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Formulation and Evaluation of Fast Dissolving Famotidine Solid Dispersion Tablet

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ABSTRACT

Fast dissolving tablets are the tablet which dissolves rapidly and shows higher bioavailability than conventional tablets. The concept of formulating Fast dissolving tablets of Famotidine (H2 –receptor antagonist) offer suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic with increase bioavailability and to know the effects of two synthetic superdisintegrant (Croscarmellose sodium and Sodium starch glycolate). In the present work two methods of solid dispersion were compared for improving the bioavailability i.e. Solvent Evaporation and Fusion method with PVP K30 as a carrier to increase the solubility of the drug. Comparison between these two synthetic superdisintegrant was done by taking different ratios and in combination. Three different combination of these superdisintegrant shows synergistic effect when it is compared to individual. Prepared tablets were subjected to different evaluation parameters such as hardness (2.84±0.15 kg/cm^2 to 3.01±0.20 kg/cm^2), friability (not more than 0.680±0.0173), weight variation (197.6±1.42 mg to 202.6±1.90 mg), drug content uniformity (97.84±0.35 to 100.23±0.71%), *in vitro* disintegration time (21.0±0.81 sec to 108.33±0.47 sec), wetting time (29.33±0.47 to 113.33±1.24 sec), *in vitro* dissolution studies and stability studies are carried out by using the best formulation. From all the formulations prepared and tested, F9 was found to the best formulation.

Keywords: Fast dissolving tablets, Solid dispersion, Croscarmellose sodium, Sodium starch glycolate.

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INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology.

Therefore, a fundamental understanding of various disciplines, including GI physiology, Pharmacokinetics, Pharmacodynamic and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. In any case, the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug The anatomic and physiologic characteristics of the GIT, and Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.[1]

USFDA defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."Fast dissolving tablets are also known as mouth-dissolving tablets, Oro-dispersible tablets, rapimelts, and porous tablets.[2] Hence in the present study fast dissolving tablets of Famotidine were prepared by direct compression method with solid dispersion technique to increase the surface area of the drug and also superdisintegrant has been utilized for faster disintegration. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets.[2]

Advantages of fast dissolving tablets: [3]

- Rapid onset of drug therapy.
- Achieve increased bioavailability/rapid absorption through GIT.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- Convenient for administration and shows better patient compliance.
- The risk of chocking or suffocation during oral administration of conventional

formulations due to physical obstruction is avoided, thus providing improved safety.

MATERIALS AND METHODS

Preparation of solid dispersions of Famotidine with pvp k30 [4, 5]

Solid dispersions of Famotidine were prepared by solvent evaporation method and Fusion method. Shown in Table 1.

Table 1: Different drug carrier ratios

Formulation code	Drug	Carrier	Drug carrier Ratio
SM1	Famotidine	PVP K30	1:1
SM2			1:2
SM3			1:3
FM1			1:1
FM2			1:2
FM3			1:3

SM: Solvent evaporation method (SM1 1:1, SM2 1:2, and SM3 1:3 ratio) FM: Fusion method (FM1 1:1, FM2 1:2, and FM3 1:3 ratio)

Solvent evaporation method:

Drug was weighed and taken in a china dish dissolved in Methanol and then carrier (PVP K30) was added in ratio of 1:1, 1:2 and 1:3. The solvent was evaporated on water bath and dried in hot air oven at 65°C for 4 hr. The resultant mass was passed through sieve No. 85 and stored in desiccators. The solid dispersion obtained was evaluated for drug content and dissolution studies.

Fusion Method

Solid dispersions (SD) were prepared by melting the accurately weighed amounts of PVP K30 on a water bath and the drug was dispersed in the molten solution. The mixtures were stirred repeatedly after 10 min, cooling either at room temperature or by placing the closed container for 15 min in an ice bath. Solid mass obtained was passed through the sieve No 85 and stored in vacuum desiccator. The solid dispersion obtained was evaluated for drug content and dissolution studies

EVALUATION OF SOLID DISPERSION

Drug content of solid dispersion

Accurately weigh solid dispersions equivalent to 20 mg of Famotidine were weighed and transfer to 100 ml volumetric flask. Dissolve in 0.1N HCl buffer and the volume was made up with the same. An aliquot of the filtrate was analyzed spectrophotometrically at 265 nm.

In-vitro release studies of solid dispersion and pure drug (Famotidine)

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (Electro lab

Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (0.1N HCl) was taken in vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and analysis in the UV Spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 265 nm.

