

Gastroretentive Ethyl Cellulose Floating Microspheres containing Ranitidine Hydrochloride

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Abstract

The aim of this study was to prepare and evaluate ethyl cellulose floating microspheres containing Ranitidine hydrochloride. Microspheres were prepared by non-aqueous solvent evaporation method using ethanol/ liquid paraffin system. The influence of formulation factors (drug: polymer, stirring speed, concentration of surfactant) on particle size, encapsulation efficiency and in vitro release characteristics of the microspheres were investigated.

The yields of preparation and encapsulation efficiencies were high for all formulations obtained. Mean particle size changed by changing the drug: polymer ratio or stirring speed of the system. Although Ranitidine hydrochloride release rates from ethyl cellulose microspheres were decreased as the concentration of ethyl cellulose increased. By applying one way ANOVA followed by Newman-Keuls Multiple Comparison value obtained ($p < 0.05$) was considered to be statistically significant.

Key words:

Ranitidine hydrochloride; Ethyl cellulose; Floating microspheres; Controlled release

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1. INTRODUCTION

Ranitidine hydrochloride (RHCl) is a histamine H₂ receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger–Ellison

erosive esophagitis.¹ The recommended adult oral dose is 150mg twice daily or 300mg once daily. A conventional dose of 150mg can inhibit the gastric secretion up to five hours only. An alternative dose of 300 mg leads to plasma fluctuation; thus a sustained release dosage form of RHCl is desirable. The short biological half life of drug (2 to 3 hours) also favors development of a sustained release formulation.⁶

A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in colon or throughout the gastrointestinal tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Colonic metabolism of Ranitidine is partly responsible for poor bioavailability of Ranitidine from the colon.² These properties of RHCl do not favour the traditional approach to sustain release delivery.

The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of GIT.⁶

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery system, also known as hydrodynamically balanced systems, swelling systems and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.⁷

Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites. Floating microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance.⁸

controlled release dosage forms. Although EC is considered insoluble, it can take up water. This is because of its hydrogen bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of polymer.⁸

The aim of this study was to prepare ethyl cellulose floating microspheres containing ranitidine hydrochloride to achieve a controlled release profile suitable for oral administration. Firstly, we investigated some formulation variables (polymer: drug ratio, stirring speed, concentration of surfactant) to obtain spherical particles.⁹ Then yield of production, particle size analysis, encapsulation efficiency, surface properties, and Ranitidine hydrochloride release rate from microspheres were investigated. The influences of formulation variables on the microspheres properties were examined and the microsphere formulations suitable to achieve our goal were determined.¹⁰

2. MATERIAL AND METHODS

Ranitidine hydrochloride, Alkem laboratories, Mumbai; ethyl cellulose, span 20, liquid paraffin, n-hexane; S.D Fine chemicals, Mumbai. Other chemicals used were all of analytical grade.

2.1 Preparation of microspheres

Ranitidine hydrochloride floating microspheres were prepared by non-aqueous solvent evaporation technique.

Different amounts of polymer (150, 300, 450, 600, and 750 mg) was dissolved in 25 ml of ethanol by using a magnetic stirrer (Popular India Limited, Mumbai). Powdered Ranitidine hydrochloride (150 mg) was dispersed in polymer solution.

The resulting dispersion was then poured into a vessel of 1000 ml containing the mixture of 270 ml liquid paraffin and 30 ml n-hexane while stirring.

Span 20 was added drop by drop into vessel during stirring. A mechanical stirrer with a blade (6 cm)

diameter (Prompt, F.H.P Motor, Uttam Electrical Industries, Varanasi) was used. Stirring was continued for an hour, until ethanol evaporated completely. Drug: polymer ratio (1:1, 1:2, 1:3, 1:4, and 1:5 w/w), span 20 (0.2, 0.3, 0.4, 0.5 %) and stirring speed (500, 750, 1000 rpm) of the system were changed to obtain spherical particles. After evaporation of ethanol, the microspheres formed were collected by filtration, washed 4-5 times with 50 ml n-hexane each and dried at room temperature for 24 hours.

