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Original Research Article

Formulation and Evaluation of Mebeverine Hydrochloride Sustained Release Capsules by Pelletization Technique

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Abstract

The objective of the present study is aimed to formulate and evaluate sustained-release Mebeverine hydrochloride capsules using the Pelletization technique. Mebeverine hydrochloride, an anti-spasmodic drug is highly water soluble with a half-life of 2h and is suitable to develop sustained action for the treatment of irritable bowel syndrome. Mebeverine hydrochloride prolongs medication release in the GIT and, as a result, into the plasma, while reducing the frequency of drug administration, adverse effects, and patient compliance. Mebeverine hydrochloride were prepared by using polymers The drug-polymer and excipient compatibility was defined by the FTIR studies in the pre-formulation study. The calibration curve for the drug is plotted and checked the physicochemical properties. Six formulations (F1-F6) of Mebeverine hydrochloride pellets were prepared using different quantities of Ethylcellulose N 50 and other standard excipients. In vitro, drug release studies were performed for the pellets for 1.2, 4, 6, 8, and 12hrs. The optimized formulation F6 showed 76.8 % drug release after 12h showing that ethyl cellulose N 50 acts as a rate-controlling agent. The drug release of the chosen formulation follows first-order kinetics with a zero-order mechanism, according to absorption kinetics.

Keywords: Formulation development, Sustained release capsules, Mebeverine hydrochloride, Ethyl cellulose, Micro Crystalline cellulose, Pelletization techmology.

INTRODUCTION

Compared to a normal dose form, a sustained-release tablet allows for a twofold or larger reduction in the frequency of medication administration. It is intended to release medicine gradually over a lengthy period of time, maintaining consistent levels of the drug in the patient's circulation. The therapeutic efficiency of the treatment is increased by maintaining stable blood levels of the drug in the bloodstream. It improves convenience and patient compliance by Reduction in dosing frequency. Sustained release formulations extend product longevity. In addition to its primary role of prolonged action, the drug's matrix coating prevents the release of unstable medication into the environment and makes it stable. Mebeverine HCL is a Musculotropic antispasmodic medication that has no adverse effects and is mostly used to treat irritable bowel syndrome. To relax the stomach muscles, Mebeverine HCL works directly at the cellular level. Its biological half-life is only 2.5 hours. Peak plasma concentration is reached in 1 to 3 hours after oral dosing and plasma protein binding is 75%. Mebeverine HCL, however, experiences significant first-pass metabolism in the gut wall and liver. Twenty to thirty minutes after oral dosing, high plasma concentrations of Veratric acid (one of Mebeverine HCL's primary inactive metabolites) were seen in addition to minimal levels of the parent medication. Mebeverine HCL was chosen as a model medication as a result because it had the necessary pharmacokinetic and physicochemical characteristics for regulated administration. Irritable bowel syndrome, often known as IBS, is a condition that is most frequently characterized by cramping, stomach discomfort, bloating, constipation, and diarrhea. IBS is extremely uncomfortable and upsetting, yet it does not destroy the intestines permanently or cause serious illnesses like cancer.

MATERIALS AND METHODS

MATERIALS

Mebeverine hydrochloride, Sugar spheres, Povidone K 29/32, Hypromellose, Ethyl cellulose N-50, Magnesium stearate, Tri ethyl citrate, Isopropyl alcohol, purified water.

INSTRUMENTS

Digital weighing balance(Sartorius), sieve shaker (Electrolab), Mechanical stirrer (Remi), Moisture analyser (Ohaus), conventional coating pan(platinum pharma tech), Tapped density tester (Electrolab), Dissolution apparatus (Electrolab), Fluidised bed coater(Anish pharma equipment), UV spectrometer(UV 1600& shimandzu).

ANALYTICAL METHOD

Standard curve of Mebeverine HCL in water

A stock solution of Mebeverine (100µg/ml) was prepared by dissolving 10mg of the drug in water and the final volume was made to 100ml. The solution in the concentration range of 5-25µg/ml was prepared by appropriate dilutions of stock solution. The UV absorbances of these solutions were determined spectrophotometrically at λmax 263 nm using a double-beam UV-visible spectrophotometer.

