FORMULATION AND EVALUATION OF FAMOTIDINE ORO-DISPERSIBLE TABLETS

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ABSTRACT

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics.tablets constitute an innovative dosage forms that overcome the problems of swallowing and provides a quick onset of action. The purpose of this study was to formulate and evaluate Orodispersible tablet of famotidine using croscarmellose sodium and sodium starch glycolate as a superdisintegrant[1]. Tablets were prepared by direct compression technique. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausners ratio. The tablets were evaluated for hardness, uniformity of weight, friability, wetting time, water absorption ratio, disintegration time and dispersion time. *In vitro* release studies were performed using Disso-2000 (paddle method) in 900ml of pH 6.8 at 50rpm. The optimum formulation was subjected for stability studies and the chosen formulation was found to be stable.

KEYWORDS: Famotidine, Croscarmellose Sodium, Sodium Starch Glycolate, OrodispersibleTablets.

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INTRODUCTION

Famotidine is a H2 receptor antagonist1. A thiazole ring containing H2 blocker which binds tightly to H2 receptor and exhibit longer duration of action despite elimination2. Famotidine after oral administration has anonset of effect within 1 hr and inhibition of gastric secretion is present for the next 10-12 hrs3. Elimination is by renal and metabolic route. It is therefore important to decrease the dose of the drug for patient with kidney or renal failure[2,3]. Famotidine not only decrease both basal, food-stimulated acid secretion by 90% or more but also promote healing of duodenal ulcer[4,5].Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medications. Mouth dissolving tablets (MDT)disintegrate and are dissolving rapidly in the saliva without the need of water. Disintegrant play a major role in the disintegration and dissolution of MDT. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system thus enhancing the disintegration and dissolution[6,7].

MATERIALS AND METHODS

Famotidine was obtained from Geltec Labs Ltd., Bangalore, India. Crospovidone and mannitol were procured from Colorcon Pvt. Ltd, Goa, India. SSG were received as gift samples from S.D. Fine-Chem Ltd., Mumbai, India. Magnesium stearate and Talc were obtained from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Isopropyl alcohol was kindly provided by Qualigens Fine Chemicals, Mumbai, India.

Preparation of Famotidine Orodispersible Tablets:

The drug and the excipients were passed through #22-sieve. Weighed amount of drug and excipients except magnesium stearate and talc were mixed in a poly bag by geometric addition method for 20 minutes manually. The blend was then lubricated by further mixing with magnesium stearate and talc (#22-sieve). The mixture blend was subjected for drying to remove the moisture content at 40 to 45ºC, the mixture was blended with sweetener and the powder blend was then compressed on ten-station rotary punching machine using concave faced punches. Concave faced punches measuring 8 mm diameter were used.

Table No: 1. Formulation of FamotidineOrodispersible tablets.

INGREDIENTS(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	40	40	40	40	40	40	40	40	40
Sodium Starch Glycolate	6	12	18	-	-	-	2.5	5	7.5
Crospovidone	-	-	-	6	12	18	2.5	5	7.5
Microcrystalline Cellulose	35	35	35	35	35	35	35	35	35

Saccharin Sodium	8	8	8	8	8	8	8	8	8
Mannitol	105	99	93	105	99	93	106	101	96
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	4	4	4	4	4	4	4	4	4
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Menthol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	200	200	200	200	200	200	200	200	200

Compatibility Studies by FT-IR Studies:
It is one of the most powerful analytical technique for chemical identification of drug[8,9]. The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Evaluation of Granules;
Prior to compression, granules were evaluated for their characteristic parameters, such as Bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose[10]. The angle of repose was determined by the fixed funnel method. Bulk density, tapped density, Carr's index and Hausner's ratio were calculated using tap density apparatus (Electrolab, USP)[11].

Evaluation of Tablets:

The prepared tablets were evaluated for uniformity of weight using 20 tablets. Hardness, thickness and friability were measured with Pfizer hardness tester, verniercalliper and Roche friabilator respectively. The results were expressed as mean ± Standard deviation[12-14].

In-*vitro* Dissolution Study:[15,16]
In vitro dissolution studies were carried out using USP dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer, maintained at 37 ± 0.5°C. 10 ml of the sample was withdrawn at suitable time intervals and immediately replaced with an equal volume of 6.8 pH buffer to maintain the volume constant. The samples were filtered through a 0.45 µm membrane filter, diluted sufficiently and analysed at 265 nm using UV/Visible double-beam spectrophotometer .

