Research Article

Preparation and Characterization of Mebeverine Hydrochloride Microspheres

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ABSTRACT

Mebeverine hydrochloride is an effective spasmolytic drug used for relieving irritable bowel syndrome. Because of relatively short biological half life, it needs to administer frequently for better therapeutic activity. Hence controlled release of this drug is highly desirable. Mebeverine is a highly soluble drug, and therefore controlled drug release from the matrix system is often difficult. Selection of right excipient is crucial and important during the development of matrix system because there is a chance of drug dumping. Hence different combinations of polymers were used to control the drug release from the matrix systems. The main aim of this study was to prepare and characterize microspheres of Mebeverine HCl using biodegradable natural polymers such as Guar gum, sodium alginate and pectin and different extended release and enteric coating polymers like ethyl cellulose (EC N100) in different combinations. The microspheres prepared were evaluated for assay, encapsulation efficiency, particle size distribution, in-vitro drug release kinetics. In vitro drug release studies were performed in 0.1N Hcl for 2hrs followed by pH 6.8 phosphate buffer for 6-12hrs. The dissolution data demonstrated that the rate of drug release decreased with increase in the enteric coating polymer concentration. The in vitro results show faster releasing in Sodium alginate when compared to pectin. The FT-IR and DSC studies indicated no possible interaction between Mebeverine hydrochloride and carriers.

Keywords: Mebeverine, matrix systems, microspheres, encapsulation, ion gelation.

INTRODUCTION

The oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. Therefore it is the most desirable and preferred method of administering therapeutic agents for their systemic effects[1].

Sustained Release (SR) indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration and, then a gradual release over an extended period. It is substantially affected by the external environment. The object of sustain release of drugs, in a general way is to modify the normal behavior of the drug molecule in physiological environment[2].

Microspheres are one of the particulate delivery system containing inner core and outer coating materials to achieve extended release and to improve bioavailability. As the name implies, microspheres are small, spherical particles. Particle sizes range from 12 to 300 microns in diameter, and wall thickness can vary from several microns to as low as 0.1 micron. Oral multi-unit dosage forms such as microspheres have received much attention as modified/controlled drug delivery systems. These systems distribute more uniformly in the gastrointestinal tract, thus resulting in more uniform drug absorption and reducing patient-to-patient variability [3].

Mebeverine hydrochloride is an effective spasmolytic drug used for relieving irritable bowel syndrome. Because of relatively short biological half life, it needs frequent administration to the patient. Hence controlled release of this drug is highly desirable. Selection of right excipient is crucial and important during the development of matrix system because there is a chance of drug dumping. Hence different combinations of polymers were used to control the drug release from the matrix systems. In the present study different bio-degradable and pH dependent polymers were used in combination with guar gum. This study was aimed to prepare microspheres of Mebeverine Hydrochloride using various polymers in different drug to polymer concentrations[4].

MATERIALS AND METHODS

Materials

Mebeverine Hydrochloride was obtained as a gift sample from Dr. Reddy labs, Hyderabad, Sodium alginate Thomas Baker chemicals pvt Limited, Mumbai, Guar gum Accord labs, secunderabad, Ethyl cellulose was obtained as gift sample from Aurobindo Pharma Ltd, Hyderabad, and Pectin CDH chemicals pvt Limited, New Delhi, Calcium chloride SD Fine chemical Pvt Limited, Mumbai.

Methods

Preparation of Microspheres

Mebeverine Hydrochloride microspheres were prepared by Ionotropic gelation technique. An aqueous solution of sodium alginate as prepared using distilled water with vigorous stirring and heating to form a clear solution. To this solution, the drug Mebeverine Hydrochloride was added and stirred continuously until a uniform suspension was obtained.

