International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 1 | JAN-MAR| 2018 | 598-605
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

FORMULATION AND EVALUATION OF FIXED DOSE COMBINATION OF MEBEVERINE AND SIMETHICONE FOR IRRITABLE BOWEL SYNDROME

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ABSTRACT

Fixed dose drug combination (FDCs), are combinations of two or more active drugs in single dosage form. Present research aims at the formulation and development of fixed dose combination (FDC) of Mebeverine & Simethicone for treatment of Irritable bowel syndrome. The irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by altered bowel habits and abdominal pain having bloating. Mebeverine is a drug used to alleviate some of the symptoms of irritable bowel syndrome. It works by relaxing the muscles in and around the gut whereas Simethicone facilitates gas elimination by its deforming activity. Various formulations were developed using polymers HPMCk100, ethyl cellulose, Xanthan gum and guar gum each of 100mg, 150mg & 200mg. Formulation F6 containing HPMC k100 of 150 mg which has shown the maximum release of Mebeverine in one hours was considered as optimized formula.

KEY WORDS

Magnesium Aluminometa silicate, Fixed dose drug combinations, Irritable bowel syndrome, Mebeverine and Simethicone.

1. INTRODUCTION

A 'Fixed Dose Combination (FDC)' is a combination of two or more active ingredients in a fixed ratio of doses. Use of FDCs is associated with many advantages like synergistic action and increased efficacy (e.g. cotrimoxazole), reduced adverse effects (e.g. levodopa with carbidopa, thiazides with potassium sparing diuretics), reduced pill burden and cost of therapy and hence better patient compliance (e.g. anti-tubercular drug combinations) [(3)]. However, certain disadvantages like incompatible pharmacokinetics, inflexible dose ratio, increased toxicity and cost, contraindication of one component of the FDC decreased their utility. Adverse effect of any one component also limits their use.

Present research aims at the formulation and development of fixed dose combination (FDC) for treatment of Irritable bowel syndrome.

The irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by altered bowel habits, abdominal pain and bloating. In view of the above described characteristics of IBS the rationale of a combination product which includes two compounds (effective in relieving the symptoms of the disease when given alone) acting on two of the main proposed pathophysiological mechanisms of the disease is rather strong. Mebeverine is a drug used to alleviate some of the symptoms of irritable bowel syndrome. It works by relaxing the muscles in and around the gut [(6)].

Simethicone facilitates gas elimination by its deforming activity.

Mebeverine is an antispasmodic that has been successfully used in the management of IBS for many years. Mebeverine is a musculotropic agent that has antispasmodic activity and regulatory effects on the bowel function. Mebeverine helps treat symptoms of intestinal disorders and irritable bowel problems, such as spastic colitis, spastic constipation, colon irritation and mucous colitis, with almost no serious adverse events and a significant improvement in the quality of life [(12)].

Simethicone is a chemical inert mixture of polydimethylsiloxane (Simethicone) and silica gel which is not absorbed by the gastrointestinal tract, it is physiologically inactive and devoid of toxic effects [(8)]. Due to its property of decreasing surface tension of a liquid, it has been frequently used orally as a single agent in patients with flatulence.

2.1 MATERIALS

Simethicone, Mebeverine & Magnesium Aluminometa silicate were Gift samples obtained from the Euro Drug Ltd, HYD. Povidone K-90, ethyl cellulose, guargum were obtained from Mark health care and HPMC k 100, xanthan gum was obtained from tiwari chemicals. Magnesium Stearate Talc Purified were obtained from SD Fine Chem Ltd., Mumbai.

2.2 METHODOLOGY

2.2.1 FORMULATION DEVELOPMENT:

Preparation of Tablets: Tablets of Mebeverine Hydrochloride and Simethicone were prepared by wet granulation method. This was prepared in two steps i.e extra granular portion and granular portion and then required quantity of granular and extra granular portion were mixed and finally lubricated with Talc and magnesium stearate and finally compressed by using 16 stationary tablet compression machines. (Punch number 10/20mm).

