



FORMULATION AND EVALUATION OF TARGETED AND CONTROLLED RELEASE MEBEVERINE HYDROCHLORIDE MICROSPHERES

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ABSTRACT

Microspheres of mebeverine hydrochloride, which treats irritable bowel syndrome. Mebeverine hydrochloride is highly water soluble drug, having poor oral bioavailability of drug. Mebeverine hydrochloride is known to suffer from first pass effect. It is an attempt to improve oral bioavailability, reduce the frequency of drug administration, and possibility to restrict its absorption only to the colon. In this study, microspheres of mebeverine hydrochloride was prepared by solvent evaporation techniques using Eudragit FS 30D, and Ethylcellulose as polymers and yield, particle size, encapsulation efficiencies and in vitro release of the prepared microspheres were evaluated. The results showed that percentage yield, encapsulation efficiencies and particle size were influenced mainly by polymer concentration, type of polymer and stirring speed. From the results of the in vitro study shows that the desired release rate is achieved by FEC 4 and FER 11 formulations are releasing the drug up to 12 hrs. DSC results showing there is no interaction between drug and polymers. SEM results of optimized microspheres showing discrete, spherical microspheres.

KEYWORDS: Mebeverine hydrochloride, ethylcellulose N 50, eudragit FS 30 D, solvent evaporation technique.



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INTRODUCTION

Microsphere is defined as “a monolithic structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles, falling in the size range 1-500 μ^1 ”. Insoluble drug carriers for prolonged and controlled delivery of therapeutic agents in biological system recently have generated interest. Microspheres belong to the same carrier system². The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration. During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases³. Diseases associated with the colon like Crohn’s disease, ulcerative colitis, irritable bowel syndrome. There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems. Coating of the drugs with pH-sensitive

polymers provides simple approach for colon-specific drug delivery³.

MATERIALS AND METHODS

Mebeverine Hydrochloride, USPRachem Pvt Ltd, Hyderabad. Ethyl cellulose N50 Liquid paraffin AR SD Fine Chemicals, Mumbai Span-80 IP Petroleum ether AR Ethanol AR Eudragit FS 30D M/s Rohm pharma, Germany Whatman Filter paper Whatman® Schleicher & Schuell.

(i) Formulation of Mebeverine Hydrochloride Microspheres:

The drug was dissolved in polymer solution made by dissolving polymer in 3:1 mixture of acetone and ethanol. The above slurry was slowly introduced into 100 ml of light liquid paraffin containing span 80 (0.5%) as surfactant while being stirred at 2200 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The stirring was continued for three-and-a half (3 ½) to four (4) hours to allow the solvents (acetone, ethanol) to evaporate completely and the formed microspheres were collected by filtration. The microspheres were washed repeatedly with n-Hexane and petroleum ether until free from oil. The collected microspheres were dried at room temperature for 24 hours. The schematic representation of formulation of eudragit microspheres of mebeverine hydrochloride was given in Table no.1

Table 1
Different Polymers drug ratio formulations

Formulation code (Etylcellulose N50)	Ratios (dg:EC)	Speed (rpm)	Formulation code (Eudragit FS 30D)	Ratios (dg:ER)	Speed (rpm)
FEC 1	1:1	2200	FER 7	1:1	2200
FEC 2	1:2	2200	FER 8	1:2	2200
FEC 3	1:3	2200	FER 9	1:3	2200
FEC 4	1:4	2200	FER 10	1:4	2200
FEC 5	1:5	2200	FER 11	1:5	2200
FEC 6	1:6	2200	FER 12	1:6	2200

(ii) Yield of microspheres^{4,5}

The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of all non-volatile components

$$\% \text{ Yield} = \frac{\text{Actual weight of the microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

(iii) Particle size analysis⁶:

The particle size of the microspheres was measured by optical microscopy. The eye piece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of microspheres. The microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer. About 50 readings were taken at random and the mean \pm standard deviation was calculated. The shape of the microspheres was visualized and the photographs were taken with the aid of a binocular microscope (Quasmo, India, model PZRM 700).