Table 1: Optimization of drug polymer ratio

Batch	Drug: polymerratio	Average diameter (µm)	DEE (%wt/wt)	Buoyancy (%)
EC 1	1:1	212(±2.36)	69.68(±1.53)	90
EC 2	1:2	234(±2.15)	71.47(±2.24)	92
EC3	1:3	260(±1.56)	72.12(±2.16)	93
EC4	1:4	285(±2.47)	74.57(±2.96)	95
EC5	1:5	294(±1.98)	73.78(±3.05)	95

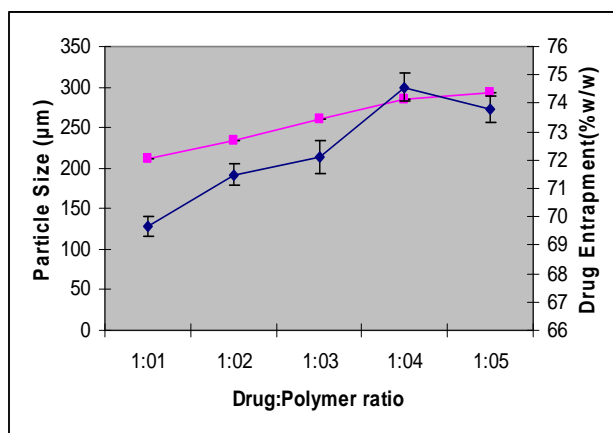


Figure1: Effect of drug polymer ratio on average particle size and Percent drug entrapment

2.2 Optimization of stirring speed

Stirring speed plays an important role in the microspheres size distribution and drug loading. Microspheres were prepared by the method described above with optimized ratio of drug and the polymer (1:4), keeping surfactant concentration (0.2%) constant, utilizing three different speeds i.e. 500, 750, and 1000 rpm.

Table 2: Optimization of stirring speed

Batch	RPM	Average diameter(µm)	DEE (%wt/wt)
EC 4	500	320 (±2.5 µm)	65.59 (±2.7)
EC 4	750	285 (±1.3 µm)	75.18 (±1.5)
EC 4	1000	260 (±2.2µm)	69.23 (±2.8)

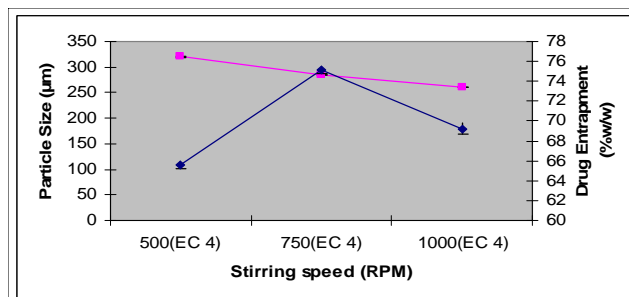


Figure 2: Effect of stirring speed on average particle size and Percent drug entrapment

2.3 Optimization of emulsifier (span 20)

Concentration of emulsifier is an important parameter which needs to be optimized for optimum particle size and stability of the microspheres. Span 20 was used as an emulsifier and various concentrations of span 20 were taken. Microspheres were prepared according to method described above with optimized drug polymer ratio i.e. 1:4 and stirring speed 750 rpm with various concentrations i.e. 0.2 %, 0.3 %, 0.4 % and 0.5 % v/v of span 20.

Table 3: Optimization of emulsifier (span 20)

Batch	Span 20 (%V/V)	Average diameter(µm)	DEE (%wt/wt)
EC 4	0.2	310 (±2.11 µm)	70.43 (±2.25)
EC 4	0.3	305 (±2.45 µm)	72.68 (±1.86)
EC4	0.4	280 (±3.15 µm)	76.43 (±2.25)
EC4	0.5	260 (±2.27 µm)	69.63 (±1.26)

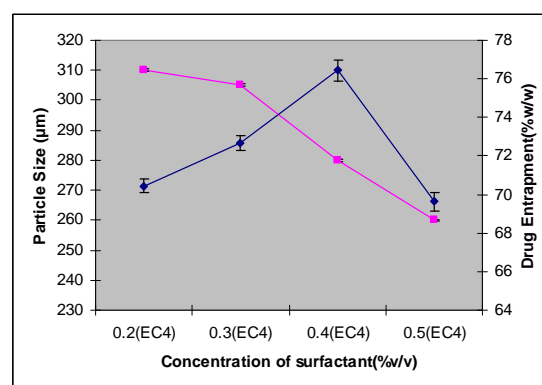


Figure 3: Effect of emulsifier concentration on average particle size and percent drug entrapment

Microspheres dried at room temperature were then weighed and yield of microsphere preparation was calculated using the formula:

$$\text{Percent yield} = \frac{\text{the amount of microspheres obtained (g)}}{\text{the theoretical yield (g)}} \times 100$$

2.4 Scanning electron microscopy

Shapes and surface characteristics of the microspheres were investigated and photographed using scanning electron microscopy.