Required amounts of Mebeverine Hydrochloride & a part of required Microcrystalline cellulose were weighed and mixed (extra-granular Portion).

Simethicone and Magnesium Aluminometa silicate were weighed and passed through sieve. The blend was mixed and remaining part of Microcryatalline cellulose and polymers were added to the above Simethicone and Magnesium Aluminometa silicate mixture. Then required quantity of Povidone K-90 + IPA Solution 5%was added until the damp mass was formed, then the wet mass passed through 22-mesh sieve. The granules were dried at 50^0 C. Then the dried granules were passed through 25-mesh sieve. These granules were then mixed with extra-granular Portion i.e Mebeverine Hydrochloride and Microcrystalline cellulose and then blended with magnesium stearate and talc. Precompression blend was evaluated. The precompression blend was then compressed into tablets having an average weight of 1300mg using 16 station rotary tablet compression.

2.2.2 Evaluation of pre-compressed blend

a) Angle of repose:

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured, and angle of repose was calculated using the following equation.

$$\tan \theta = h/r, \text{ Therefore, } \theta = \tan h/r$$

Where, θ = angle of repose, h = height of the pile, r = radius of the pile base

b) Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula: Weight of the powder Bulk density (pb) = Bulk volume of the powder

Weight of the powder Tapped density (p,) = Tapped volume of the powder

c) Carr's index: -

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by:

Carr's index (%) = [(TBD - LBD) x 100]/TBD

Where, LBD = weight of the powder/volume of the packing TBD = weight of the powder/tapped volume of the packing.

Hausner's Ratio: It is the ratio of tapped density to the bulk density

2.2.3 Evaluation of Mebeverine and Simethicone tablets

a) Tablet Hardness:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

b) Tablet Thickness:

Thickness of tablets was important for uniformity of tablet size. The thickness of tablets was determined using Digital Vernier Caliper. It is expressed in mm.

c) Friability: -

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were re- weighed and the percentage loss in tablet weight was determined.

% loss = Initial wt. of tablets - Final wt. of tablets x 100
Initial wt. of tablets

d) Content Uniformity:

The Mebeverine content in tablets was determined by powdering 10 tablets in each batch. Powder equivalent to 100 mg of Mebeverine was dissolved in 0.1 N HCL of filtrate was further diluted to 100 ml with 0.1 N HCL and it was determined by spectroscopy at 263 nm.

e) Weight variation:

Twenty tablets were weighed individually, and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table) and none deviates by more than twice that percentage.

f) Dissolution studies:

The release rate of Mebeverine from tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using 900 ml of 0.1 N HCl (pH 1.2) for 2 h at 37 ± 0.5 °C. 10 ml of the sample was withdrawn at regular intervals and replaced with the same volume of fresh dissolution medium. The amount of drug released was detected by using UV-Visible spectrophotometer at λ_{max} 263nm.

2.2.4 FORMULATION OF TABLETS

Table 1. FORMULATION OF TABLETS

S. No.	Name of the Raw Material For Tablets	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Extra Granular Portion													
1	Mebeverine Hydrochloride	135	135	135	135	135	135	135	135	135	135	135	135
2	Microcrystalline cellulose	100	100	100	100	100	100	100	100	100	100	100	100
Granular Portion													
3	Simethicone	300	300	300	300	300	300	300	300	300	300	300	300
4	Magnesium Aluminometa silicate	330	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**
5	EC	100				150				200			
6	HPMC k100		100				150				200		
7	Xanthan gum			100				150				200	
8	Guar gum				100				150				200
9	Povidone K-90 + IPA Solution 5%	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
7	Microcrystalline cellulose	320	320	320	320	280	**280**	**280**	**280**	230	**230**	**230**	**230**
10	Talc Purified	10	10	10	10	10	10	10	10	10	10	10	10
11	Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
	Total	1300	1300	1300	1300	1300	1300	1300	1300	1300	1300	1300	1300

