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Design and development of Orally Disintegrating Tablets of Famotidine Prepared by Direct Compression Method Using Different Superdisintegrants

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ABSTRACT

Orally disintegrating tablets (ODT) are gaining popularity over conventional tablets due to their convenience in administration and suitability for patients having dysphagia. Moreover no water is required for swallowing the tablets and hence suitable for geriatric, pediatric and traveling patients. Super disintegrants (such as Ac-Di-Sol, Crospovidone, sodium starch glycolate), Diluents (Dibasic calcium phosphate) along with sweetening agent (aspartame) were used in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, in-vitro disintegration time (DT), in-vitro disintegration time in oral cavity and *in vitro* drug release. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum DT were observed with Crospovidone excipient prepared by direct compression.

Key Words: Orally disintegrating tablets, Ac-Di-Sol, Crospovidone, Dibasic calcium phosphate

INTRODUCTION

Recent advances in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration. Difficulty in swallowing (*i.e.* dysphagia) is experienced by patients such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy (Bi et al, 1996). To improve the quality of life and treatment compliance of such patients fast disintegrating or orally disintegrating tablets (ODT) dosage form is a better alternative for oral medication (Kornblum et al, 2001). ODTs are the solid dosage form containing medicinal substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilitate swallowing (Bi et al, 1995). ODTs can be prepared by different methods as direct compression, freeze-drying, spray drying, sublimation and wet granulation method. The aim of this study was to formulate ODTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, spray dried excipient base was used for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants like Ac-Di-Sol, sodium starch glycolate (SSG) and Crospovidone in the formulation of tablets. Famotidine as a model drug was used in the formulation. Famotidine is a H₂ receptor antagonist. A thiazole ring containing H₂ blocker which binds tightly to H₂ receptors and exhibits longer duration of action despite an elimination

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Materials and Methods

Materials

Famotidine was obtained as gift sample from Cadila Pharmaceutical Ltd. Dholka (Ahemdabad), (SSG), Crospovidone, Avicel pH 102, obtained as gift samples from Signet Chemicals Mumbai. Sodium Saccharine and Mannitol from Ranbaxy Research Lab, Gurgaon .and other reagents were of analytical grade.

METHOD

Preparation of orally disintegrating tablets by direct compression technique:

Orally disintegrating tablets of Famotidine were prepared by direct compression method according to the formula given in table. All the ingredients were passed through 60 mesh sieve separately. The drug and diluents was mixed by small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 8 mm sizes flat round punch to get tablet using single punch Machine show in **Table. 1**

Preparation and Evaluation of Blend of Drug and Excipients:

Preparation of powder blend:

All ingredients were passed through sieve no. 40. Required quantities of ingredients were taken for particular formulation and using laboratory mixer the blend was mixed.

Evaluation of Mixed Powder Blend of Drug and Excipients:

Evaluation of mixed blends of drug and excipients were carried out for all the formulations for angle of repose, bulk density, tapped density, % compressibility and flowability.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5cm at 2 seconds intervals (Bi et al, 1995.). The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula.

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}$$

Compressibility index

Compressibility index of the powder was determined by Carr's compressibility index

$$\text{Carr's index (\%)} = \frac{[(\text{TBD}-\text{LBD}) \times 100]}{\text{TBD}}$$

Angle of repose

Angle of repose (a) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the heap (*r*) was measured and angle of repose was calculated.

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

Where θ is the angle of repose

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by following Formula:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}$$

$$\text{Bulk density}$$

Post-compression Characterization of Tablet

After compression of powder blends, the prepared tablets were evaluated for Organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time.

General appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. This includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws etc.

Weight variation

The weight variation test would be satisfactory method of determining the drug content uniformity. As per USP, twenty tablets were taken and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

Thickness variation: Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

Hardness and Friability: Hardness of the tablets was measured using the Pfizer hardness tester. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation (Sallam et al, 1998.)

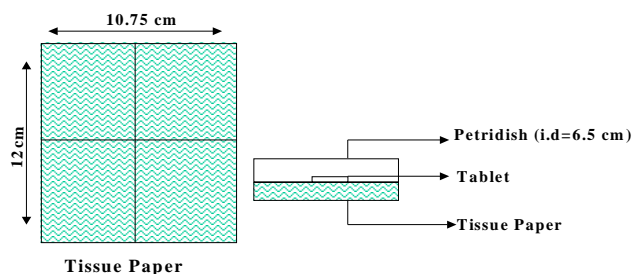
$$R = 100 \times (W_a - W_b) / W_b$$

Where W_b = Weight of tablet before water absorption

W_a = Weight of tablet after water absorption.