Table 1: Formulation details of Mebeverine microspheres

Formulation	Mebeverine	Sodium Alginate	Pectin	Guar gum	Ethyl cellulose	Water
F-1	0.5 gm	2 gm	--	--	--	10
F-2	0.5 gm	2 gm	--	0.5 gm	--	12
F-3	0.5 gm	2 gm	--	1 gm	--	15
F-4	0.5 gm	2 gm	--	0.5 gm	0.25 gm	15
F-5	0.5 gm	2 gm	--	0.5 gm	0.5 gm	18
F-6	0.5 gm	2 gm	--	0.5 gm	0.75 gm	20
F-7	0.5 gm	--	2 gm	--	--	10
F-8	0.5 gm	--	2 gm	0.5 gm	--	12
F-9	0.5 gm	--	2 gm	1 gm	--	15
F-10	0.5 gm	--	2 gm	0.5 gm	0.25 gm	15
F-11	0.5 gm	--	2 gm	0.5 gm	0.5 gm	18
F-12	0.5 gm	--	2 gm	0.5 gm	0.75 gm	20

The suspension was extruded into a beaker containing calcium chloride (10%) using a 5 ml of hypodermic syringe with 18gauze needle and stirred at 100 rpm for 15 min. After extrusion the microspheres were washed with water allowed to solidify for a period of 30 minutes and then dried at 45^0 C for complete drying of microspheres[5].

RESULTS AND DISCUSSION

The prepared microspheres were spherical and free flowing. They were analyzed for various physico chemical properties such as entrapment efficiency, particle size distribution and in vitro dissolution studies.

Determination of the drug content

Mebeverine microspheres equivalent 100mg was taken powdered and transferred in to a 100 ml volumetric flask. The volume was made up to the mark with 6.8pH PHOSPHATE BUFFER and then kept aside for 12 hrs with occasional shaking. Then the solution filtered through the membrane filter (0.45µg pore size) and 1 ml of this solution was diluted using phosphate buffer of pH 6.8 and analyzed using a spectrophotometer to get the particle drug content. All the experimental units are analyzed in triplicate (n=3)[6].

Drug encapsulation efficiency

Drug encapsulation efficiency was calculated using the formula[7]:

$$\text{Drug encapsulation efficiency} = \frac{\text{ACTUAL DRUG CONTENT}}{\text{THEORETICAL DRUG CONTENT}} \times 100$$

Particle Size distribution of microspheres

Particle size analysis of the microspheres was done by optical microscopy method by using a calibrated stage micrometer. Particle size was calculated by using equation[8]

$$X_g = 10 \times [(n_i \times \log X_i) / N]$$

Where, X_g is geometric mean diameter, n_i is number particle in range, X_i is the midpoint range and N is total number of particles

Table 2: Drug Content estimation, Drug Encapsulation Efficiency and Particle size determination of Mebeverine microspheres

Formulation	Drug content Estimation (mg)	Encapsulation efficiency	Particle size (µm)
F-1	53.43	80.16	276.6
F-2	33.08	66.19	281.7
F-3	21.37	72.21	264
F-4	54.73	74	291.2
F-5	36.67	54.5	276.1
F-6	27.86	64.1	282.4
F-7	51.02	66.59	268.9
F-8	34.56	64.37	269.7
F-9	20.89	60	284.6
F-10	54.14	64.76	272
F-11	36.04	52.14	272.8
F-12	24.66	54.23	286

***In vitro* drug release studies of prepared microspheres:**

The in vitro dissolution studies were performed for the prepared microspheres using USP dissolution apparatus I. The microspheres were filled in a capsule shell and then kept in the basket of the dissolution medium. The dissolution medium consisted of 0.1N HCl (900 ml) for 2 hours. Later the dissolution medium was replaced with 6.8 pH phosphate buffer (900 ml) at 100 rpm speed, maintained at 37.5°c. An aliquot (5ml) was withdrawn at specific time intervals and filtered through 0.45 µ (millipore) filter. After appropriate dilution, the samples were analyzed and cumulative percentage of the drug release was calculated [9-11].

Table 3: *In vitro* drug release studies of Mebeverine microspheres

Time (in hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	12.9	11.52	9.18	6.3	4.7	3.6	10.8	6.9	8.1	3.8	2.7	1.4
2	26.5	19.5	16	11	8.5	6.3	21.3	16.8	14	9.9	7.4	4
3	33.2	25.5	21.7	16.2	13.2	8.5	29.8	23.5	18.9	14	10.4	6
4	36.7	31.6	27.5	21.7	17.9	13.7	34.9	30	25	19.3	14.3	10.4
6	54.9	47.1	40	34.1	27.7	22.3	51.4	44.3	37.6	32.2	26.1	19.8
8	76.9	66.5	58.8	50.8	44	35.4	73.1	61.6	53.8	45.9	38.1	32.1
10	90.4	84.29	74.7	66.8	60.76	54.1	86.3	78.3	69.5	62.6	56.3	46.2
12	98	90.9	84.9	78.8	72.3	64.29	97	88.5	81.3	75.3	67.3	58.5
14	--	97	89.8	82.1	76.21	70.9	--	94	86	78.3	73.1	65.1
16	--	--	94.5	86.79	81.72	75.3	--	98	91.8	84.6	76.9	70.6
18	--	--	99	92.8	86	80.5	--	--	96.7	89.3	83	75.1
20	--	--	--	95.1	90.4	85.2	--	--	--	93.1	88.5	80.7
22	--	--	--	--	94.8	89.6	--	--	--	99	92.9	86
24	--	--	--	--	97	92.3	--	--	--	--	95.1	88.72