All quantities are in Milligrams

3 RESULTS &DISCUSSION

Table 2. Standard graph of Mebeverine Hydrochloride in 0.N HCl

CON Mcg/Ml	Absorbance
0	0
4	0.115
8	0.211
12	0.313
16	0.414
20	0.507
24	0.584
28	0.689
32	0.767
36	0.848

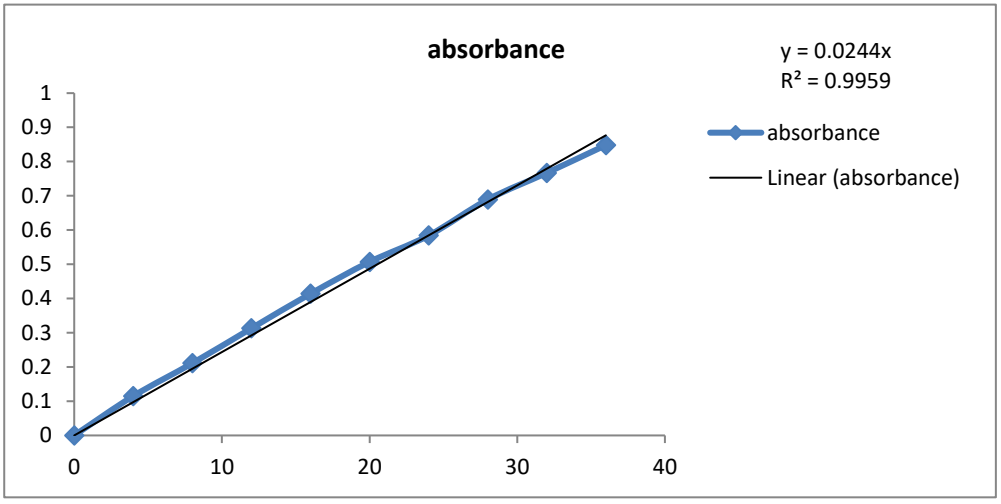

Figure.1. Standard graph of Mebeverine Hydrochloride in 0.N HCl

Table 3. Physical Properties of Precompression Blend

Formulation code	Angle of repose θ	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner's ratio
F1	24.3	0.415	0.465	10.75	1.12
F2	23.89	0.40	0.469	14.71	1.17
F3	22.68	0.396	0.474	13.08	1.19
F4	23.76	0.409	0.480	16.45	1.17
F5	24.29	0.403	0.483	16.56	1.19
F6	24.3	0.504	0.581	13.25	1.15
F7	24.2	0.425	0.489	13.08	1.15
F8	24.56	0.404	0.440	8.18	1.11
F9	22.84	0.468	0.551	15.06	1.17
F10	25.64	0.468	0.521	10.17	1.11
F11	21.58	0.398	0.481	17.25	1.20
F12	24.29	0.391	0.465	15.91	1.189

From the above pre-compression parameters, it was clear evident that dry blend has good flow properties. These are in the limits between 1.12 - 1.20 for Hausner's ratio, less than 30 angle of repose and cars index between 8 – 17.

Table 4: Tablet Physical Evaluations

Formulation code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability %	Content uniformity (%)
F1	1294	5.2	5.8	0.53	97.8
F2	1288	5.5	5.7	0.66	98.3
F3	1290	5.1	5.8	0.50	98.6
F4	1305	5.2	5.6	0.53	98.0
F5	1298	5.4	5.5	0.49	97.7
F6	1307	5.3	5.6	0.63	98.2
F7	1315	5.0	5.5	0.57	99.4
F8	1280	5.5	5.8	0.42	98.6
F9	1315	5.4	5.6	0.43	99.1
F10	1302	5.6	5.5	0.52	99.5
F11	1284	5.2	5.4	0.48	99.8
F12	1292	5.4	5.7	0.45	98.8

Results of evaluation of post-compression parameters are as follows. Hardness of tablets are in the range of 5.0-5.6 kg/cm2, friability was in the range of 0.42- 0.66, thickness of uncoated tablets were found to be in the range 5.4-5.8. Weight of the tablets was found to be from1288mg-1315mg and % drug content were in range of 97.8% - 99.8%.