Disintegration Time:[17,18]
The test was carried out on six tablets using distilled water at $37^0C \pm 2^0C$ was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Wetting Time:

Five circular tissue paper of 10cm diameter were placed in a petridish with a 10cm diameter. 10 ml of simulated saliva pH (phosphate buffer pH 6.8) was poured into the tissue paper placed in the petridish. Few drops of eosin solution were added to the petridish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.[19]

Water Absorption Ratio:
The weight of the tablet before keeping in the petridish was noted (Wb). Fully wetted tablet from the petridish was taken and reweighed (Wa)[20]. The water absorption ratio R can be determined according to the followingformula.

R= (Wa – Wb)/Wa x 100

Estimation of Drug Content:

Ten tablets from each formulation were powdered. Thepowder equivalent to 100mg of famotidine was weighedand dissolved in phosphate buffer pH 6.8 in 100mlstandard flasks. From this suitable dilution was preparedand the solution was analyzed at 265nm using UV doublebeam spectrophotometer (Elico SL164) using pH 6.8 as blank[20].

Stability Studies:

Stability studies were carried out at 25^0 C and 40^0 C for the selected formulation for three months.The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25^0 C and 40^0 C for three months and evaluated for their physical appearance, hardness and in vitro drug release at specified intervals of time[20].

RESULTS AND DISCUSSION

The data obtained from angle of repose for all the formulations were found to be in the range of22.52°and29.32°. All the formulations shows the angle of repose less than 30°, which reveals good flow property for compression into tablets. Loose bulk density (LBD) and tapped bulk density (TBD) forth blend was performed. The loose bulk density variedfrom0.3738 ± 0.019g/cm^3 to0.4276 ± 0.089 g/cm^3. The tapped density for the entire formulation blend varied from 0.4837 ± 0.032g/cm^3 to 0.4531 ± 0.042 g/cm^3. Hausner's ratio of entire formulation showed between 1.0907 ± 0.045to 1.2121± 0.082 indicates better flow properties. The results of Carr's consolidation index or compressibility index(%) for the entire formulation blend drangedfrom12.83 ± 1.83 %to15.54 ± 1.72%. All the formulations show good results which indicate good flow properties. The peaks obtained in the spectra of each sample of drug and excipient correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. Tablets are in circular, flat shape and white in color. The directly compressed tablets showed hardness of 2.7 kg/cm^2 to 3.5 kg/cm^2. The friability values ranges from 0.42to0.60% .The friability study results were tabulated.

The weight variation for all the formulations was found to be in the range 198.30±1.11 to 200.50 ± 1.71 mg. Allthetabletspassedweightvariationtestastheaveragepercentageweight variation was within 7.5%i.e. in thepharmacopoeiallimits.Themeanthicknesswasalmostuniforminalltheformulationsand values ranged from3.95±0.10mmto4.10±0.12mm.The standard deviation values indicated that all the formulations were within the range. The percentage drug content of the tablets was found to be between 96.92 ± 0.65 to 99.26 ± 0.79 % of Famotidine. The results were within the range and that indicated content uniformity of drug in all formulations. The wetting time of formulations were found to be in the range of 40 to79sec. Wetting time was closely related to time of *in vitro* disintegration. As the concentration of the superdisintegrants increased, wetting time decreased up to optimum concentration of superdisintegrants. FormulationsF9with super disintegrant Crospovidone and SSG showed least wetting time of 40secs. Formulations with Crospovidone and SSG have shown least wetting times of all, attributing to the high wicking, swelling and rapid

dispersing property. The formulations shows water absorption ratio in the range 60 ±1.18 to 85 ±1.13. The values of *in vitro* dispersion time for the formulations prepared were tabulated in table. As the concentration of super disintegrants increased, the *in vitro* time for dispersion decreased up to optimum concentration. The *in vitro* dispersion times for the formulations were 25 to 41 sec respectively. The formulation F9has shown the least time for *in vitro* dispersion i.e. 25 seconds. The *in vitro* disintegration time of formulations were found to be in the range of 23 ±1.36 to 49 ±2.01 fulfilling the official requirements. Disintegrating study showed that the disintegrating times of the tablets decreased with increase in the concentration of the superdisintegrants SSG and Crospovidone up to optimum concentration.