FTIR COMPATIBILITY STUDIES:

Studies on the interactions between drugs and excipients were conducted to see whether there were any interactions. FTIR was used to conduct investigations on excipient compatibility. These investigations aid in the appropriate excipient choice for formulation. The KBr pellet approach is used for FTIR compatibility. Pure drug and physical combinations were created as discs, and the FTIR was used to analyze their compatibility. In order to ascertain the chemical interaction between API and excipients, the spectrum of the pure drug was compared with a physical combination of the drug and excipients. To research and find any incompatibilities, the spectra of the excipients and the pure drug are compared.

METHOD OF FORMULATION:

All required materials are dispensed. Mebeverine HCL passed through sieve no #40.

Binder solution 1 preparation: required quantity of povidone is dissolved in IPA and kept for stirring until a clear solution is obtained.

Binder solution 2 preparation: required quantity of HPMC is taken and dissolved in water until a clear solution is obtained. So the above binder solution 2 is added to binder solution 1 by slow addition and kept for stirring until it gets a clear solution. After filtering through a nylon cloth filter.

Drug loading

Sugar spheres are taken into a conventional coating pan and the binder solution with Mebeverine HCL is sprayed on the sugar spheres. so the drug-loaded pellets are placed in a tray dryer and kept for air drying for up to 10 minutes. So the LOD should not be more than 0.5%. So the time taken for drying the pellets will be up to three and a half hours and the LOD should be 0.3%

SUSTAINED RELEASE COATING

The required quantity of EC N 50 is dissolved in IPA and triethyl citrate is dissolved in water and these are kept for stirring until a clear solution is obtained. Here the TEC is added to the EC solution and kept for stirring up to 45 minutes. Magnesium stearate is added and then allows it for stirring for 30 minutes up to a uniform dispersion is obtained. Load drug-loaded pellets into the FBC bowl.

Set the inlet temperature to 55°C to reach the bed temperature of 45°C.

Coat the drug-loaded pellets by a bottom spray wurster at peristaltic pump rpm of 2-5 and atomizing air pressure of 0.6-1-1.5 kg/cm² till the target weight gain has been achieved.

After completion of coating, dry the pellets in FBC for about 15 minutes at a given bed temperature of about 45°c and unload the pellets into pre-lined with double polyethylene bags.

Record the inlet temperature, bowl temperature, fluidization, atomization air, and pump rpm for every 30 minutes in a record book.

Sift the dried pellets through #18 and collect #20 retains and passing separately into double-lined polythene bag HPDE containers

Table-1

S.NO	Ingredients	F1 mg/unit	F2 mg/unit	F3 mg/unit	F4 mg/unit	F5 mg/unit	F6 mg/unit
I	**DRUG LOADING**						
01	Mebeverine HCL	200.0	200.0	200.0	200.0	200.0	200.0
02	Sugar spheres(#40)	29.97	29.97	26.00	30.00	31.52	28.00
II	**BINDER SOLUTION**						
03	Povidone	4.15	6.15	5.8	4.5	5.2	8.0

S.NO	Ingredients	F1 mg/unit	F2 mg/unit	F3 mg/unit	F4 mg/unit	F5 mg/unit	F6 mg/unit
04	Hypromellose	0.42	0.42	0.42	0.42	0.42	2.5
05	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
06	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
III	**S.R Coating**						
07	Ethylcellulose N 50	8.20	8.20	10.58	7.08	4.66	8.3
08	Magnesium stearate	5.85	5.85	5.20	4.80	4.2	2.2
09	Tri ethyl citrate	1.42	1.42	2.0	3.20	4.0	1.0
10	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
11	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Total	250.0	250.0	250.0	250.0	250.0	250.0

EVALUATION OF PELLETS

Particle size distribution

PSD was carried out using the sieve analysis technique. In decreasing sequence of mesh size, the sieves are placed one on top of the other. Weigh each empty sieve before filling it with a precisely measured quantity (50gm). Placing a receiver at the bottom to catch the sample after sifting and covering the sieve at the top with the supplied lid. Fix and secure the sieves in the sieve shaker, set the timer for 10 minutes, set the power level for 10, and turn on the shaker. Take the sieves when the allotted time has passed, weigh each sieve with the sample, and then determine the sample weight. The figures were given**.**

Flow properties:

Evaluations included bulk density, tapped density, Hausner's ratio, and angle of repose. Using a tap density tester, bulk density and tapped density were calculated. The fixed funnel method was used to estimate the angle of repose.