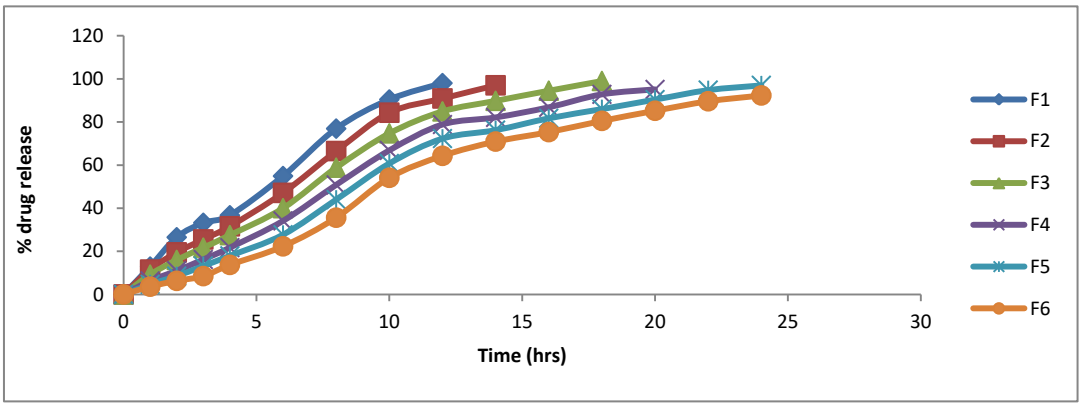

Figure 1: *In vitro* drug release profile of formulations F1- F6

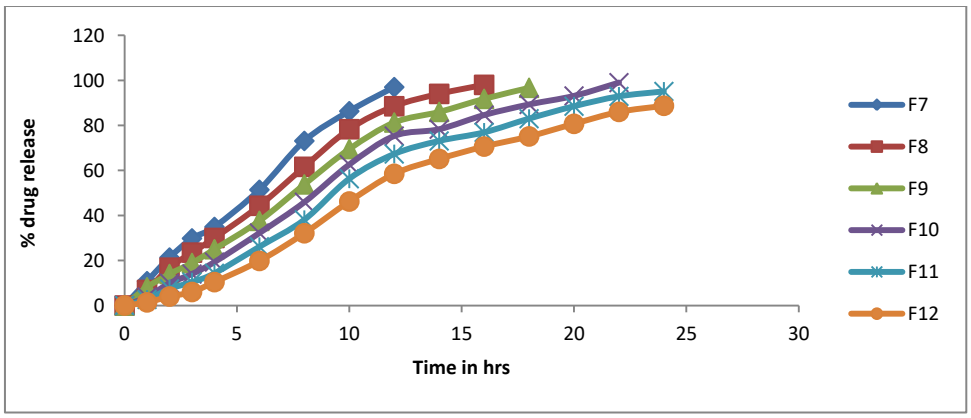

Figure 2: *In vitro* drug release profile of formulations F7- F12

DISCUSSION

The prepared microspheres were spherical and free flowing. They were analyzed for various physic chemical properties such as entrapment efficiency, particle size distribution, and in vitro dissolution studies. The entrapment efficiency was increased with the decrease in the polymer content. The particle size distribution of microspheres was obtained in the range of 291.2 µm for all the formulations[12].

The drug release from the microspheres prepared with Sodium alginate and Guar gum, Pectin and Guar gum prolonged for about 18 hrs. The release kinetics showed that the release followed zero order. The kinetics was best fitted to the Higuchi model clearly indicates that the release mechanism was diffusion mechanism where as the drug release from the microspheres prepared with Sodium alginate, Guar gum and Ethyl cellulose, Pectin, Guar gum and Ethyl cellulose prolonged for about 24 hrs. The release kinetics showed that the release was followed first order. The kinetics was best fitted to the Higuchi model clearly indicates that the release mechanism was diffusion mechanism[13-14].