DissolutionStudy:

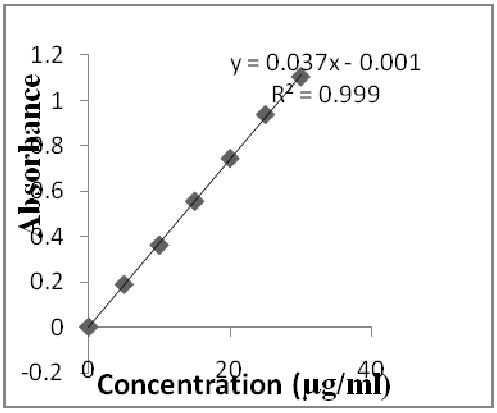
From the *in vitro* dissolution study data, it was found that the drug release increased as the concentration ofsuperdisintegrants increased irrespective of the superdisintegrant employed. The maximum drug release for the directly compressed tablets with superdisintegrants 9% SSG shows 87.16% drug release, 9% CP shows 90.02%, 4.5% of SSG and 4.5% of CP shows maximum drug release of 97.18%. Stability Studies:

The slight increase in the disintegration time was observed, this may be due to increase in hardness of the tablets during storage. No significant changes in other parameters were observed in the tablets, the formulation was within the acceptable limits.

Table No:2 Standard Calibration Curve of Famotidine at 265 nm in pH 6.8 phosphate Buffer

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.1981
3	10	0.3522
4	15	0.5682
5	20	0.7468
6	25	0.9370
7	30	1.1162

Figure 1: Standard Calibration curve of Famotidine in pH 6.8Phosphate Buffer



Results for pre-compression parameters

Table-3 Pre compression parameters of powder blend

Batch Code	Angle of Repose(°)*	Bulk Density (g/cc)*	Tapped Density	Carr's Index (%)*	Hausner's Ratio*
F1	28.69 ±0.232	0.3738±0.019	0.4531± 0.017	14.24± 1.72	1.2121±0.082
F2	29.32 ±0.302	0.4102±0.016	0.4539 ±0.024	14.08± 1.81	1.1066±0.025
F3	24.21± 0.297	0.3827±0.034	0.4509± 0.039	13.63± 1.63	1.1782±0.038
F4	26.32± 0.338	0.4033±0.014	0.4763± 0.017	14.61± 1.67	1.1810±0.026
F5	28.14± 0.175	0.4152±0.045	0.4792± 0.026	12.32± 1.53	1.1541±0.023
F6	27.91± 0.192	0.4072±0.009	0.4837± 0.032	15.54± 1.72	1.1878±0.033
F7	26.54 ±0.239	0.3747±0.049	0.4681± 0.022	14.87± 1.27	1.2491±0.062
F8	24.59 ±0.365	0.4276±0.089	0.4664 ±0.037	13.12± 1.37	1.0907±0.045
F9	22.52± 0.129	0.4104±0.019	0.4532± 0.042	12.83± 1.83	1.1042±0.038

Results for drug polymer interaction studies- FTIR studies:

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

Drug-Excipient Interactions Studies by FT-IR:

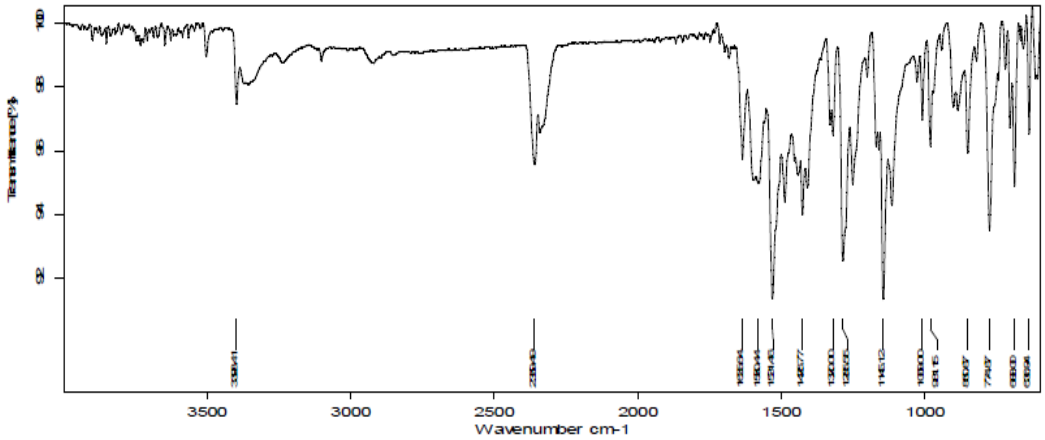


Figure No. 2: IR spectrum of Famotidine

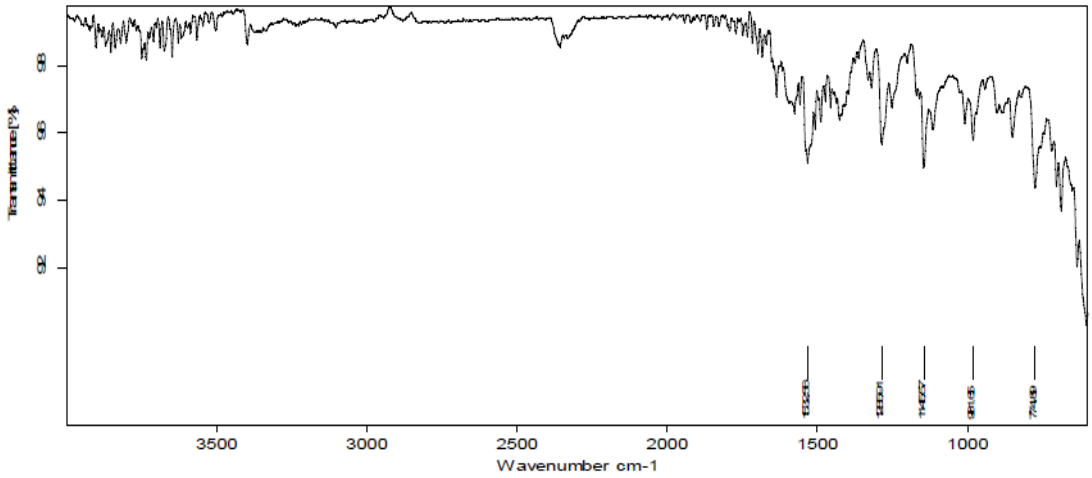


Figure No. 3: IR spectrum of Famotidine+ SSG

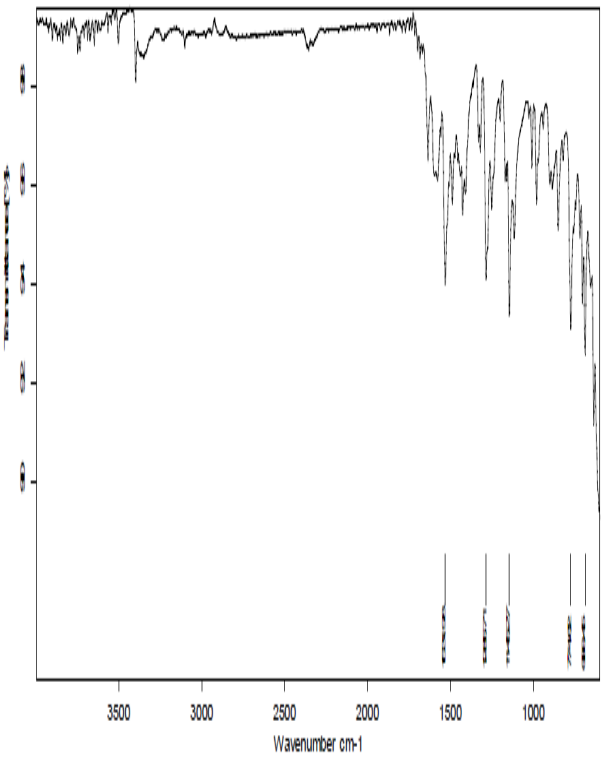


Figure No. 4: IR Spectrum of Famotidine+ Crospovidone

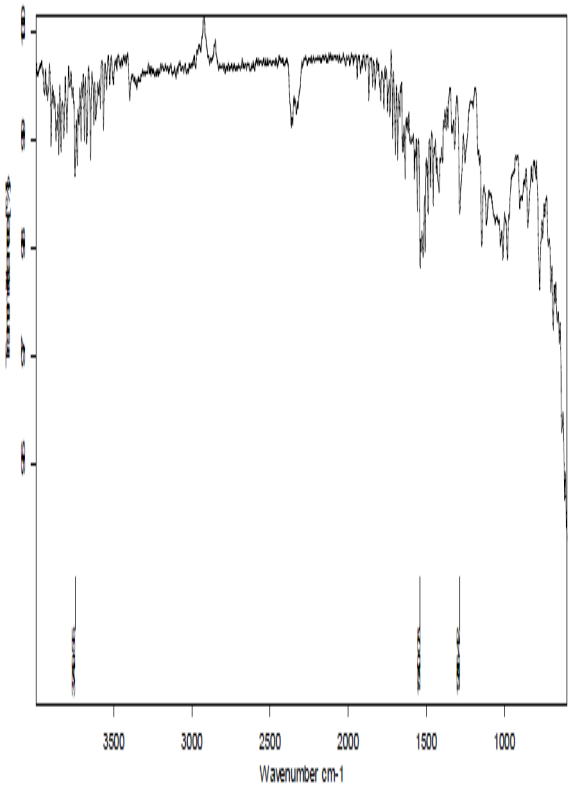


Figure No. 5: IR spectrum of Famotidine + Mannitol

Table No. 4: Interpretation of IR spectrum of pure Famotidine and combination with Polymers