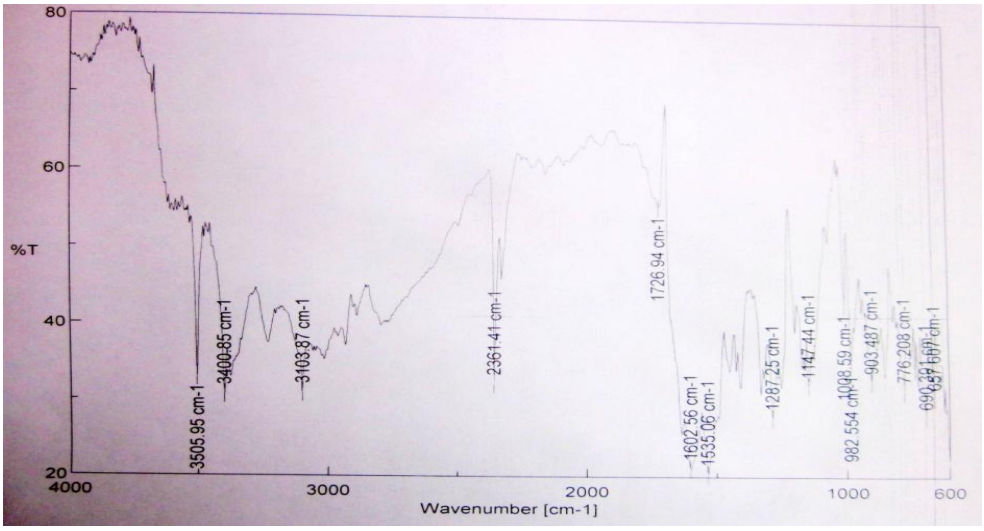

Figure 1: FT-IR spectrum of Famotidine solid dispersion + CCS + SSG

PREFORMULATION STUDIES OF POWDER BLEND [6, 7]

Angle of Repose (θ):

$$\tan(\theta) = h / r$$

θ Where, θ is the angle of repose**,** h is the height in cm, r is the radius in cm.

Bulk Density (D_b):

$$D_b = M / V_b$$

Where, M is the mass of powder ,V_b is the bulk volume of the powder.

Tapped Density (D_t):

$$D_t = M / V_t$$

Where, M is the mass of powder ,V_t is the tapped volume of the powder.

Hausner's ratio:

$$\text{Hausner's ratio} = D_t / D_b$$

Where, Dt is the tapped density., D_b is the bulk density.

Carr's index (or) % compressibility:

$$I = (D_t - D_b / D_t) \times 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder

Preparation of Tablets Containing Solid Dispersions of Famotidine by Direct Compression Method [8]

The solid dispersions equivalent to 20 mg of drug was taken. Then it mixed with directly compressible diluents and superdisintegrant in a plastic container. Magnesium stearate and talc were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Tablet compression

The tablets were compressed by using multi station tableting punching machine. The compressed weight of each tablet was 150 mg. The tablet was compressed using 6 mm flat-faced punches. The hardness was adjusted to 2.5 to 3.0 kg/cm^2.

Table .2 Formulation chart for fast dissolving tablet.

Ingredients(mg)	Formulation code									
	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion equivalent to 20mg	80	80	80	80	80	80	80	80	80	80
C.C.S	--	6	12	18	--	--	--	9	4.5	13.5
S.S.G	--	--	--	--	6	12	18	9	13.5	4.5
M.C.C	110	104	98	92	104	98	92	92	92	92
Sod. Saccharin	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
Total	200	200	200	200	200	200	200	200	200	200

EVALUATION OF FAST DISSOLVING TABLETS

Weight variation [9, 10, 11]

Twenty tablets were selected at a random from each formulation and average weight was determined. Then individual tablets were weighed using digital electronic balance and the individual weight was compared with the average weight. The mean ± SD (standard deviation) values were calculated.

Hardness: [9, 10]

Hardness or tablet crushing strength (f_c). The force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2. Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated.

Friability (F): [10, 11]

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the

combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = (W_{initial} - W_{final} / W_{initial}) \times 100$$

In-vitro Disintegration time: [9]

The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time: [9, 10]

Wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{o}C.

