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FORMULATION AND EVALUATION OF MEBEVERINE HYDROCHLORIDE SUSTAINED RELEASE TABLETS

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ABSTRACT

The present research work is aimed to design oral twice a daily sustained release matrix tablets of Mebeverine hydrochloride 135mg, used for treating or preventing spasmodic conditions of the lower gastrointestinal tract which can release the drug for 10 to 12 hours. The tablets were prepared by the Wet granulation method using varying concentrations of sustained release polymers HPMC, Eudragit and Ethyl cellulose. The compatibility of the polymers was ruled out by FT-IR studies and found to be compatible. Total nine formulations were prepared. The Mebeverine hydrochloride powder and the powder-blends of tablets were evaluated for their physical properties like angle of repose, bulk density and compressibility index and found to have good flow property. The prepared tablets were evaluated for in process and finished product quality control tests including appearance, dimensions, weight variation, hardness, friability, drug content, and *in vitro* drug release. The dissolution medium used was pH 6.8 phosphate buffer. All formulations showed acceptable pharmaco-technical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated all formulations released up to 12hours and formulation containing Ethyl cellulose (5%) i.e. F_7 was the most successful formulation with 96.72% drug release at the end of 12 hours.

Key words: Spasmodic; Irritable Bowel Syndrome; Mebeverine hydrochloride; Sustained release polymers; sustained release; matrix tablets formulation.

INTRODUCTION

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended [1]. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system [2-3].

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. Factors such as repetitive dosing and unpredictable absorption led to the concept of sustained drug delivery systems [4]. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ [5]. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects [5].

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the

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Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix®technology) and osmotic pumps with laser drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients.

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxy propylmethylcellulose (HPMC), Xanthan gum, Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Sodium alginate, Poly ethylene oxide and cross linked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface [6-7].

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder of unknown cause. Common symptoms include abdominal cramping or pain, bloating and gassiness, and altered bowel habits. Irritable bowel syndrome has also been called spastic colon, functional bowel disease, and mucous colitis. However, IBS is not a true "colitis." Irritable bowel syndrome is not contagious, inherited, or cancerous. It is estimated that 20% of adults in the U.S. have symptoms of IBS. It occurs more often in women than in men, and the onset occurs before the age of 35 in about half of the cases [8].

Mebeverine hydrochloride is highly soluble in water and is readily absorbed into the systemic circulation from upper GIT. It has mean plasma half time of 2.5 hrs. A dose of 135 mg Mebeverine appears to provide effective relief from the symptoms of irritable bowel syndrome but higher frequency of administration of drug may lead to high plasma concentration, resulting in to systemic side effects like decreased heart rate and blood pressure. Sustained release oral drug delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. Considering this aspect, it is desirable to develop a 12 hrs sustained release formulation of Mebeverine hydro chloride [9].

MATERIALS AND METHODS

Drug Excipient Compatibility-Fourier Transform Infrared Spectroscopy (FT-IR)

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-450 cm-1 using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due presence excipients.

Formulation development

Sustained release tablets containing 135mg of Mebeverine Hydrocloride drug were prepared with a total tablet weight of 200mg. Considering the preformulation studies and the literature survey conducted the excipients were selected and an attempt to produce Sustained release tablets with basic tablet properties was made [10-11].

Method

The drug and the excipients were passed through sieve no: 40 except lubricant and glidant. Weighed amount of drug and excipients (diluent, binder and sustained release agents) were mixed using Isopropyl alcohol as granulating agent. The blend was subjected to drying at 60^{o}c for 5hrs, for removal of moisture. After drying the powder is collected and the remaining excipients i.e. Glidant and lubricant were added (perceived through sieve no: 80) and was compressed by using flat faced punches in CADMACH 16 punches tablet punching machine. Round punches measuring 8.7mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly**.**

Evaluation of Sustain release tablets of Mebeverine Hydrocloride

Pre Compression Parameters

The powder blend is evaluated for various precompression parameters such as bulk density, tapped density, angle of repose, hausner's ratio, compressibility index to determine the flow properties of the powdered blend [12].

Post compression parameters

Weight variation test: 20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight. The Mean ± S.D. were noted.