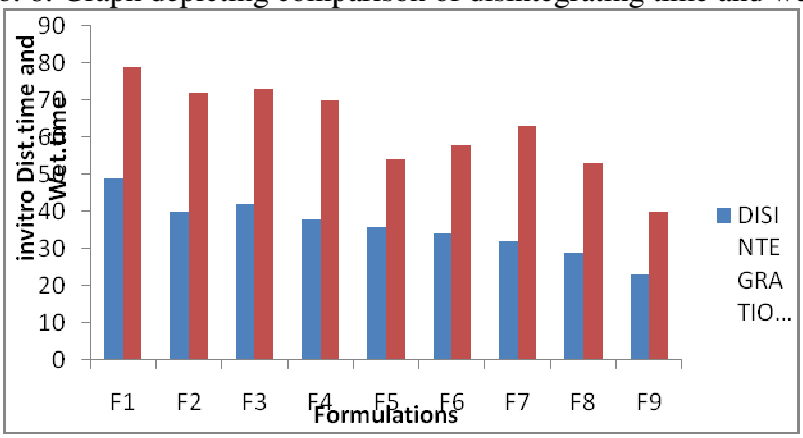
Compound Frequency (cm^{-1})	ABSORPTION PEAKS (cm^{-1})			
	Actual Frequency	PureDrug	Drug + SSG	Drug + CCS
N-H str	3420-3620	3440.93	3575.16	3596.18
O-H str	3260-3400	3336.66	3300.29	3264.92
C-Hstr	2900-3300	2932.66	2929.40	2917.12
$N-H_1$	2645	-	2152.79	2164.79

Table No.5: Post-Compression Parameters of formulations byDirectCompression:

Batch Code	In-vitro dispersion time*(sec)	In-vitro Disintegration Time*(sec)	Wetting time*(sec)	Water absorption ratio*	Drug Content* (%)
F1	41± 1.32	49± 2.01	79± 2.02	67± 1.43	98.05± 1.71
F2	33± 1.27	40±1.63	72± 2.07	62± 1.29	99.15± 1.43
F3	38± 1.49	42± 1.79	73± 1.67	60± 1.18	97.32± 0.56
F4	35± 1.37	38± 1.63	70± 1.73	61±1.16	96.92± 0.65
F5	32± 1.42	36± 1.57	54± 2.18	68±1.15	97.87± 0.54
F6	27± 1.53	34± 1.42	58± 3.18	79±2.23	98.46± 0.71
F7	30± 1.23	32± 1.38	63± 1.02	76± 2.01	99.26± 0.79
F8	26± 1.18	29 ± 1.42	53± 1.02	78± 1.75	98.32± 0.88
F9	19± 1.22	23± 1.36	40± 1.25	85± 1.13	98.76± 0.36

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

Figure No. 6: Graph depicting comparison of disintegrating time and wetting time



RESULTS FOR DISSOLUTION STUDY

Results of Dissolution study for the formulations

Table No. 7: In vitro release characteristics of formulations:

F.code	% Drug Release				
	3mins	6mins	9mins	12mins	15mins
F1	19.52	41.52	63.75	71.32	84.52
F2	23.81	46.35	62.86	79.16	86.65
F3	20.52	48.48	67.18	77.49	87.16
F4	17.86	43.25	64.39	72.23	88.13
F5	22.59	50.28	71.52	75.05	89.14
F6	27.72	54.62	55.32	79.03	90.02
F7	21.32	39.18	62.23	80.05	91.03
F8	25.54	57.32	69.42	82.23	92.82
F9	33.85	57.68	71.32	85.25	97.18

Figure No. 7: Drug release profile of formulations containing SSG (F1-F3)