Table 5. Cumulative % drug release from formulations containing HPMC K100M & Ethyl cellulose

Time In Minutes	Cumulative % drug release					
	HPMC K100M			ETHYLCELLULOSE		
	F2	F6	F10	F1	F5	F9
5	35.28±1.232	25.81±1.37	21.35±1.77	40.64±1.08	31.24±2.45	21.83±0.56
10	49.78±0.633	37.69±1.78	29.18±1.65	65.89±1.29	41.88±1.33	30.91±1.68
15	64.35±0.671	49.38±2.32	45.38±2.37	85.52±1.31	60.67±1.97	47.86±1.04
20	76.23±1.56	60.59±1.89	54.33±1.89	99.84±1.37	73.89±1.71	60.67±1.49
25	87.74±1.8	69.95±1.65	62.64±1.91	-	82.58±1.62	67.79±1.92
30	96.98±1.73	79.62±1.29	69.49±1.09	-	90.84±1.30	75.46±2.63
40	-	89.21±1.61	76.77±0.39	-	99.62±2.39	81.73±0.79
50	-	95.73±2.49	82.15±0.71	-	-	88.42±1.72
60	-	99.82±1.89	87.89±1.82	-	-	93.63±1.96
70	-	-	92.64±1.79	-	-	98.5 ±1.59
	-	-	95.71±1.59	-	-	-
90	-	-	97.98±2.79	-	-	-