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The tablets meet USP specifications if not more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit [13-15].

a) Thickness measurement

Randomly 10 tablets were taken from each formulation and their thickness was measured using a vernier caliper. The Mean ± S.D. were noted. The tablet thickness should be controlled within a ± 5% variation of standard value.

b) Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 5 - 7 kg/cm^2 is considered acceptable for uncoated tablets. The hardness for sustained release tablets should be preferably 4-6 kg/cm^2.

c) Friability

This test is performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated.

$$\% \text{ Friability} = \frac{(w1-w2)}{w1} \times 100$$

Where, W1 = Initial weight of the 20 tablets before testing, W2 = Final weight of the 20 tablets after testing.

d) Drug Content Uniformity

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to 100mg of mebeverine HCl was dissolved in 100 ml of methanol, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with methanol. Absorbance of this solution was measured at 263 nm using methanol as blank and content of drug was estimated.

Assay calculation: The amount of drug present was calculated by given formula,

$$\text{Assay} = \text{Avg. Wt.} \times \frac{\text{A1 x Std. Wt. x 1 x 100 x P x 100}}{\text{A2 x 100 x 100 x Sam. Wt. x 1 x 100 x LC}}$$

Where,

A1 - Sample Absorbance; A2 - Standard Absorbance; P - Potency of drug; LC - Label Claim**.**

e) Dissolution test

Dissolution test was carried out using USP rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900 ml) and was maintained at 37 ± 1^{0}C. Samples of 5ml were withdrawn at interval of every 30mins for 12hrs, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the Mebeverine hydrochloride at 263 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken [16-17].

Release kinetics

As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero, first-order, diffusion and exponential equations .The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation and Peppas-Korsemeyer's equation.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release [18].

RESULTS AND DISCUSSION

FT-IR Studies

In the present study, it has been observed that there is no chemical interaction between drug and the polymers used. It was observed that there were no changes in these main peaks in FT-IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The peaks obtained in the spectra's of each polymer correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. The results are shown in figures 1 to Figure 8.

EVALUATION OF TABLET BLEND

Pre-Compression Parameters

a. Bulk density and tapped density

The bulk density of the tablet blend was measured by Bulk Density apparatus. The bulk density and tapped bulk density for all formulations were found in the range of 0.39- 0.45 gm/cm^3 and 0.46- 0.52 gm/cm^3 respectively. The results are shown in Table 2.

b. Carr's index and Hausner's Ratio

The results of Carr's consolidation index or (%) compressibility index for the entire formulation blend ranged from 13 to 17 shows excellent compressibility index result in good to excellent flow properties. Hausner's ratio was found in the range of 1.15 to 1.19

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shows good flow and compressibility property. The results are shown in Table 2.

c. Angle of repose

It is determined by Fixed Funnel Method and is the measure of the flow ability of powder/granules. All the formulations prepared by wet granulation method showed the angle of repose was in the range of 22-25, which reveals the powder blend has excellent flow property. It is shown in Table 2.

EVALUATION OF TABLETS (POST COMPRESSION PARAMETERS)

a) Hardness test

The tablet hardness values ranged from 5.7 to 5.9 kg/cm^2 for all formulations and were almost same. The results are shown in Table 3.

b) Weight variation test

The entire tablet passes weight variation test as the average % weight variation was within the pharmacopoeial limit of 7.5%. It was found to be 198±1.3 mg to 203.5±1.72 mg. The results are shown in Table 3.

c) Thickness

In all formulations, tablet thickness was within mean ±5%. The thickness of all the tablets ranges between 3.8±0.02 mm to 3.9±0.04 mm. The results are shown in Table 3.

d) Friability test

The friability values were found to be within the limit (0.1 – 0.2%). The above evaluation parameter shows no significant difference between F1, F2, F3, F4, F6, F7, F8, F9 formulations. The results are shown in Table 3.

e) Drug content uniformity

The maximum drug content among all the formulations was found to be 101.48±0.5 and minimum % drug content from the all formulation was found to be 96.23±1.22. The results of drug content of all batches are shown in Table 3.