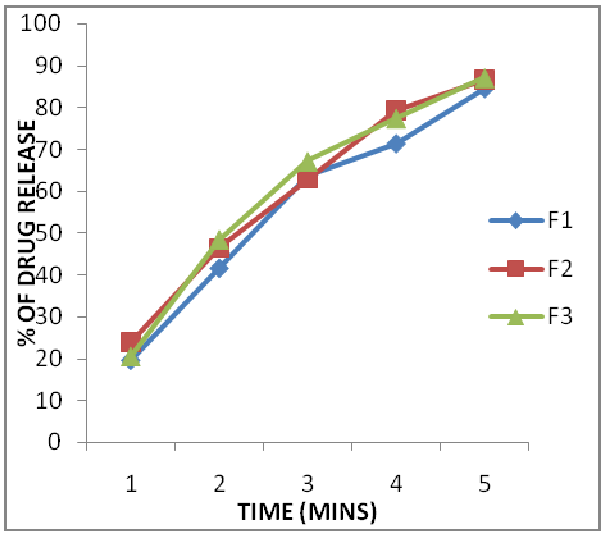


Figure No. 8: Drug release profile of formulations containing Crospovidone (F4-F6)

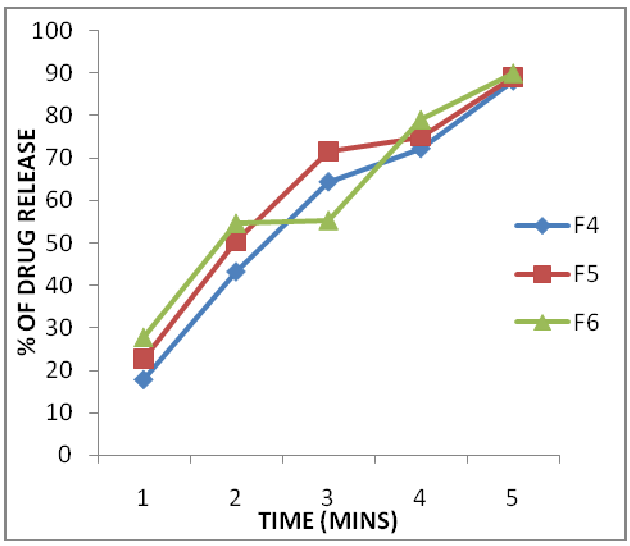
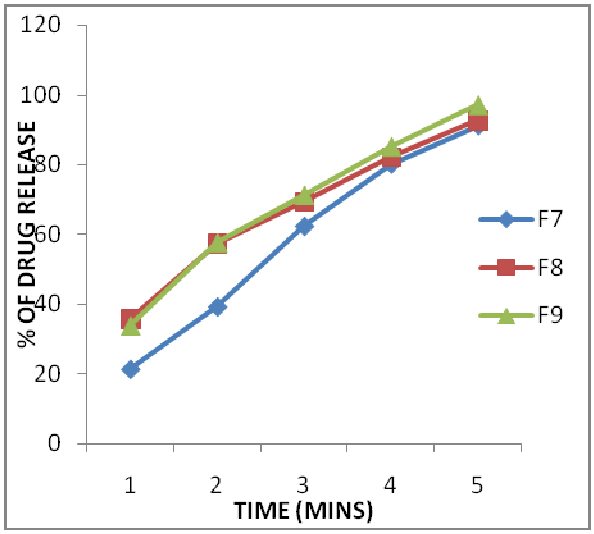


Figure No. 9: Drug release profile of formulations containing SSG+CPV (F7-F9)



Result of Stability Study

The promising formulations were subjected to short term stability study by storing the formulations at 40^0C/75% RH up to one month. The formulation F9 was selected. After one month the tablets were again analyzed for the hardness, *in vitro* disintegration time, wetting time and percentage drug release.

Table No. 8: Result for 25°C for three months

Sr. No	Month	Formu	Hardness (kg/cm^2)	*In vitro* disintegration	Wetting time (sec)	%Drug Release
1	1	F9	No change	No change	No change	No change
2	2	F9	3.3	25	42.5	95.86
3	3	F9	3.0	27	44	95.40

Table No. 9: Result for 40°C for three months

Sr. No	Months	Formulation c	Hardness (kg/cm^2)	*In vitro* disintegration time (sec)	Wetting time (sec)	%Drug Release
1	1	F9	No change	No change	No change	No change
2	2	F9	3.3	27	44.5	94.65
3	3	F9	3.4	28	46	92.85

CONCLUSION**:**

The release of drug from the F-9 formulation was quickwhen compared to F-3 and F-6 formulation. It shows thatthe combined effect of cross crospovidone and sodium starch glycolate gives synergistic effect. Undoubtedly the availability of various technologies and the manifold advantages of MDT 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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