Wetting time

Wetting time of the tablets was measured using a piece of tissue paper (12 cm X 10.75 cm) folded twice, placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer (pH 6.8)^{8,12}. A tablet was put on the paper, and the time for the complete wetting was measured (Koizum et al, 1997.)



Simple Method for the Measurement of Wetting Time of a Tablet

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Uniformity of drug content

10 tablets were randomly selected and weighed. Average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 20mg weighed and the weighed amount was dissolved in 30ml of methanol in different volumetric flasks to obtain a stock solution of 1000 μ g/ml. 1ml was pipetted out and diluted with methanol to 10 ml in each case, so as to get 100 μ g/ml solutions. The absorbance was noted down after filtering off the solutions at 265nm. The average Weight of drug present in each tablet was calculated and compared with the claimed amount.

Disintegration test

Disintegration of orally disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh a screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve (Fig.1). To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and

the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

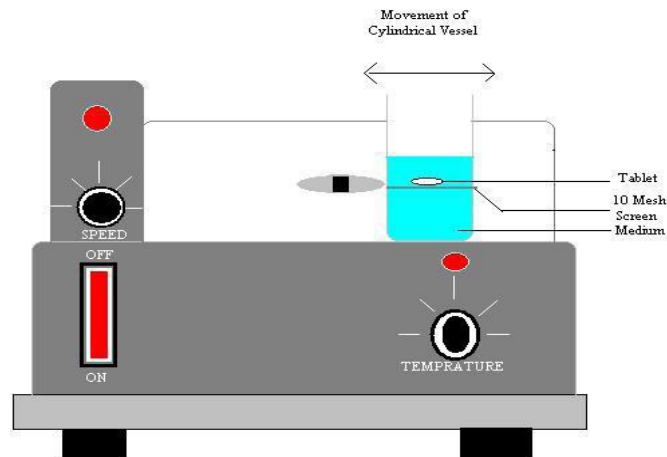


Fig.1 : Disintegration Test Apparatus

In vitro dissolution studies

In vitro dissolution studies for all the prepared tablets was carried out using USP paddle method at 50rpm in 500ml of phosphate buffer pH 6.8 as dissolution media, maintained at 37 \pm 5 $^{\circ}$ C. five ml aliquots were withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 265nm. An equal volume of fresh medium, which was pre-warmed at 37 \pm 5 $^{\circ}$ C, was replaced into the dissolution media after each sampling to maintain the constant volume thought the test. Dissolution studies were performed in triplicate.

RESULT AND DISCUSSIONS

The present study was carried out to develop orally disintegrating tablets of Famotidine by direct compression method. Hence it was necessary to find suitable excipients with good compatibility and disintegrating ability.

Preformulation study

The gift sample of Famotidine procured was analyzed by various Organoleptic, physicochemical and Spectrophotometric methods. The sample of Famotidine possessed similar color, odour, taste and texture as given in officials. The melting point of the sample was analyzed by capillary fusion method and found to be 163 $^{\circ}$ C. . The FT-IR spectrum of drug sample was concordant with reference spectra as given in Clarke analysis of drug and poison. The IR spectra of drug and drug and excipients are shown in Fig.2 and Fig.3, Fig.4, Fig.5 Fig.6. respectively. The FT-IR spectra verified the authenticity of the procured sample as the characteristic peaks of the drug. The absorption maxima of Famotidine was observed at 265.5 nm in Sorenson's buffer (pH

6.8), which was concordant with the value given in Clarke analysis of drug and poison.

The qualitative solubility of Famotidine was determined in various solvents. Very slightly soluble in water and in dehydrated alcohol. Freely soluble in dimethyl formamide and in glacial acetic acid. Practically insoluble in ether and in ethyl acetate

EXPERIMENTAL WORK

In direct compression method, Dicalcium phosphate was selected as directly compressible diluent. Crospovidone, Croscarmellose sodium, Sodium starch glycolate and Low-substituted Hydroxypropyl cellulose were used as disintegrants. In all the formulations, Pregelatinized starch was used as a binding agent to attain hardness. Aspartame was used as a sweetening agent. Magnesium stearate and talc were used as lubricant and glidant respectively.