f) *In-vitro* Dissolution studies

All the 9 formulations of Mebeverine hydrochloride sustained release tablets are subjected to dissolution studies. Dissolution is carried out in USP 2 type apparatus at 50rpm in the volume of 900ml dissolution media (phosphate buffer pH 6.8) for 12hours. Formulations F1, F2, and F3 which contained HPMC shows percentage drug release of 93.71%, 87.69%, and 82.11% Formulations F4, F5, and F6 which contained Eudragit shows percentage drug release of 94.57%, 88.98%, and 83.83% respectively. Formulations F7, F8, and F9 which contained ethyl cellulose shows percentage drug release of 96.72%, 90.27%, and 82.54% respectively. The percentage drug release of all the formulations are shown in table 4 (F1-F5) and table 5 (F6-F9) and the comparative release profile are shown in figure 9. It has been observed that the dissolution rate was found to decrease linearly with increasing concentration of Sustained release agent.

Release kinetics

Different models like zero order, first order, higuchi's, and peppas plots were drawn for formulation f-7. The regression coefficient (r^2) value for zero order, first order, higuchi's, and peppas plots for formulation f-7 was found to be 0.942, 0.933, 0.966, and 0.999 respectively. The formulation f-7 follows first order release and peppas plot. Since the regression coefficient of peppas was 0.999 and slope 'n' value is less than 0.5 which confirms that the drug release through the matrix was fickian diffusion.

Fig 1. FT-IR spectra of Mebeverine hydrochloride

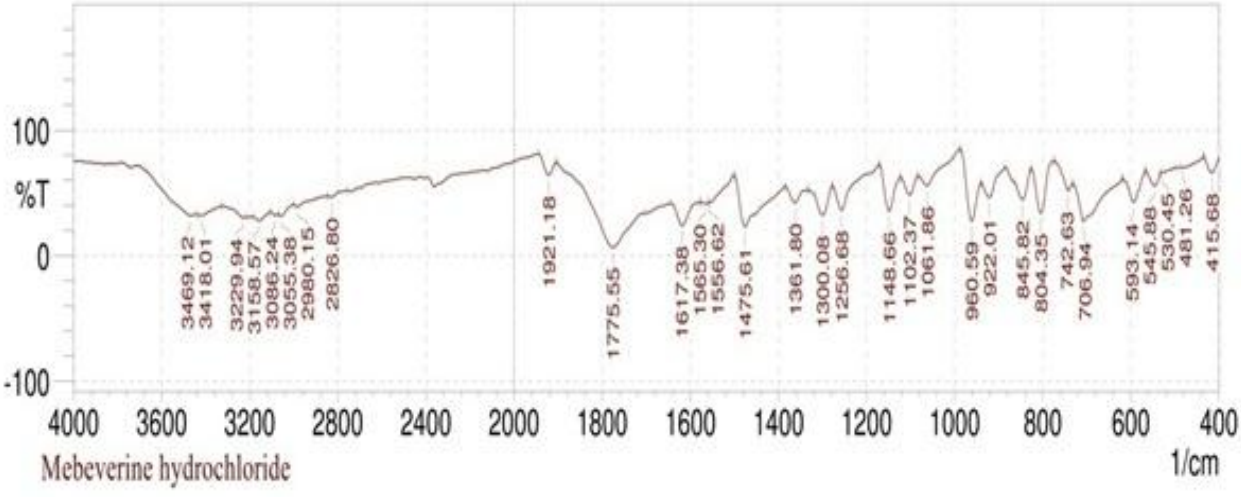

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Fig 2. FT-IR spectra of Mebeverine hydrochloride+ Di-calcium phosphate