Content uniformity test:

Firstly, the % purity of the active component in 10 capsules is assessed separately. Additional tests must be done on the remaining capsule since nine out of ten are beyond the normal range. The combined analysis of the 30 capsules should demonstrate that at least 27 of them fall between the required extremes, or between 85 and 115%, and that none of them fall outside of the specified range, or between 75 and 125%.

Water content by KF titration:

30 ml of methanol was taken in a clean, dried karl fisher titration flask and titrated with KF reagent until the endpoint to neutralize the free water. Mebeverine pellets were powdered finely. Accurately weighed quantity of 0.5gm of sample is transferred to the titration flask and dissolved by stirring and titrate with KF reagent to the endpoint and percentage water content was calculated by the following formula.

%Water content= v×f×100/w×100

Where,
V= volume of reagent consumed by the sample
F= factor of KF reagent
W= weight of sample in grams.

In-vitro Drug Release Studies:

Dissolution parameters
Medium: 0.1N HCL and pH 7.4 phosphate buffer
Volume:1000ml
Apparatus : USP Type-I(Basket)
RPM :100
Time intervals: 2,4,8 and 12 hours
Preparation of pH 7.4 phosphate buffer:

Dissolve 6.8 g of potassium hydrogen orthophosphate in 1000ml, and the pH 7.4±0.05 with 2N sodium hydroxide.

Weigh accurately about 25mg of Mebeverine working transfer 50ml volumetric flask add 20ml of methanol, sonicate to dissolve the content and makeup to the mark with methanol. Transfer 1ml of the above solution into a 50ml volumetric flask and makeup to the mark with dissolution medium. Filter through 0.45 µm nylon filter.

Procedure: Measures the absorbance of standard and sample preparations in 1 cm cell on a suitable UV spectrophotometer at 264nm, using the medium as blank. Record the absorbance.

In-vitro Drug Release Kinetic Studies:

The In vitro drug release kinetic studies of sustained release capsules of Mebeverine HCL were fitted into five kinetics models. i.e., Zero-order, first-order release kinetics, Hi-guchi plot, Korsemayer-peppas, Hixson-crowell model. These studies were used to determine the pattern of drug release and mechanism.

RESULTS AND DISCUSSION

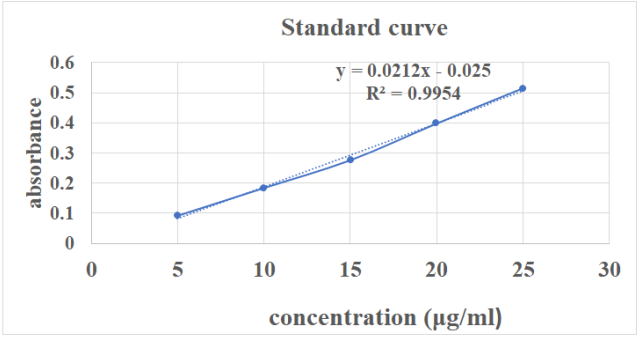

Figure-1: Standard curve of Mebeverine HCL in water

FTIR COMPATIBILITY STUDIES:

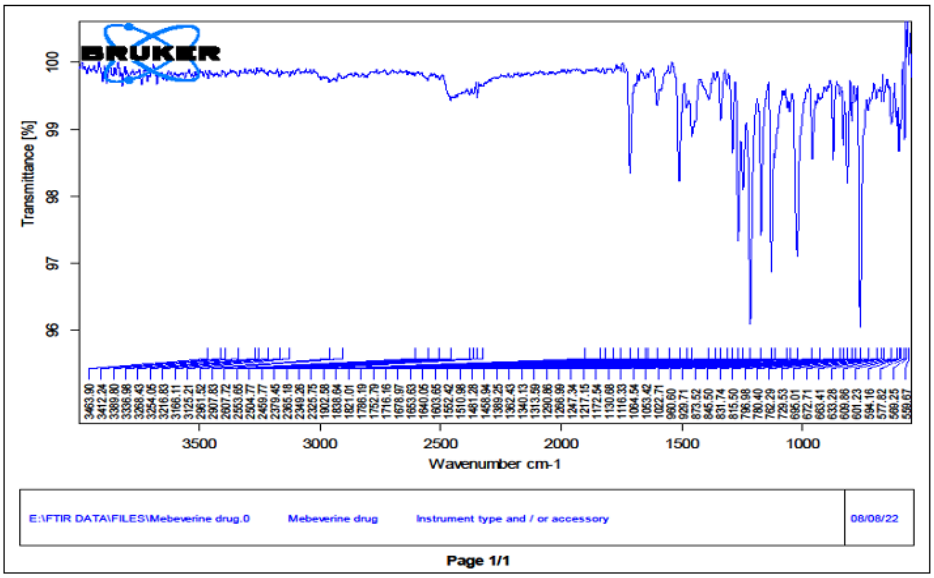

Figure-2: FTIR of Mebeverine HCL

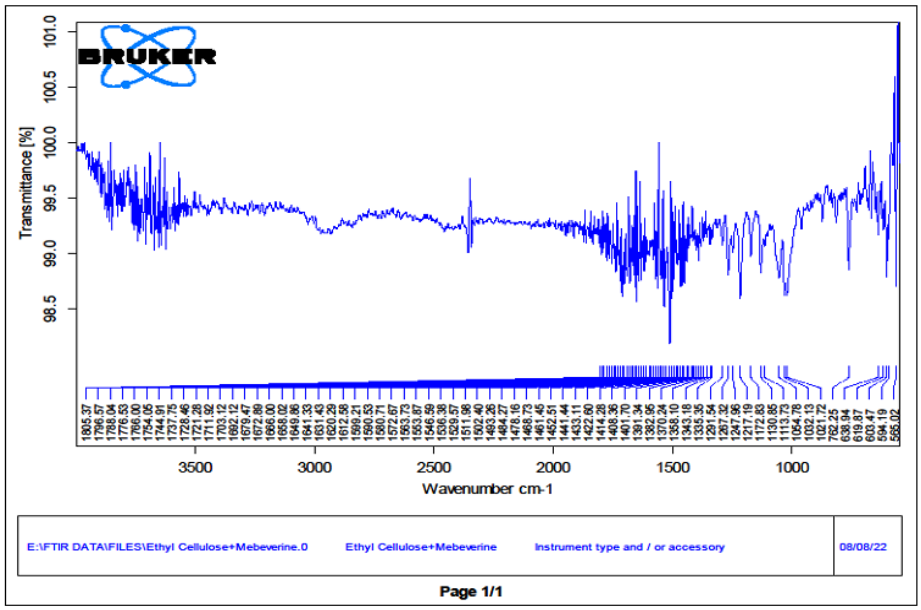

Figure-3: FTIR of Mebeverine HCL+ETHYL Cellulose N 50

Particle size distribution: cumulative retain pellets (%)

Table-2

Mesh No	Sieve weight	Sample + sieve	Retains	%Retains	Cumulative% retains
#14	424.0	424.0	0	0	0
#16	363.2	386.2	23	46	46
#18	374.4	398.0	23.6	47.2	93.2
#20	380.2	383.6	3.4	6.8	100
#25	372.8	372.8	0	0	0
Down	369.4	369.4	0	0	0

Table-3: Flow properties

FORMULATION	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio
F1	0.65±0.13	0.68±0.02	1.05±0.09
F2	0.63±0.04	0.66±0.05	1.05±0.073
F3	0.65±0.02	0.67±0.87	1.06±0.02
F4	0.63±0.66	0.68±0.03	1.05±0.53
F5	0.64±0.07	0.69±0.72	1.05±0.02
F6	0.66±0.08	0.72±0.08	1.04±0.75