Precompression Parameters

Parameter	Formulations D1-D12
Bulk density	0.53-0.71
Tapped density	0.63-0.88
Carr's index	14.49-19.76
Angle of repose	21.7-35.6

POST-COMPRESSION PARAMETERS

Hardness

The hardness was determined for all the formulations and the results were as follows.

The hardness of all the formulations was kept at 3.0 ± 1 kg / cm² to compare the disintegration time between the formulations

Friability

The percentage friability of all the formulations were found to be not more than 0.6 %, which is well within the 1 % limit. The results of friability indicated that the tablets were mechanically stable.

Weight variation

The weights of the tablets were between 239.0 mg to 258.0 mg. As the weight of tablets was 250 mg, the acceptable weight variation range is between 232.5 mg to 267.5 mg (± 7.5 %). Hence all the tablet formulations were within the pharmacopeial limits.

Assay

The percentage drug content of all the tablets was found to be between 94.37 % and 99.7 % of Famotidine, which was within the acceptable limits.

Disintegration time as per IP, Wetting time and Disintegration time in Oral cavity was determined for all the formulations.

Disintegration Time as per IP

Disintegration time as per IP, for all the formulations was found to be within 74 seconds, which was well within IP limit. (IP limit is 180 seconds)

Formulations with Crospovidone and Sodium starch glycolate as disintegrants exhibited quicker disintegration of tablets than compared to Croscarmellose sodium & low-substituted Hydroxypropyl cellulose (L-HPC). It indicated that amongst the disintegrants used Sodium starch glycolate and Crospovidone were better disintegrants to formulate orally disintegrating tablets by direct compression method for Famotidine than Croscarmellose sodium and L-HPC. This can be attributed to the extent of water uptake and consequently the strong swelling power of these disintegrants caused

Sufficient hydrodynamic pressure to induce complete disintegration. These disintegrants swell to a large extent when they come in contact with water to disintegrate tablets and has a fibrous nature that allows intraparticulate, as well as extraparticulate, wicking of water even at low concentration levels (10%)

Wetting time

Wetting time, for all the formulations was found to be within 62seconds.

Formulations with Crospovidone and Sodium starch glycolate as disintegrants exhibited quicker Wetting time of tablets than compared to Croscarmellose sodium & Low-substituted Hydroxypropyl cellulose. It indicated that amongst the disintegrants used, Sodium starch glycolate and Crospovidone were better disintegrants to formulate orally disintegrating tablets by direct compression for Famotidine than Croscarmellose sodium and L-HPC. This may be due to the low porosities of these disintegrants.

Disintegration Time in Oral Cavity

It was observed that all the tablets disintegrated in oral cavity within 69 seconds.

Tablets prepared with Dicalcium Phosphate as diluent disintegrated in oral cavity between 31.45 second to 59.45 seconds

Rapid disintegration of tablets containing Dicalcium Phosphate as diluent was attributed to the penetration of water into

Table 1: Tablet formulations

*INGREDIENTS	D ₁	D ₂	D ₃	D ₄	D ₅	D ₆	D ₇	D ₈	D ₉	D ₁₀	D ₁₁	D ₁₂
Famotidine	20	20	20	20	20	20	20	20	20	20	20	20
Calcium phosphate dibasic	180	177.5	175	180	177.5	175	180	178	175	180	178	175
Cross Povidone	5	7.5	10	-	-	-	-	-	-	-	-	-
Crosscarmellose Sodium	-	-	-	5	7.5	10	-	-	-	-	-	-
L-HPC	-	-	-	-	-	-	5	7.5	10	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	-	-	-	10	12.5	15
Pregelatinized Starch	30	30	30	30	30	30	30	30	30	30	30	30
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
TOTAL	250	250	250	250	250	250	250	250	250	250	250	250

All the quantities expressed are in mg / tablet

Table 2: Pre-compression parameters of formulations

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's Ratio
D1	0.65	0.78	32.5	16.66	1.2
D2	0.68	0.84	32.6	19.04	1.23
D3	0.69	0.86	34.12	19.76	1.24
D4	0.61	0.75	30.21	18.66	1.22
D5	0.67	0.79	24.2	15.18	1.17
D6	0.62	0.74	35.6	16.21	1.19
D7	0.53	0.63	25.2	15.87	1.18
D8	0.69	0.83	21.7	16.86	1.20
D9	0.71	0.88	33.5	19.31	1.23
D10	0.59	0.69	23.5	14.49	1.16
D11	0.57	0.69	34.6	17.39	1.21
D12	0.62	0.73	32.8	15.06	1.17

the hydrophilic tablet matrix by means of capillary action of the pores and by subsequent disruption of the hydrogen bonds.