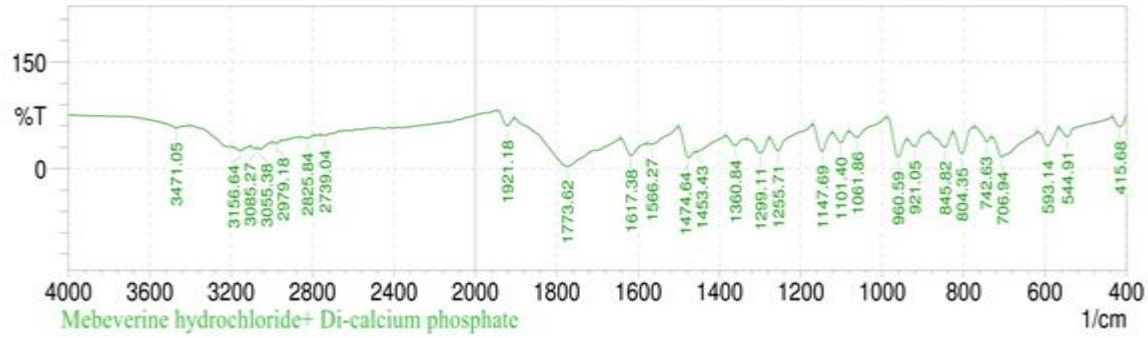

Fig 3. FT-IR spectra of Mebeverine hydrochloride+ Starch

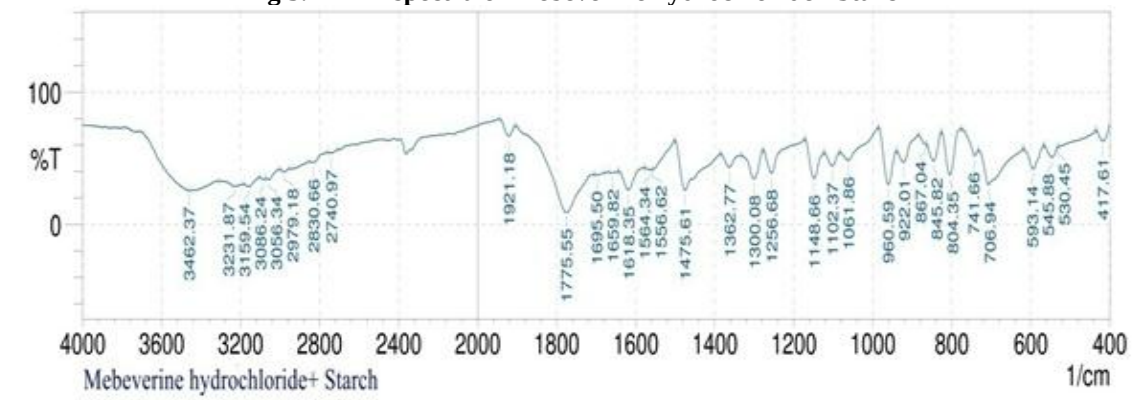

Fig 4. FT-IR Spectra of Mebeverine hydrochloride+ HPMC

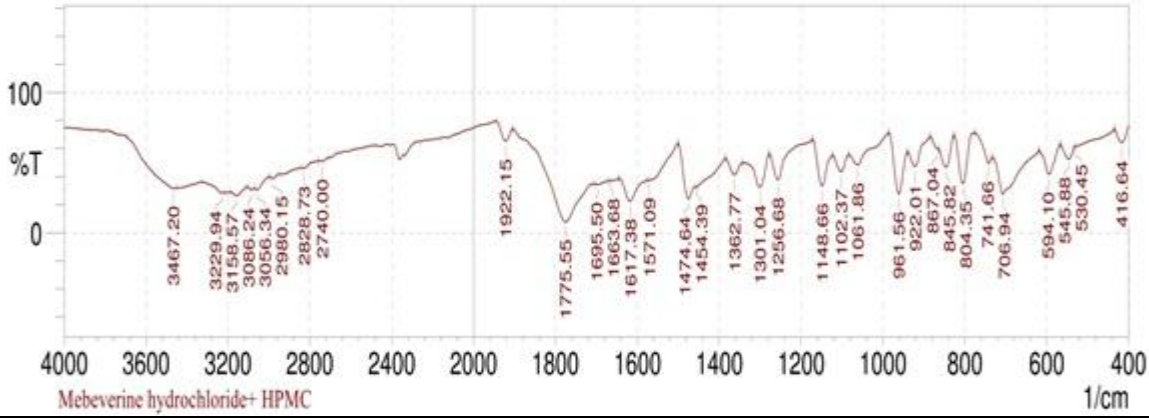