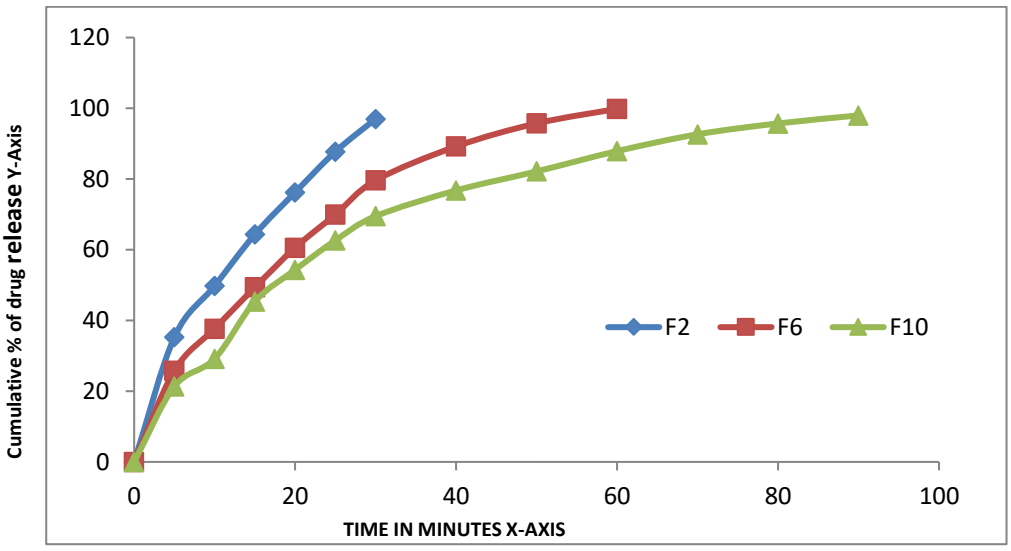

Figure.2. Cumulative % drug release from formulations containing HPMC K100M

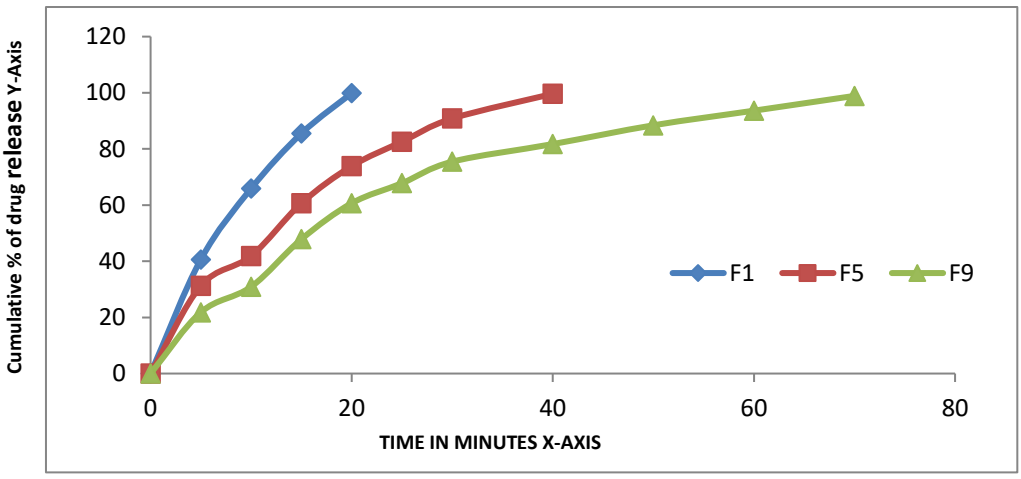

Figure.3. Cumulative % drug release from formulations containing Ethyl cellulose

Table 6. Cumulative % drug release from formulations containing Xanthan gum& Guar gum

Time In Minutes	Cumulative % drug release					
	Xanthan gum			Guargum		
	F3	F7	F11	F4	F8	F12
5	21.85±1.23	18.56±1.88	15.31±1.91	23.76±1.37	20.35±1.77	16.74±.168
10	28.58±0.99	24.68±1.29	22.78±1.69	32.38±1.76	27.61±1.63	24.19±1.39
15	45.43±1.54	34.43±1.73	33.69±2.34	48.64±1.65	37.25±1.29	35.74±1.81
20	55.33±1.48	42.89±1.23	39.57±1.48	57.98±1.33	45.34±131	42.93±1.55
25	63.41±1.89	48.49±1.43	45.09±1.67	65.42±1.45	51.56±1.22	49.16±2.49
30	70.29±1.75	54.38±2.48	50.80±1.45	72.15±1.89	57.18±1.89	55.25±1.91
40	77.62±2.10	59.17±2.76	55.98±1.63	79.60±2.34	62.58±1.33	60.38±1.72
50	83.51±2.2	64.73±3.25	59.78±2.14	84.45±1.79	67.23±0.35	64.97±1.63
60	88.89±1.89	69.90±1.98	63.18±2.52	89.22±1.32	71.40±1.81	68.73±1.29
70	93.64±1.98	75.97±1.69	69.23±2.78	94.05±1.56	76.29±2.47	72.37±1.31
80	97.71±1.78	81.73±2.34	73.48±1.73	97.91±1.85	82.16±1.19	75.85±1.22
90	98.98±1.69	85.29±1.48	78.11±1.64	99.59±2.31	87.49±2.15	79.31±1.89
100	-	89.62±1.67	82.04±1.55	-	91.36±1.68	84.29±1.33
110	-	92.51±1.82	85.18±1.78	-	94.09±1.39	86±2.35
120	-	95.89±1.71	87.25±1.89	-	97.73±1.21	89.9±2.97