Dissolution rate study

The dissolution study was carried out using 500 ml of Phosphate buffer (PH 6.8) as dissolution medium at 50 rpm at 37⁰C ± 0.5⁰C in USP Type II apparatus. All the formulations showed rapid dissolution rate and the percentage cumulative drug release (%CDR) after 5 minutes was more than 81.64 % and complete dissolution was achieved within 10 minutes.

Table 3: Post-compression parameters of formulations

Formulation code	Hardness (kg/cm ²)	Friability	Drug Content (%)	Thickness
D1	3.5	0.45	95.65	5.34
D2	4.0	0.36	98.47	5.23
D3	3.5	0.62	96.68	5.35
D4	3.4	0.73	98.80	5.26
D5	3.2	0.36	99.76	5.51
D6	3.3	0.57	99.74	5.27
D7	3.2	0.87	98.34	5.36
D8	3.5	0.36	98.23	5.46
D9	3.1	0.53	97.65	5.27
D10	4.3	0.74	99.65	5.76
D11	3.6	0.56	97.56	5.83
D12	3.1	0.48	98.27	5.26

CONCLUSION

In the present work, an attempt was made to develop orally disintegrating tablets of Famotidine. From the study conducted, the following conclusions are drawn: Amongst the various combinations of superdisintegrants used in the study, tablets that were formulated (direct compression) using Croscopovidone and Sodium starch glycolate exhibited quicker disintegration of tablets than compared to those of L-HPC and Crosscarmellose sodium.

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Table4: Wetting Time, In-vitro disintegration Time, In-vitro Disintegration Time in Oral cavity

Formulation code	Wetting Time	In-vitro disintegration Time	In-vitro Disintegration Time in Oral cavity
D1	35.67	39.67	36.34
D2	34.00	35.33	32.00
D3	25.00	29.00	31.45
D4	48.00	65.00	54.12
D5	43.00	52.00	48.23
D6	41.12	54.12	46.00
D7	59.10	74.00	59.45
D8	51.00	45.12	58.00
D9	47.67	37.15	54.87
D10	46.00	50.10	45.00
D11	42.33	45.67	43.12
D12	40.67	43.67	37.00

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Fig.2: IR Spectra of Famotidine, Determined Experimentally