Fig 5. FT-IR spectra of Mebeverine hydrochloride+ Eudragit

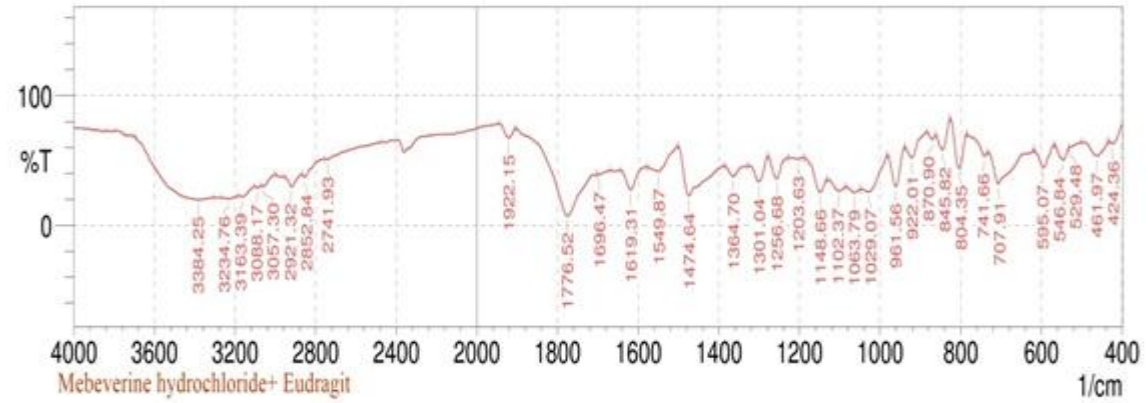

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Fig 6. FT-IR spectra of Mebeverine hydrochloride + Ethyl cellulose