(iv) Drug entrapment efficiency (DEE)⁴ :

The amount of drug entrapped was estimated by crushing 50 mg of microspheres using mortar and pestle, and extracting drug with aliquots of 6.8 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 6.8 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically at 263 nm against an appropriate blank

The amount of drug entrapped in the microspheres was calculated using the following formula

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

(v) In vitro drug release study⁷

In vitro drug release studies were carried out for all formulations in USP type II dissolution test apparatus (TDT 06P, Electrolab, India). Microspheres equivalent to 135 mg of mebeverine hydrochloride taken and Studies were carried out using USP dissolution apparatus II, microspheres were placed In musli cloth and tied to paddle temperature maintained at $37 \pm 0.50^\circ\text{C}$. The dissolution medium, stirred at 50 r.p.m., consisted of 900 ml 0.1N HCl for 2hours followed by buffer of pH 7.4 for 2hrs and followed by pH 6.8 up to 12hours. Samples (1ml) were withdrawn at predetermined time

intervals, compensated with fresh dissolution medium and assayed spectrophotometrically at 263 nm in 0.1N HCl at pH 6.8, 7.4. No interference occurred excipients at this wavelength. This solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer (elico India) at 263 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release. The results are presented in tables and figures.

(vi) Surface morphology of the microspheres

The surface morphology of the targeted and controlled release microspheres was studied with the aid of a Scanning Electron Microscope (SEM).

