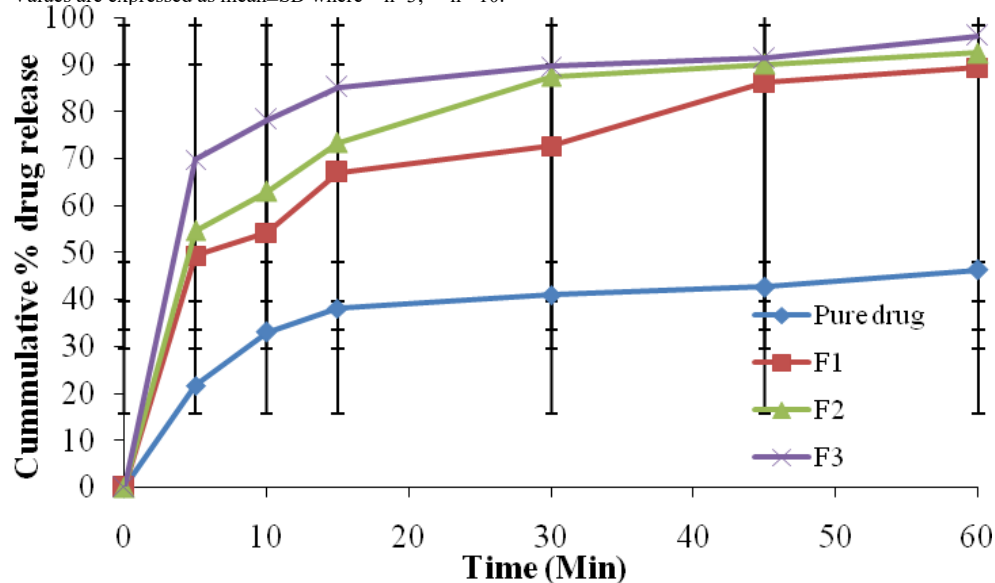
Values are expressed as mean±SD where * n=20; **n=5; ***n≈6.5 gm of total weight.

Table 4: Physicochemical properties of the Cimetidine FDT

S. No.	Wetting time (sec)*	Water absorption ratio (%)*	Disintegration time (sec)*	Drug content (%)**
F1	39±0.14	87.9±0.41	108±1.61	99.86±0.14
F2	38±0.16	89.6±0.25	101±1.24	99.71±0.40
F3	41±0.18	96.2±0.18	95±1.22	98.94±0.68
F4	39±0.12	95.6±0.29	85±1.44	100.07±0.12
F5	43±0.22	96.8±0.36	120±1.35	99.88±0.43
F6	37±0.19	99.5±0.15	101±1.32	100.16±0.15
F7	45±0.22	83.2±0.24	116±1.06	99.27±0.48
F8	39±0.15	98.7±0.39	91±1.03	101.29±0.11

F9	37±0.19	99.6±0.43	107±1.32	100.15±0.13
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Values are expressed as mean±SD where * n=3; **n=10.



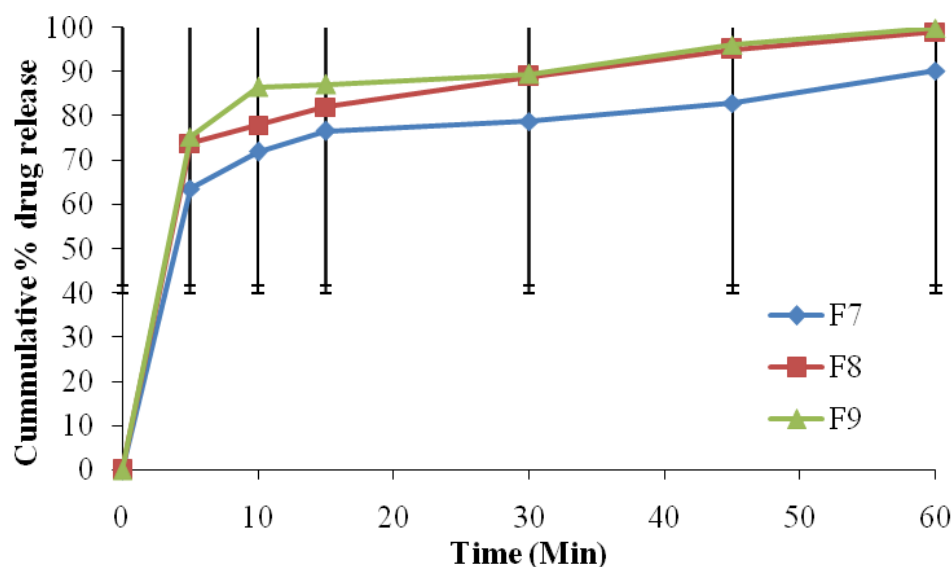


Fig. 6: Cumulative % drug release of Cimetidine pure drug and formulations F1 to F9 prepared with synthetic superdisintegrants (n=3, mean±SD)

In vitro dissolution studies

The in vitro dissolution studies of fast dissolving tablets were conducted in simulated gastric fluid 0.1 N HCl for 1 h. The results of the drug release studies of all the prepared formulations are shown in fig. 6.

The F1-F9 Cimetidine FDT formulations prepared with different ratios of synthetic superdisintegrants, have shown release profile similar >66% drug release in 1 h.