In-vitro drug release: [11]

Release of the drug *in-vitro*, was determined by estimating the dissolution profile.USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. 0.1N HCl (900 ml) was used as a dissolution medium at 37±0.5°C temperature. Determination of amount of drug dissolved form tablets was carried by UV spectrophotometer at 265 nm. In this test, single tablet from each formulation was used for the studies. At specified time intervals, 5 ml samples were collected and immediately replaced with an equal volume of fresh medium. Samples were analyzed by using UVspectrophotometer (Shimadzu 1700, Japan) at 265 nm.

Stability study: [12]

Selected formulations were subjected to stability studies as per I.C.H. Guidelines.

Following conditions were used for stability studies

- ✶ 30°C/65 % RH analyzed at a time interval of 3 month till a period of 6 month
- ✶ 40°C/75 % RH analyzed at a time interval of 3 month till a period of 6 month

RESULTS AND DISCUSSION

In this work initially standard graph of Famotidine was taken in 0.1N HCl pH1.2, the absorption maxima was found at 265 nm. Solid dispersion of Famotidine were prepared by solvent evaporation and fusion method by using carrier PVP K30, the drug release of pure Famotidine

drug and solid dispersed was compared which is shown in (Figure 2).

Table 3: *In-vitro* release of Famotidine pure drug and solid dispersion (solvent evaporation method in the ratio 1:1, 1:2, 1: 3 & fusion method in the ratio 1:1, 1:2, 1: 3)

	%Cumulative Drug Release						
Time (min)	**Pure Drug**	**SM1**	**SM2**	**SM3**	**FM1**	**FM2**	**FM3**
1	8.08	25.67	29.52	**32.35**	15.79	21.87	26.48
2	10.62	45.07	52.92	**58.53**	36.36	39.57	45.15
3	14.57	60.86	63.97	**67.42**	41.61	45.56	58.44
4	18.62	64.85	67.79	**73.49**	43.40	46.36	60.78
5	21.80	68.06	71.24	**82.65**	45.82	48.27	61.57
6	25.49	71.01	75.45	**92.21**	49.22	52.44	64.31
7	30.12	74.00	83.15	**101.16**	50.31	55.05	67.43

SM: Solvent evaporation method, FM: Fusion method

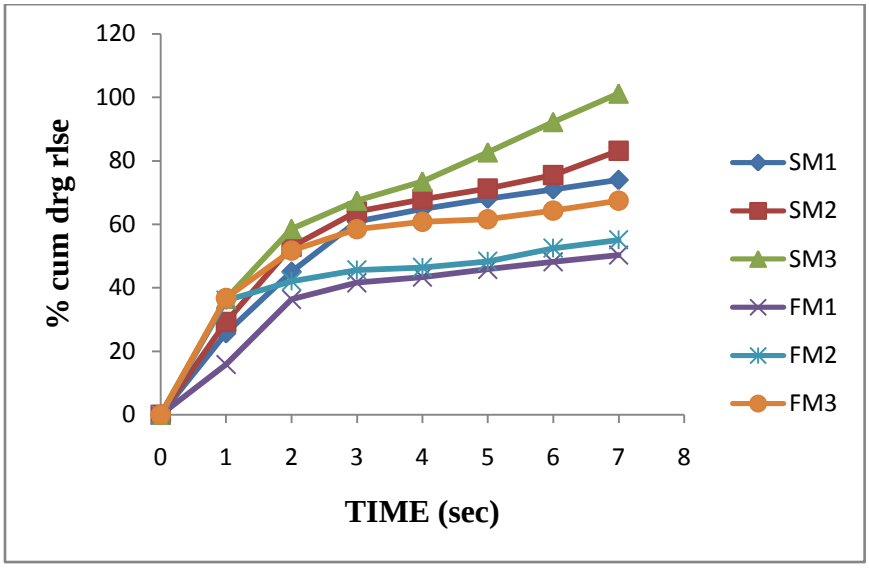

Figure 2: *In-vitro* release of Famotidine Pure Drug and Solid dispersion (Solvent evaporation method in the ratio 1:1, 1:2, 1: 3) & *In-vitro* release of Famotidine Pure Drug and Solid dispersion (Fusion method in the ratio 1:1, 1:2, 1: 3) (SM: Solvent evaporation method & FM: Fusion method)

The percentage drug content of all the solid dispersions was found to be between 97.95% to 101.45% of Famotidine which was within the limits. Percentages of drug released from SM1 to SM3 were ranged between 74.00 % and 101.16 %, percentages of drug released & from FM1 to FM3 were ranged between 50.31 % and 67.43% at 7 min and the pure drug (Famotidine) released only 30.12% at 7 min.