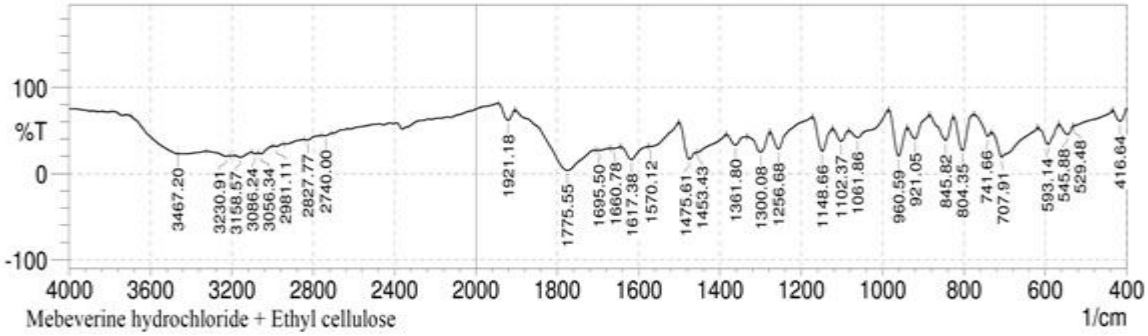

Fig 7. FT-IR spectra of Mebeverine hydrochloride+ Talc

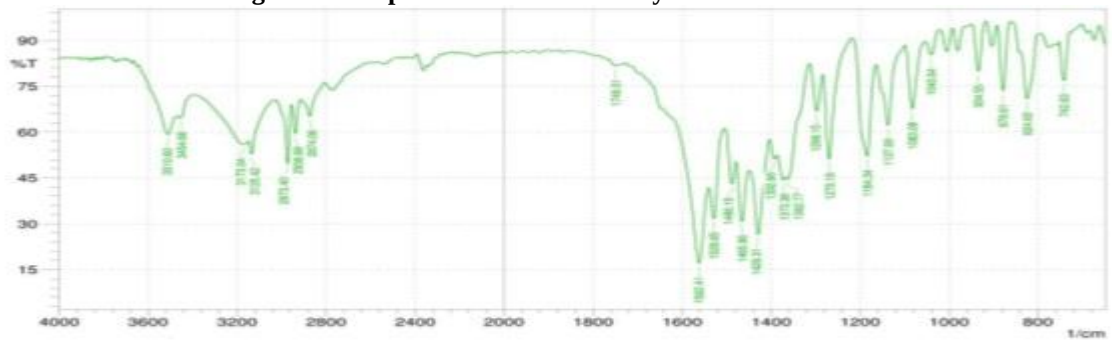

Fig 8. FT-IR spectra of Mebeverine hydrochloride+ Magnesium Stearate

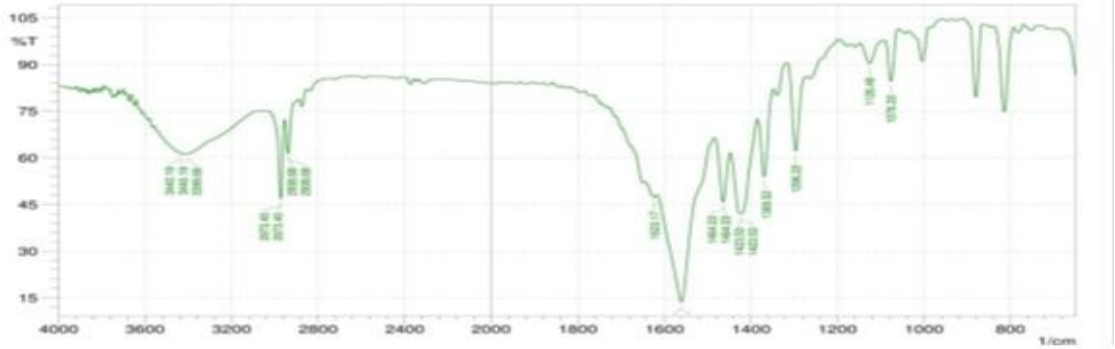

Fig 9. Drug Release of All Mebeverine hydrochloride SR Formulations

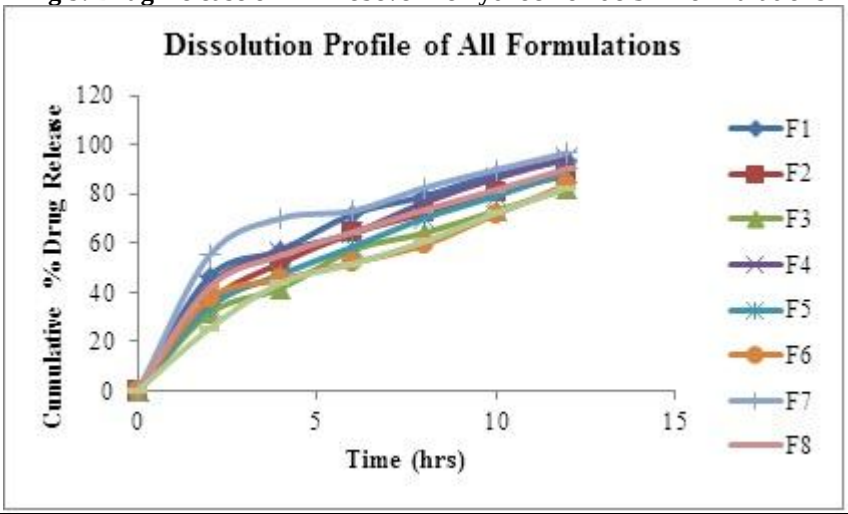

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Table 1. Formulations of Different Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mebeverine hydrochloride	135	135	135	135	135	135	135	135	135
Starch 1500	75	75	75	75	75	75	75	75	75
Ethyl Cellulose N-20	-	-	-	-	-	-	30	45	60
Eudragit S-100	-	-	-	30	45	60	-	-	-
HPMC K_4M	30	45	60	-	-	-	-	-	-
Dicalcium Phosphate	45	30	15	45	30	15	45	30	15
Magnesium Stearate (2%)	6	6	6	6	6	6	6	6	6
Talc (3%)	9	9	9	9	9	9	9	9	9
Total weight(mg)	300	300	300	300	300	300	300	300	300

Table 2. Evaluation of tablet blend (F1-F9)