RESULTS

**Compatibility Studies
IR Spectroscopy**

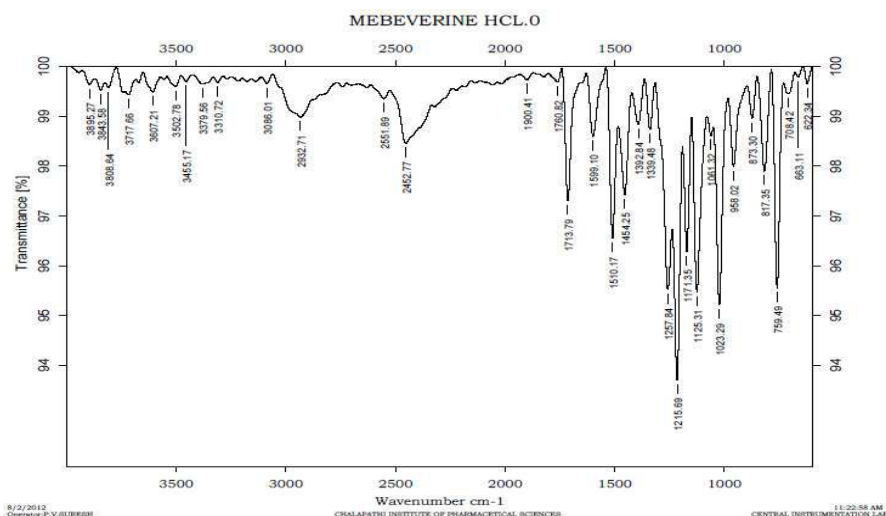


Figure 1
FT-IR graph of pure drug

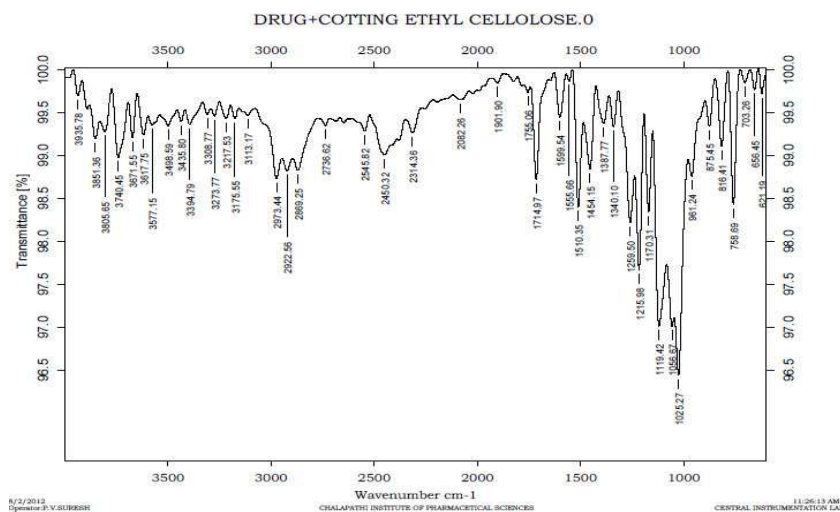


Figure 2
FT-IR graph for drug and Ethylcellulose polymer

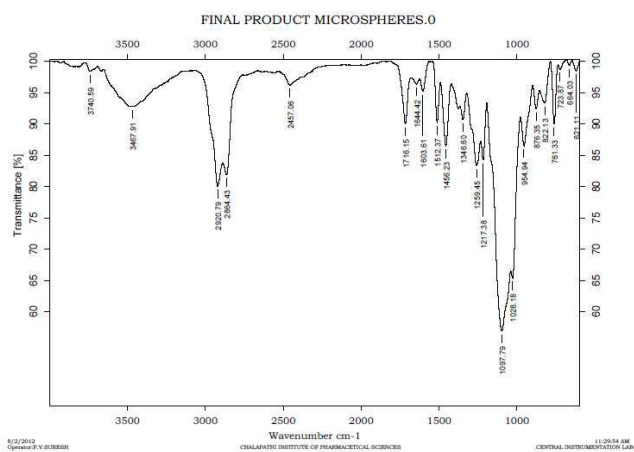


Figure 3
FT-IR graph for ethylcellulose microspheres

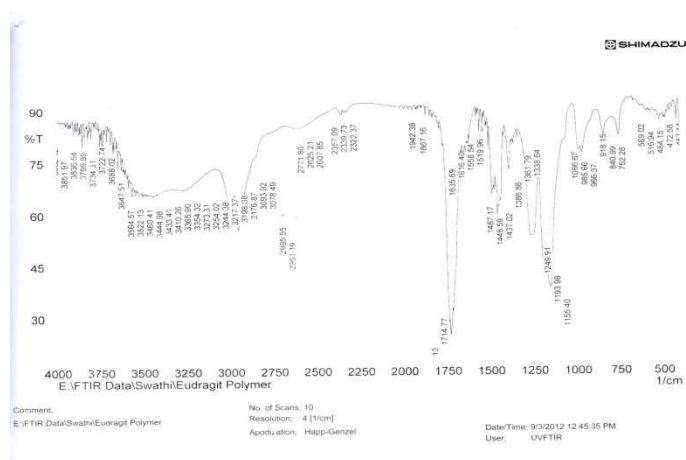


Figure 4
FT-IR graph for Eudragit polymer

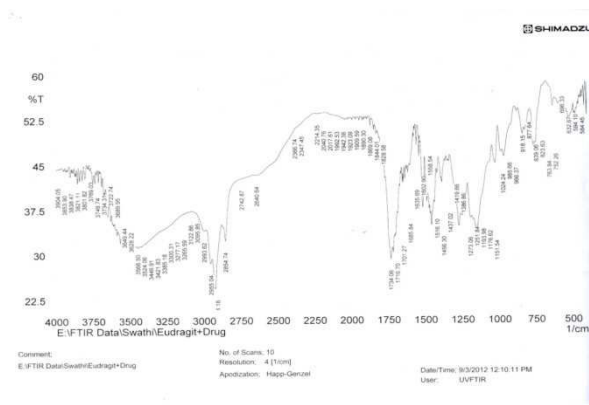


Figure 5
FT-IR graph for Eudragit final product

Table 2
Yield of all formulations

FORMULATION CODES	% YIELD	FORMULATION CODES	%YIELD
FEC1	56.5	FER7	45.7
FEC2	64.1	FER8	60.3
FEC3	72.8	FER9	75.6
FEC4	83.5	FER10	78.4
FEC5	85.9	FER11	85.9
FEC6	93.3	FER12	76.2

Table 3
Particle size analysis of the formulation

Formulation code	Particle size (in microns)	Formulation Code	Particle size (in microns)
FEC 1 (1:1)	17.99	FER 7 (1:1)	8.39
FEC 2 (1:2)	18.84	FER 8 (1:2)	9.64
FEC 3 (1:3)	19.55	FER 9 (1:3)	9.72
FEC 4 (1:4)	13.66	FER 10 (1:4)	10.44
FEC 5 (1:5)	21.44	FER 11 (1:5)	12.25
FEC 6 (1:6)	27.57	FER 12 (1:6)	15

The formulated microspheres were evaluated for the size with the aid of an optical microscope. From table 6.3 the mean particle size of the ethyl cellulose microspheres at increasing ethyl cellulose concentrations (*i.e.*, at drug-polymer ratios 1:1 to 1:6) increased from 17.99 to 27.27 μ m at 2200 rpm. This increase in particle size of the microspheres can be due to

an increase in viscosity with increasing polymer concentrations, which resulted in larger emulsion droplets leads to the formation of greater microspheres. The mean particle size of the Eudragit microspheres at increasing Eudragit concentrations (*i.e.*, at drug-polymer ratios 1:1 to 1:6) increased from 8.39 to 15 μ m at 2200 rpm respectively.