Table-4 Content uniformity

Formulation	Average weight(mg)	%Drug content
F1	252.4±2	98.2±0.2
F2	252.1±2	99.6±0.3
F3	251.3±2	100.2±0.2
F4	253.0±2	99.5±0.4
F5	253.0±2	98.4±0.3
F6	252.5±2	99.6±0.4

Table-5: Moisture content by KF titration

Formulation	%Moisture content
F1	1.05±0.23
F2	1.03±0.34
F3	1.11±0.36
F4	1.04±0.34
F5	1.06±0.22
F6	1.05±0.26

In-vitro drug release studies:

The In-vitro drug release studies were carried out using USP type-I dissolution test apparatus (Basket type).

F1 formulation by using ECN-50 as a coating excipient and different concentrations on a binding agent. That drug release is 53.7%.

F2 formulation by using ECN-50 as a coating excipient and different concentrations on a binding agent. That drug release is 58.4%

F3 formulation by using ECN-50 as a coating excipient and different concentrations on a binding agent. That drug release is 61.0%

F4 Formuation by using ECN-50 as coating excipients and different concentrations on a binding agent. That drug release is 90.2%

F5 Formulation by using ECN-50 as coating excipient and different concentrations on a binding agent. That drug release is 64.5%

F6 formulations all these formulations comparison then Reduced the EC N-50 concentration. The drug release will be 76.70%

Table-6: Cumulative Percentage Drug Release

Time(hrs)	F1	F2	F3	F4	F5	F6
0	**0**	**0**	**0**	**0**	**0**	**0**
1	**6.4±0.1**	**8.6±1.9**	**11.2±2.2**	**20.5±2.0**	**12.5±1.5**	**13.6±1.6**
2	**17.2±1.5**	**22.8±1.2**	**28.2±1.3**	**37.6±1.0**	**30.2±1.6**	**22.5±2.2**
4	**28.6±2.5**	**31.8±2.5**	**35.5±1.0**	**51.2±1.5**	**37.2±1.5**	**44.8±1.0**
6	**37.4±1.3**	**39.5±1.0**	**41.5±1.8**	**65.6±1.6**	**45.4±1.7**	**51.7±1.9**
8	**46.5±2.0**	**48.6±2.5**	**51.6±1.5**	**75.2±1.6**	**52.8±1.5**	**58.6±2.1**
12	**53.8±1.8**	**58.5±1.9**	**61.2±1.7**	**90.4±1.5**	**64.6±1.8**	**76.8±1.0**

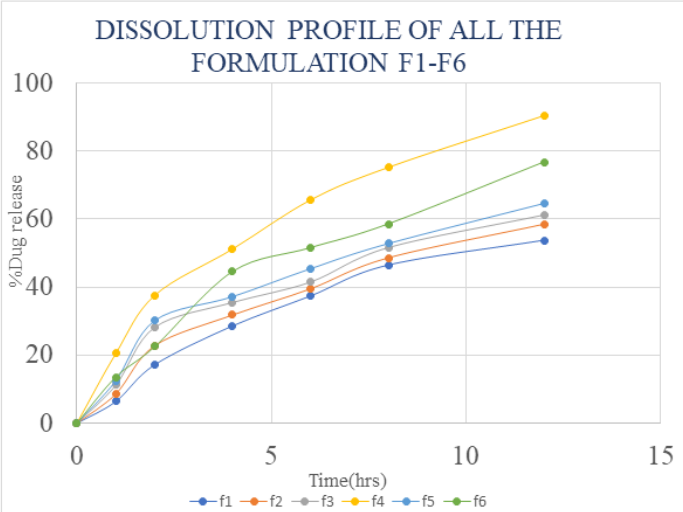

Figure-4: In-vitro drug release profile of Formulations

CONCLUSION

Mebeverine hydrochloride SR capsules 200mg were prepared and evaluated physically and chemically. The optimized formulation F6 was found to be 76.7% at the end of 12hrs. On the basis of the evaluation parameters, the optimized formulation f6 be used once a day administration in the management of Antispasmodic.

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