Formulations	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	% Compressibility	Hausner's ratio	Angle of repose (θ)
F1	0.405	0.47	13.82	1.16	24.15
F2	0.43	0.511	15.85	1.18	24.2
F3	0.41	0.496	17.33	1.20	24.61
F4	0.39	0.462	15.58	1.18	24.23
F5	0.43	0.515	16.50	1.19	24
F6	0.41	0.48	14.58	1.17	23.6
F7	0.42	0.496	15.32	1.18	22.61
F8	0.45	0.52	13.46	1.15	22.9
F9	0.41	0.478	14.22	1.16	23.42

EVALUATION OF TABLETS (POST COMPRESSION PARAMETERS)

Table 3. Evaluation of mebeverine hydrochloride sustained release tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight Variation(mg)	Thickness (mm)	Drug content Uniformity (%)
F1	5.85±0.37	0.139	303±1.72	3.85±0.02	98.18±0.86
F2	5.85±0.45	0.1	300±1.8	3.86±0.04	96.23±1.22
F3	5.8±0.52	0.1	302±1.54	3.86±0.019	98.05±1.58
F4	5.9±0.52	0.27	304±1.3	3.5±0.04	98.62±1.51
F5	5.87±0.49	0.139	301±1.9	3.85±0.03	97.59±0.52
F6	5.9±0.61	0.139	299±1.42	3.86±0.03	100.11±1.78
F7	5.85±0.32	0.29	299.5±1.8	3.85±0.03	99.5±0.5
F8	5.9±0.68	0.17	298±1.3	3.86±0.02	98.83±1.04
F9	5.85±0.44	0.15	302±1.6	3.85±0.02	101.48±0.5

Table 4. Cumulative % drug release of Mebeverine hydrochloride (F1 to F5)

Time (hrs)	% Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	46.42±0.92	36.11±1.16	29.45±1.27	30.23±0.37	25.16±0.09
4	57.17±0.67	52.01±0.79	41.70±1.03	41.56±0.31	33.71±1.72
6	71.79±1.33	64.05±0.51	57.17±0.67	59.34±87	47.69±1.26
8	79.10±1.16	72.22±1.32	64.05±1.51	76.52±0.72	64.12±0.9
10	88.12±0.95	80.82±1.12	73.08±1.03	84.23±0.15	79.1±0.24
12	93.71±0.82	87.69±0.96	82.11±1.09	92.7±0.28	88.98±0.93

Mean ± S.D., n=3

CONCLUSION

Sustained Release tablets of Mebeverine hydrochloride to prolong the release of drug for treating or preventing spasmodic conditions of the lower gastro intestinal tract were prepared.

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Table 5. Cumulative % drug release of Mebeverine hydrochloride (F6 to F9)

Time (hrs)	% Drug Release			
	F6	F7	F8	F9
0	0	0	0	0
2	18.23±0.13	28.4±1.3	24.13±0.66	20.36±0.44
4	29.77±0.95	44.1±0.32	39.02±0.61	33.1±0.17
6	43.54±0.79	62.3±0.67	52.48±0.46	45.68±0.61
8	56.32±0.62	79±1.12	70.51±0.84	60.61±0.62
10	71.79±1.33	89.7±0.28	81.68±0.26	72.22±0.29
12	83.83±0.05	96.72±0.16	90.27±0.62	82.54±0.91

Mean ± S.D., n=3

By performing compatibility studies using IR spectrophotometry, no interaction was found. About 9 Formulations of Sustained Release tablets were formulated by using different concentrations of Sustained release polymers (HPMC, Eudragit, and Ethyl cellulose) by Wet Granulation method.

Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, bulk density, Tapped density, Percent Compressibility, and Hausner ratio. All the 9 formulations showed good flow properties.Post compression evaluation of prepared tablets were carried out with the help of different pharmacopoeia and non-pharmacopeia (industry specified) tests. The shape, colour and texture of all the formulations were found to be disk shape, white in colour and smooth surface. The thickness was found to be uniform in all formulations. The Weight variation, hardness, friability are within the permitted limits. *In vitro* release studies were carried out at time interval of 120 minutes till 12hours. The Formulation F7 (Ethyl cellulose 5%) shown best release than other formulations. The release kinetic studies of best formulation shows following zero order release with fickian diffusion release mechanism.

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