Table 4
Entrapment efficiency of all formulations

Formulation code	Entrapment efficiency	Formulation code	Entrapment efficiency
FEC 1 (1:1)	90.159	FER 7 (1:1)	84.127
FEC 2 (1:2)	85.714	FER 8 (1:2)	77.143
FEC 3 (1:3)	81.27	FER 9 (1:3)	73.333
FEC 4 (1:4)	78.73	FER 10 (1:4)	71.111
FEC 5 (1:5)	74.921	FER 11 (1:5)	69.524
FEC 6 (1:6)	70.159	FER 12 (1:6)	59.048

Percentage drug entrapment efficiencies of microspheres by using different type polymers were shown in table 4. Eudragit polymeric microspheres having 56.67% (FER 11) as higher Percentage of drug entrapment efficiency for 1:4 ratio of drug to polymer. But ethyl cellulose microspheres having around 63.00% (FEC 6) as higher percentage drug entrapment efficiency for 1:6 ratio of drug to polymer, and by increasing the ratio percentage drug entrapment efficiency value is gradually increasing. This may be attributed by increase in viscosity of polymeric solution with respectively by increasing drug polymer ratio for Eudragit and ethyl cellulose polymers.

***In vitro* dissolution studies of mebeverine hydrochloride microspheres**

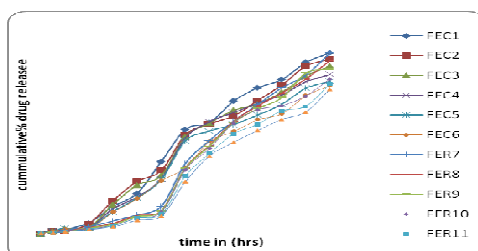


Figure 1
Cumulative percentage drug release graph.

The results of the *in vitro* drug release studies were shown in the figure 1. From the obtained dissolution data following inferences were made. On increasing the drug to polymer ratio, the drug release could be prolonged. The 1:4 ratio of drug to Eudragit FS 30D at 2200 rpm speed could sustain the release for 12 hours releasing about 82.6% of the drug. The difference in the release from the polymers may be attributed to their permeability characteristics. The available literature suggests that the quaternary ammonium groups in FS 30D are 8.85 - 11.96 % and respectively and they have a profound influence on the permeability of the polymer. Drug release from 1:4 ratio of Drug:Ethyl cellulose N50 (FEC 4) showing controlled release of drug from the microspheres about 12 hours. Therefore, a high core to coat was essential to prolong the release of the drug from microspheres. While increasing core to coat ratios of drug and polymers the cumulative % drug release was decreased it was 79.47% for FER and 81.78% for FEC 6.

SEM photograph of Ethylcellulose N50 microspheres (FEC 5)

Figure no.2 shows SEM photograph of optimized Ethylcellulose microspheres (FEC 5). SEM photographs showed discrete, spherical and uniform microspheres with smooth surface, high entrapment efficiency when compared to Eudragit microspheres, because of higher viscosity of Ethylcellulose polymer.

SEM photograph of Eudragit FS 30D microspheres (FER 11)

Figure no.3 A shows SEM photograph of optimized Eudragit microspheres (FER11). SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface. The drug crystals on microspheres may be due to the presence of untrapped drug in dispersion medium.

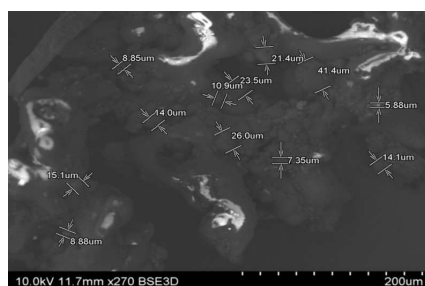


Figure 2
SEM photograph of Ethylcellulose N50 microspheres (FEC 5)

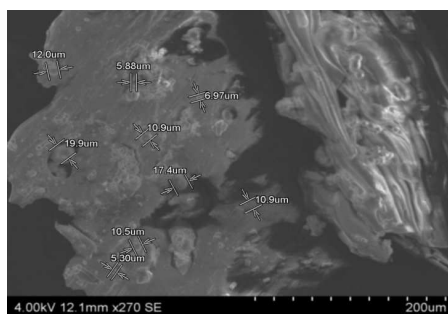


Figure 3
SEM photograph of Eudragit FS 30D microspheres (FER 11)