Table 4: Comparison of FT-IR spectra of pure drug and Excipients. (PVP K30: Polyvinyl pyrrolidone K30, SD: Solid dispersion, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate)

Pure drug(cm^{-1})	Drug +PVP K30 (cm^{-1})	SD + CCS(cm^{-1})	SD + SSG (cm^{-1})	SD+CCS+SSG(cm^{-1})	Description
3399.89	3399.89	3399.89	3399.89	3400.85	N-H Stretching
3103.87	3103.87	3103.87	3103.87	3103.87	C-H Stretching
1601.59	1601.59	1601.59	1600.63	1602.56	C=C Stretching
1253.5	1252.54	1253.5	1253.5	1287.25	C-N Stretching
1009.55	1009.55	1009.55	1009.55	1008.59	C-N aliphatic amine
904.451	904.451	902.523	905.415	903.487	C-S Stretching

- The values of angle of repose from formulation F0 to F9 ranged from 26.37±0.27 to 28.49±0.26. The Hausner's ratio values for all F0 to F9 formulation were ranged from 1.132±0.012 to 1.205±0.006. The Carr's Index values for all F0 to F9 formulation were ranged from 15.876±0.310 to 17.916±0.315%. Then formulation was done using various concentrations of superdisintegrant croscarmellose sodium and sodium starch glycolate as well as with combinations of these two. The average weight and percentage variation of twenty tablets was calculated for each formulation which is in the range from 197.6±1.42 mg (-2.4%) to 203.6±1.90 mg (+3.4%).
- The hardness for all the formulations F0 to F9 were ranged from 2.84±0.15 kg/cm^2 to 3.01±0.20 kg/cm^2, the percentage friability of all the formulations was found to be not more than 0.680±0.0173%.
- The disintegration time of formulations F1 to F9 were ranged from 21.0±0.81 sec to 108.33±0.47 sec and for F0 was found to be maximum of 139.1±0.81 sec. because of absence of disintegrating agent.
- The wetting time for all the formulations F1 to F9 was in the range of 29.33±0.47 to 113.33±1.24 sec. The wetting time for formulation F0 was found to be 175.0±0.81. The formulation F9 has minimum (29.33±0.47sec) wetting time because of wicking, swelling and deformation effect of disintegrating agent.
- The percentage drug content of all the formulations were found to be between 98.04±0.35% to 100.23±0.71%, The percentage drug release of Famotidine dispersion tablet for F0 is 59.33 for 4 min and F1 to F9 was determined between 80.72% to 108.28%. The evaluation of precompression parameters is given in table no. 4 and post compression parameters are given in Table 5-7.

Table 5: Micromeritic properties of precompressional powder blend.

Batch no.	Angle of repose (Ɵ)± SD	Bulk Density (gm/cc)± SD	Tapped Density (gm/cc)± SD	Hausner's Ratio± SD	Carr's Index (%)± SD
F0	26.54±0.27	0.4344±0.019	0.56847±0.021	1.216±0.011	16.706±0.206
F1	27.12±0.95	0.4545±0.0195	0.5595±0.009	1.171±0.005	16.533±0.338
F2	26.97±0.69	0.4846±0.0065	0.583±0.004	1.184±0.004	16.883±0.465
F3	26.78±0.37	0.4717±0.0071	0.5639±0.006	1.175±0.005	15.876±0.310
F4	28.49±0.26	0.4859±0.0072	0.5616±0.012	1.205±0.005	17.387±0.424
F5	26.22±0.71	0.4747±0.1156	0.5843±0.006	1.183±0.004	16.736±0.175
F6	27.01±0.59	0.4817±0.0532	0.5681±0.004	1.205±0.006	16.886±0.820
F7	26.44±0.61	0.4882±0.0083	0.5715±0.008	1.125±0.002	17.916±0.315
F8	27.04±0.22	0.4807±0.0047	0.5872±0.006	1.132±0.012	17.775±0.879
F9	26.37±0.27	0.4755±.0047	0.5791±0.009	1.189±0.008	17.146±0.551