FTIR and DSC study was conducted on the pure drug and various formulations. The studies indicated that there is no drug polymer interaction.

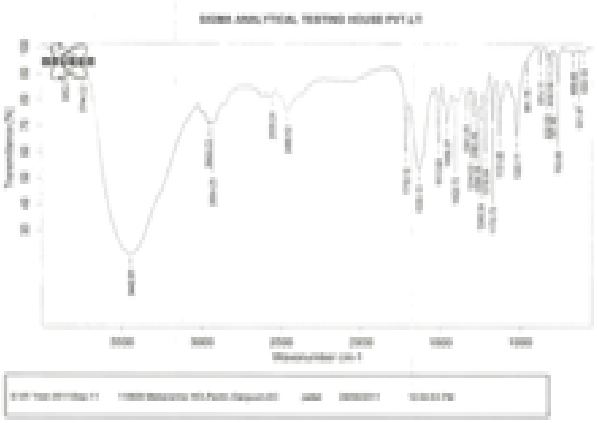

Figure 3: FTIR of Mebevarine, Sodium alginate, Guar gum and Ethyl cellulose

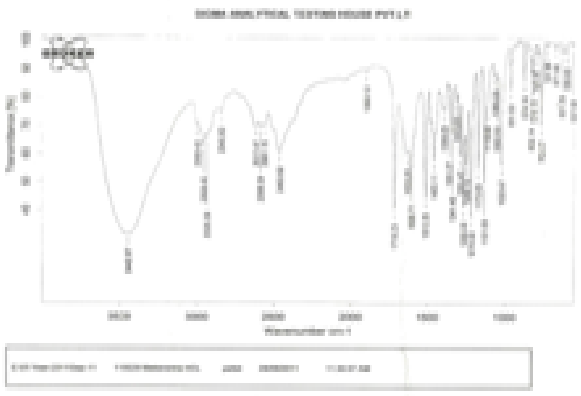

Figure 4: FTIR of Mebevarine, Pectin Guar gum and Ethyl cellulose.

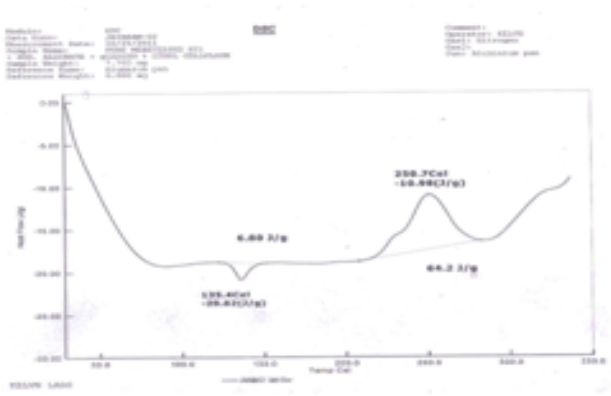

Figure 5: DSC thermogram of pure drug Mebevarine, Sodium alginate, Guar gum and Ethyl cellulose

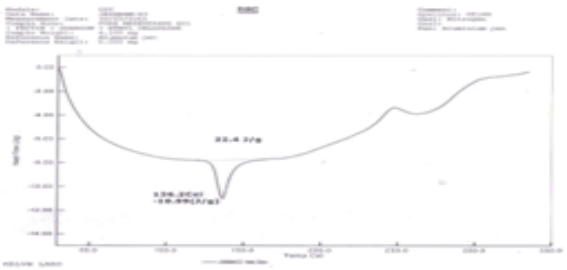

Figure 6: DSC thermogram of pure drug Mebevarine, Pectin, Guar gum and Ethyl cellulose

CONCLUSION

Mebeverine Hydrochloride microspheres were prepared using various polymers. The microspheres prepared using guar gum follow zero order kinetics with diffusion mechanism but the microspheres are prepared with the combination of Ethyl cellulose and guar gum showed first order with diffusion mechanism. The microspheres prepared in combination of Ethyl cellulose released drug for a longer period of time when compared to the formulations which do not contain Mebeverine.

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