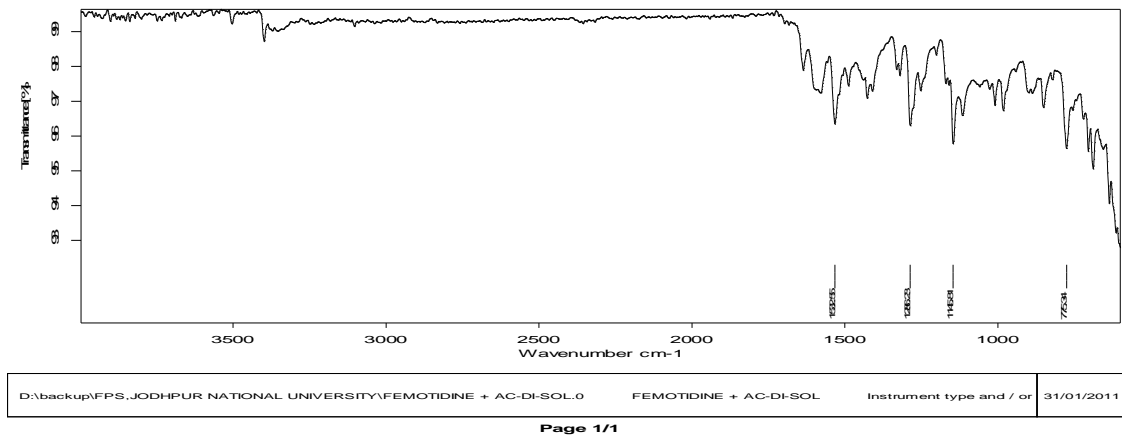


Fig. 3: FT- IR Spectra of Famotidine + Ac-di-sol

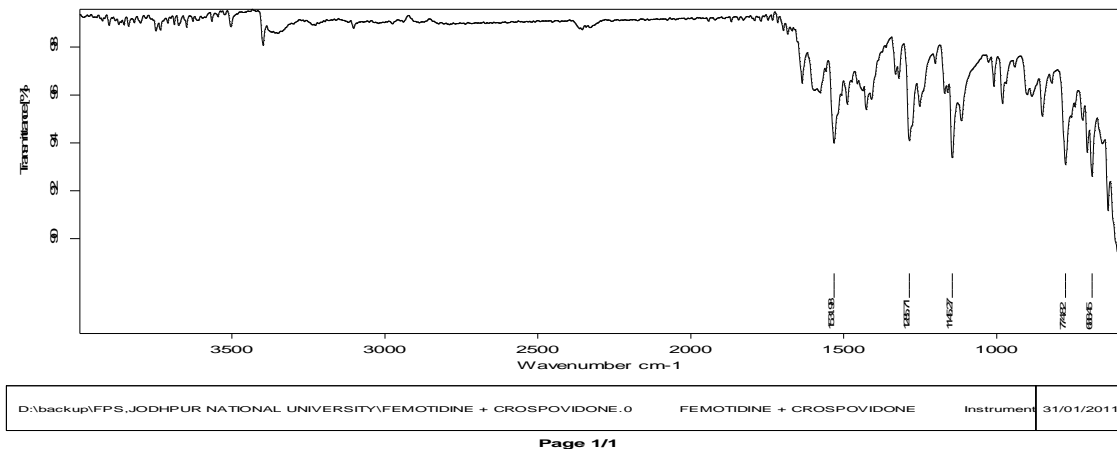


Fig. 4: FT- IR Spectra of Famotidine + Crospovidone

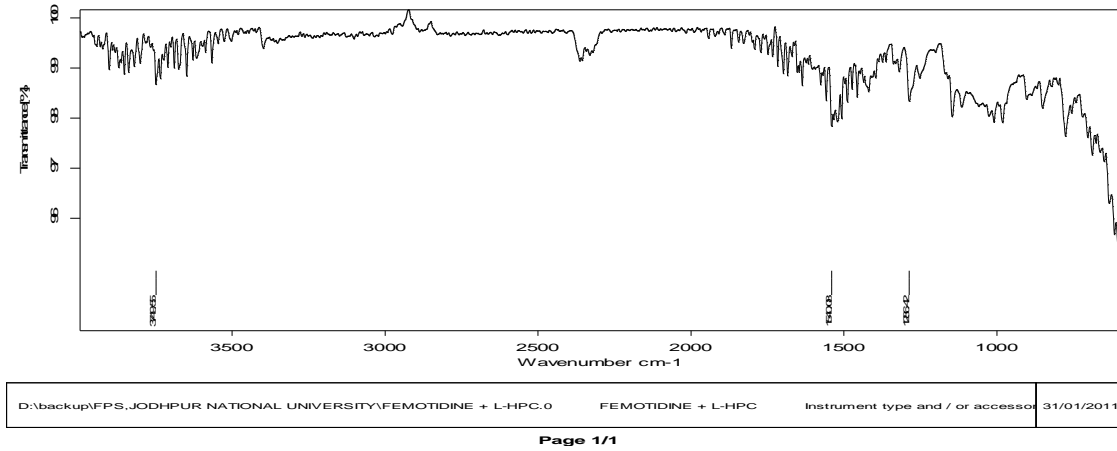


Fig. 5: FT- IR Spectra of Famotidine + L-HPC

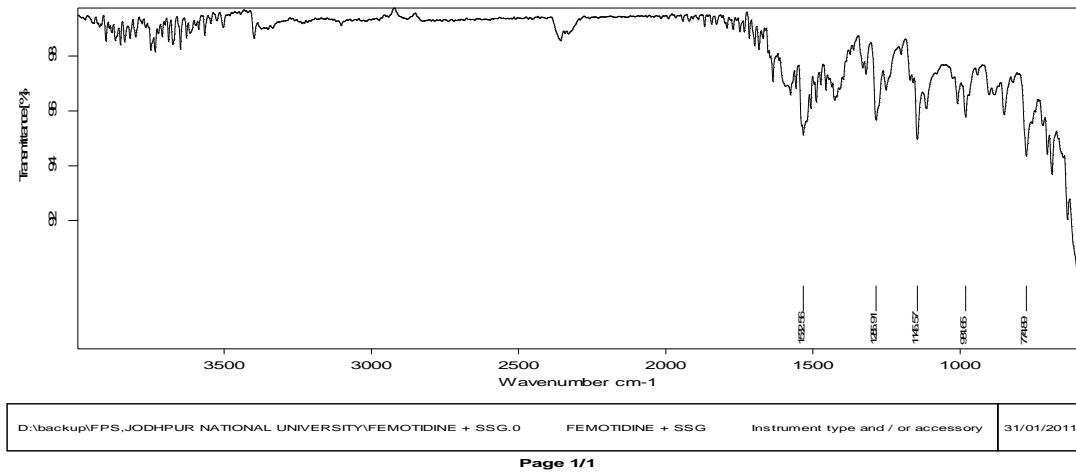


Fig. 6: FT- IR Spectra of Famotidine + S.S.G.