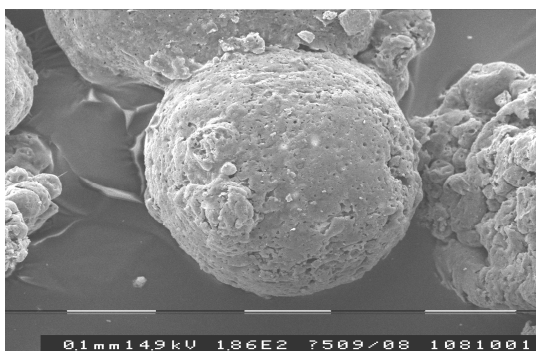


Figure 4: Surface morphology of floating microspheres of Ranitidine hydrochloride

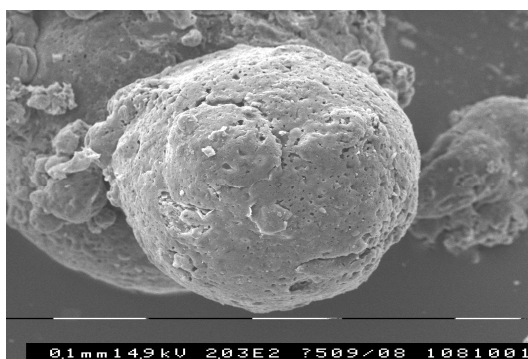


Figure 5: Surface morphology of floating microspheres of Ranitidine hydrochloride

2.5 Determination of mean particle size

Mean particle size of microspheres was determined by using optical microscopy (Table 1).

2.6 Drug entrapment efficiency

A quantity of microspheres containing 100mg equivalent of Ranitidine hydrochloride were incubated in 0.1 N HCl for 24 hours to determine drug entrapment efficiency. Ranitidine hydrochloride concentration was determined by measuring absorbance at 315 nm against reagent black (Table 1).

2.7 % Buoyancy

% buoyancy was carried out using 0.1 N HCl containing 1% span 20 as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37± 0.5 °C. A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collected at a predetermined time point. The collected samples were weighed after drying.

$$\% \text{ Buoyancy} = \frac{\text{weight of microspheres floating on the surface}}{\text{initial total weight of microspheres}}$$

2.8 In vitro release studies

In vitro drug release study of all the batches were carried out by paddle method using USP type 2 apparatus using 900 ml of 0.1 N HCl as dissolution medium at 750 rpm and 37±0.5°C. A quantity of microspheres containing 100mg equivalent of Ranitidine hydrochloride was placed in the dissolution medium. The samples were withdrawn at a predetermined time interval, diluted approximately and were analyzed spectrophotometrically at 315 nm against reagent blank.

Table 4: In vitro release profile of all formulations in 0.1 N HCL

Time (hrs)	Percent cumulative drug release± S.D				
	EC 1	EC 2	EC3	EC 4	EC 5
01	20.17 (±1.0)	19.23 (±1.10)	19.23 (±0.68)	19.22 (±0.75)	20.64 (±0.68)
02	27.75 (±1.2)	24.91 (±1.19)	23.49 (±1.17)	26.80 (±1.34)	31.53 (±1.22)
03	33.9 (±2.1)	32.95 (±2.14)	31.53 (±2.12)	34.85 (±2.35)	41.49 (±2.32)
04	41.49 (±1.8)	41.01 (±1.84)	37.69 (±1.95)	43.38 (±2.9)	51.42 (±2.09)
05	47.17 (±2.2)	50.49 (±2.16)	44.33 (±2.07)	50.12 (±1.98)	58.06 (±2.01)
06	54.27 (±2.2)	58.53 (±2.23)	52.38 (±2.29)	56.17 (±2.47)	65.17 (±2.37)
07	59.95 (±2.8)	65.17 (±2.08)	59.49 (±2.36)	63.27 (±2.42)	69.42 (±2.84)
08	67.53 (±2.7)	69.90 (±2.81)	65.86 (±2.08)	69.42 (±2.38)	73.22 (±2.18)
09	74.17 (±3.2)	74.64 (±3.14)	73.22 (±3.11)	73.69 (±3.05)	74.64 (±3.10)
10	78.42 (±3.4)	78.91 (±3.4)	77.49 (±3.3)	76.53 (±3.05)	76.53 (±3.40)
11	82.6 (±3.1)	80.33 (±3.01)	79.84 (±2.10)	78.42 (±3.05)	77.95 (±3.10)
12	85.11 (±3.2)	84.08 (±3.10)	83.27 (±3.0)	81.33 (±3.15)	80.91 (±2.55)