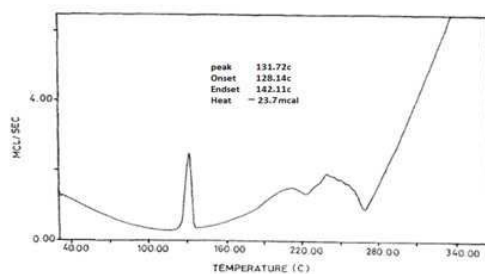


Figure 4
DSC of pure drug

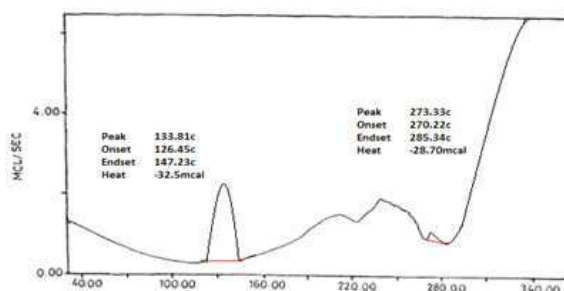


Figure 5
DSC of formulation

Kinetic graphs for prepared microspheres

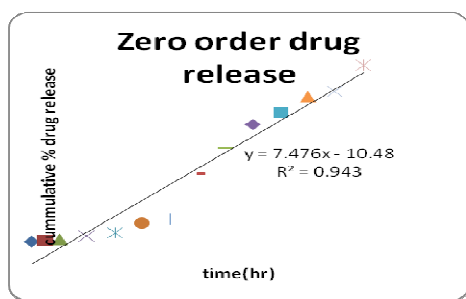


Figure 7

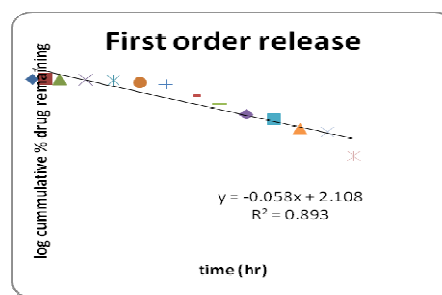


Figure 8

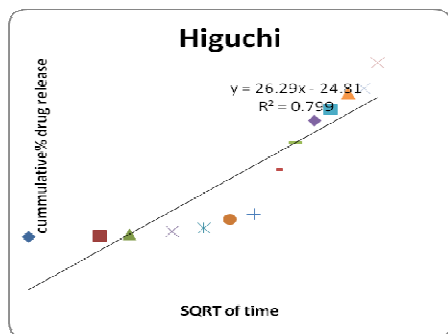


Figure 9

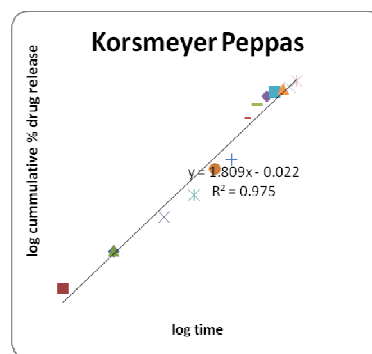


Figure 10

DISCUSSIONS

Mebeverine hydrochloride is known to suffer from first pass effect. It's an attempt to improve oral bioavailability and possibility to restrict its absorption only to the colon, mebeverine hydrochloride microspheres are prepared by solvent evaporation method. By using polymers like Ethylcellulose N50, Eudragit FS30D. Different formulations were prepared with various ratios to deliver the drug at targeted site. Mebeverine hydrochloride having short biological half life (2-3hrs) it has been selected as an ideal drug for design of oral controlled and targeted drug delivery. All formulations were formulated with various proportions, all the formulations were subjected to various evaluation tests. FT-IR, %yield, micrometric properties, entrapment efficiency, invitro release studies, DSC had shown satisfactory results. FT-IR spectra revealed that there is no interaction between polymer and drug mebeverine hydrochloride. Both the polymers are compatible. On the basis of the release data, there is increase in release time with increase in polymer ratio. Based up on evaluation parameters best formulation has been subjected to stability studies as per ICH guidelines. Formulation subjected for stability

studies have been checked for drug entrapment efficiency, physical appearance up to 90 days at 25°C/ 60% RH and 40°C/ 75% RH. The formulations were found to be stable because there was no significant change has been observed in the various evaluated parameters of the formulation.

CONCLUSION

Based on results obtained it is concluded that the yield and entrapment efficiency was good for Ethyl cellulose microspheres FEC5 and eudragit microspheres FER 11 Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and SEM photographs of optimized formulations FEC 5, FER 11 showed discrete, spherical microspheres. FER 11 formulations are showing good micrometric properties more targeted and controlled release than FEC 5. Therefore FER 11 formulation may be used for reducing dosing frequency thereby improving the effectiveness of drug.

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