- All values are expressed as mean ± SD, n=3

Table 6: Evaluation of fast dissolving tablets of Famotidine

Batch no.	Weight variation#(mg) ±SD	Hardness## (kg/cm^2)±SD	%Friability† ±SD	Disintegration Time*(sec)± SD	Wetting Time**(sec) ± SD	Drug Content (%)±SD
F0	198.6±1.56	2.83±0.22	0.611±0.0090	139.1±0.81	175.0±0.81	98.43±0.49
F1	198.5±1.62	2.84±0.15	0.553±0.0122	102.67±1.24	106.0±1.63	98.36±0.59
F2	199.4±1.62	2.87±0.17	0.552±0.0041	69.58±1.24	83.0±2.16	98.53±0.77
F3	202.6±1.90	2.93±0.11	0.426±0.0430	39.78±01.24	43.66±0.47	100.23±0.71
F4	197.6±1.42	2.93±0.22	0.680±0.0173	108.33±0.47	113.33±1.24	97.84±0.35
F5	200.5±2.48	2.91±0.14	0.512±0.0182	78.67±0.47	87.66±1.24	99.06±0.36
F6	199.0±1.26	2.84±0.20	0.429±0.0345	46.73±1.24	50.66±1.24	98.01±0.08
F7	201.4±1.42	2.92±0.24	0.476±0.0175	50.67±0.47	61.67±1.24	99.66±1.18
F8	199.5±1.28	2.79±0.20	0.496±0.0191	66.0±0.81	69.33±1.24	99.72±1.33
F9	201.8±1.31	3.01±0.20	0.558±0.0182	21.0±0.81	29.33±0.47	100.1±1.21

All values are expressed as mean ± SD, n = $10^{\#}$, $10^{\#\#}$, $10^{\dagger}$, 6*, 3**

Table 7: *In-vitro* release of Famotidine Fast Dissolving Tablets from formulations F0 to F9

Time (min)	Cumulative Drug Release (%)									
	F0	F1	F2	F3	F4	F5	F6	F7	F8	
0.5	15.28	17.39	19.87	20.13	3.59	4.90	10.62	19.87	19.40	**20.11**
1.0	25.39	34.56	36.41	38.45	8.56	9.46	15.93	44.49	32.81	**46.59**
1.5	30.94	45.42	51.42	55.46	13.69	15.51	21.22	59.54	53.86	**87.53**
2.0	41.32	61.13	63.93	69.76	28.74	34.56	39.67	77.56	66.48	**108.28**
2.5	45.20	65.34	70.79	75.67	38.99	42.62	48.53	94.53	80.52	-
3.0	51.19	72.18	76.20	80.62	46.27	54.80	60.53	-	91.29	-
3.5	56.18	74.53	82.22	87.55	57.74	60.57	71.97	-	-	-
4.0	59.33	80.72	86.43	101.30	69.64	75.80	89.68	-	-	-

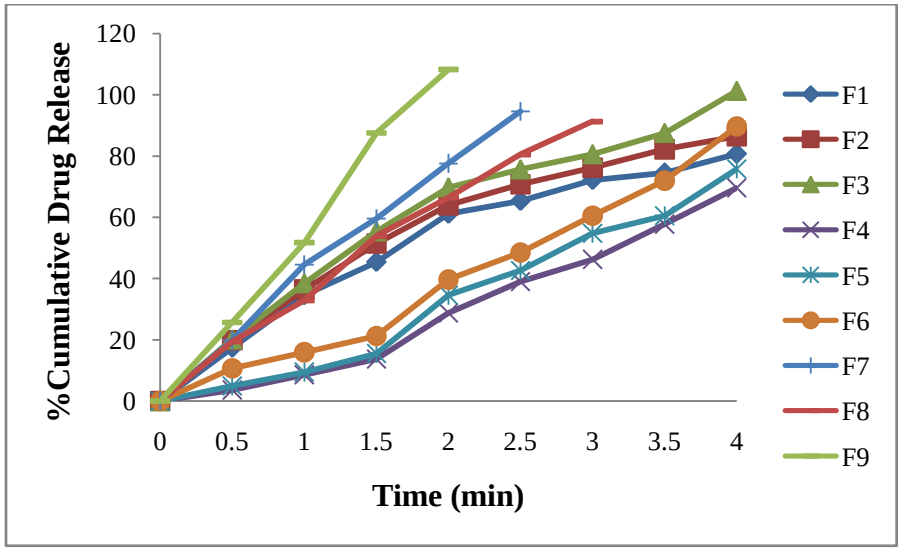

Figure 3: *In Vitro* release of Formulation F1 to F9

CONCLUSION

From the above work it was concluded that the release of drug from the F9 formulation was quick when compared to F3 and F6 formulation. It shows that the combined effect of croscarmellose sodium and sodium starch glycolate gives synergistic effect. Undoubtedly the availability of various technologies and the manifold advantages of FDT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in near future.

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