The drug release from F1, F2 and F3 were composed of sodium starch glycolate 4 %, 8 % and 12 % was found to be 90.32, 94.41 and 95.04 % in 60 min. The drug release from F4, F5 and F6 were composed of croscarmellose sodium 4 %, 8 % and 12 % was found to be 85.62, 92.47 and 95.32 in 60 min. The drug release form formulations F7, F8 and F9 were composed of crosspovidone was found to be 79.62, 99.98 and 99.89 in 60 min.

From all the above studies formulation F8 prepared with 8 % of crosspovidone showed more than 70 % and 95 % of drug release within 5 min and 1 hour, might be due to low water uptake and more gelling nature of CCS, SSG than CP [20], which is shown to have low swelling efficiency, high water uptake capacity and spongy nature, which yield porous tablets that disintegrate in fraction of seconds. Hence, formulation F8 is selected as the best formulation among all the other formulations.

The in vitro drug release profiles of famitidine were applied on various kinetic models in order to evaluate the mechanism of drug release. The different kinetic models evaluated were zero order, first order, Higuchi,



Hixson-Crowell. The data obtained were also put in Korsmeyer-Peppas model in order to find out n value, which describes the drug release mechanism.

All the formulations followed First order release with Fickian mechanism of drug release, due to the dominant erosion pattern, results were given in table 5. This may be due to the use of synthetic superdisintegrants in these formulations exhibited dominant erosion pattern with burst release of the drug from the formulation.

Table 5: Release kinetics data of Cimetidine prepared formulations F1 to F9

Formulation code	Zero order (r)	First order (r)	Higuchi (r)	Korsmeyer-peppas (r)	Hixson-crowell (r)	Korsmeyer-peppas (n)	Mechanism of release
Pure Drug	0.609	0.682	0.855	0.866	0.658	0.269	Fickian
F1	0.680	0.929	0.900	0.968	0.864	0.249	Fickian
F2	0.602	0.892	0.855	0.969	0.808	0.223	Fickian
F3	0.436	0.826	0.712	0.958	0.689	0.121	Fickian
F4	0.687	0.925	0.909	0.961	0.860	0.284	Fickian
F5	0.635	0.932	0.870	0.981	0.856	0.214	Fickian
F6	0.460	0.816	0.739	0.877	0.689	0.151	Fickian
F7	0.459	0.759	0.726	0.952	0.654	0.123	Fickian
F8	0.472	0.945	0.738	0.981	0.825	0.124	Fickian
F9	0.430	0.877	0.700	0.982	0.819	0.108	Fickian

Comparative studies

The Cimetidine pure drug, optimised formulations F8 with 8 % crosspovidone was compared with the marketed product. The drug release profiles were shown in fig. 7. The drug release was found to be 21.67 % for pure drug in 5 min, where as 54.61 % and 73.82 % for marketed product and optimised formulations F8.

Hence, the in vitro drug release for the optimised formulation F8 was found to be better than the marketed product.

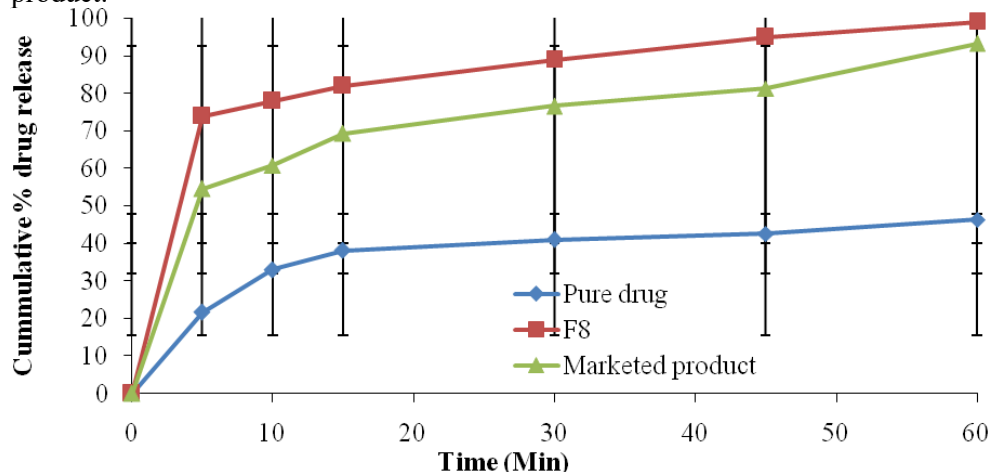


Fig. 7: Cumulative % drug release of Cimetidine pure drug, optimised formulations F8 in comparison with marketed product (n=3, mean±SD)



CONCLUSION

The present study was carried out to develop the fast dissolving tablets of Cimetidine by using various superdisintegrants at different ratios in comparison with marketed product. The formulations prepared with 8 % w/w concentration of CP F8 for fast dissolving tablets were found to be more suitable than the formulation prepared with other synthetic superdisintegrants and gave maximum drug release (%) within 5 min. It was found that the release rate was found to be more influenced by crospovidone superdisintegrant and the concentration of the disintegrant employed in the preparation of the tablets. The optimised formulation F8 drug release with crospovidone is slightly greater than that of the other synthetic superdisintegrant.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

All authors have none to declare

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