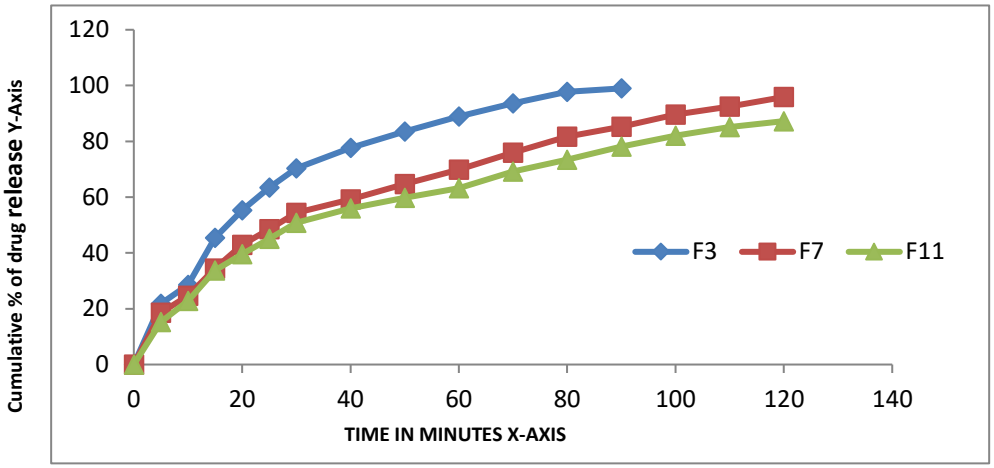

Figure.4. Cumulative % drug release from formulations containing Xanthan gum

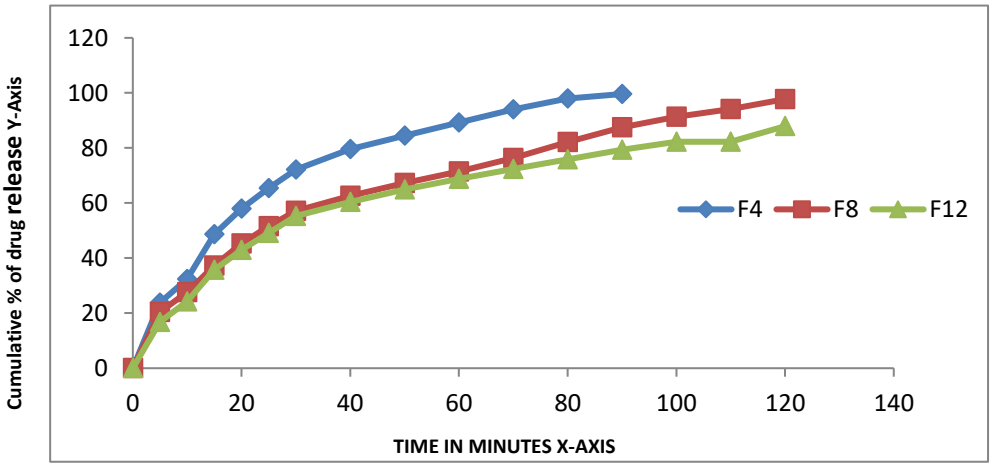

Figure.5. Cumulative % drug release from formulations containing Guar gum

Based on the cumulative % drug release F6 formulation was considered the best as the maximum release of drug was within one hour. In few formulations the drug was released within 30min and in other formulations the drug release was retarded and took more than two hours.

CONCLUSION:

The present research formulation contains two drugs Mebeverine & Simethicone. During the formulation, Mebeverine was mixed with the some of the total part of MCC and it was considered extra granular part. This was then mixed with granular part Containing Simethicone. As Simethicone is an oil, it was mixed with absorbent and to maintain the integrity of the tablets a small percentage of different polymers as binding agents along with pvp-k90. In the formulation i.e., granular part contains the Simethicone which cannot be analyzed using analytical techniques. The selection of optimized formulation is based on the percentage of release of Mebeverine. As Mebeverine is immediate release and the analysis of the Simethicone is not possible. The formulation which is releasing the maximum percentage of Mebeverine in one hour is considered as the optimized formula. As a part of polymers were used it might have affected or retarded the drug which is present in the extra-granular portion i.e. Mebeverine. F6 formulation containing HPMC k100 of 150 mg which has shown the maximum release of Mebeverine in one hours was considered as optimized formula.

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