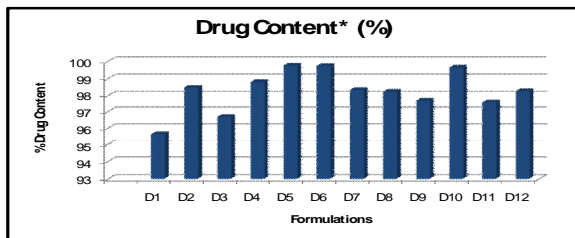


Fig.7: % Drug content of different formulations

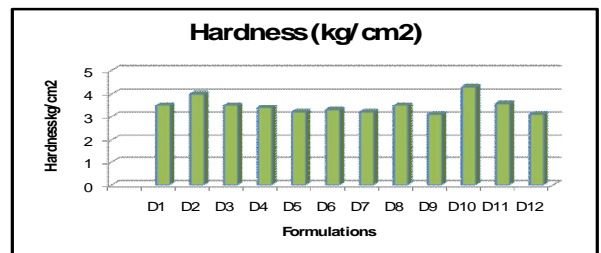


Fig.8: Hardness of different formulations

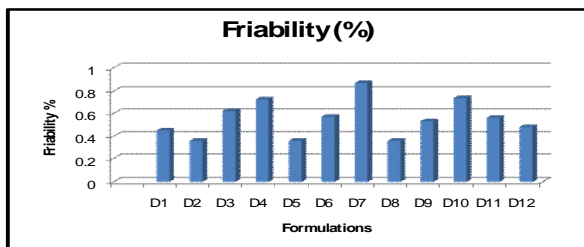


Fig.9: Friability of different formulations

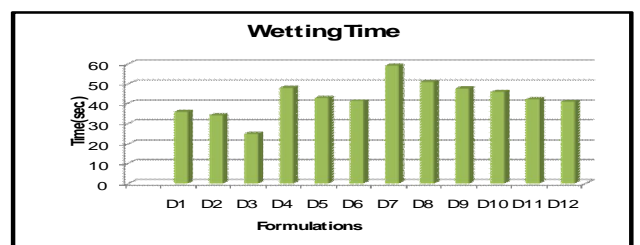


Fig.10: Wetting Time Profile of different Formulations

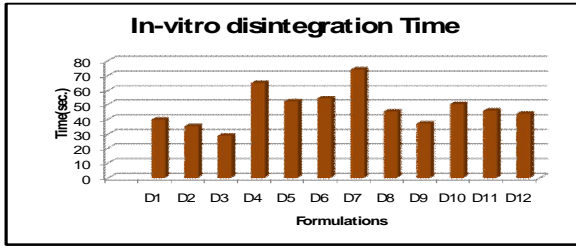


Fig. 11: *In-vitro* Disintegration Time Profile of different Formulations

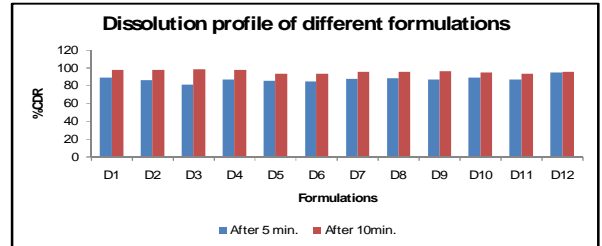


Fig.13: *In Vitro* Release rate profile of formulations in phosphate Buffer (pH 6.8) after 5 and 10 mins

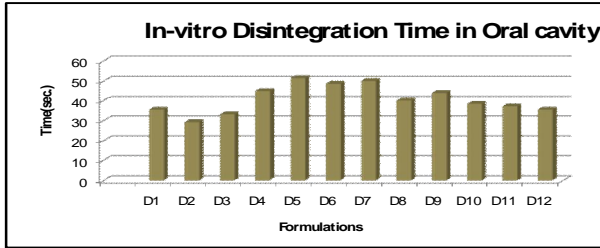


Fig.12: *In-vitro* Disintegration Time in oral cavity Profile of different Formulations