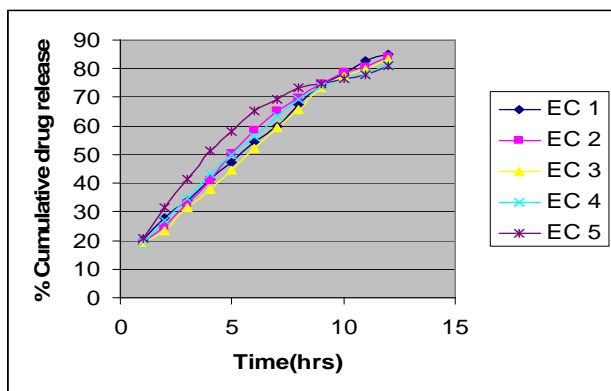


Figure 6: In vitro release curve of Ranitidine Hydrochloride in 0.1 N HCL

Table 5: correlation coefficient of optimized batch (EC 4)

No.	Zero order	First order	Hixon crowell plot	Higuchi plot	korsmeyer peppas
1	0.9671	0.9956	0.918	0.9925	0.8784

2.9 Statistical analysis

The data obtained release rate determination studies of Ranitidine hydrochloride microspheres were analyzed statistically with one-way ANOVA followed by Newman-Keuls Multiple Comparison value obtained ($p < 0.05$) was considered to be statistically significant.

3. RESULT AND DISCUSSION

Non aqueous solvent evaporation method was used to prepare Ranitidine hydrochloride floating microspheres. First, trial was made to prepare microspheres by using a solvent evaporation technique in the water phase, using ethanol water system; but although many formulations were investigated, no spherical particles could be obtained. Then ethanol/liquid paraffin system was used and various formulations with different drug: polymer ratios were tried, stirring speed was also changed to obtain spherical particle.

When drug: polymer ratio was too low (1:1, w/w) no spherical particle were obtained independent of stirring speed of the system (500, 750 or 1000). These results show that the amount of solid, thus the

viscosity of the inner phase is an important factor for the preparation of microspheres. Keeping the drug amount and the solvent amount volume constant, spherical particles were obtained as the amount of polymer increased to give a polymer drug ratio (3:1) (stirring speed 750 or 500 rpm) or 4:1 (stirring speed 750 rpm). However, when polymer : drug ratio was (4:1), the shape of particles were irregular at 500 rpm, because for this high polymer concentration, this stirring speed was not fast enough to disperse inner phase in outer phase. When stirring speed was 750 rpm the best spherical particles with good surface characteristics were obtained with the polymer: drug ratio of 4:1. Two examples of the scanning electron micrographs of the microspheres prepared are shown in figure 4 and 5.

On the other hand, drug entrapment efficiency was found to increase with increase in polymer concentration. At 4:1 polymer: drug ratio (EC 4) drug entrapment efficiency was found to be maximum $74.57(\pm 2.96)$. % buoyancy of optimized formulation (EC 4) found to be 95%.

Most of the microspheres obtained were collected in the size range of 200-300 μm by all formulation (Table 1). Increasing the polymer: drug ratio caused the mean particle size to shift towards a higher particle size. Higher concentration of polymer produced a more viscous dispersion which formed larger droplet and consequently larger microspheres.

Increasing the stirring speed decreased the particle size of microspheres. The yield of preparation and Ranitidine hydrochloride entrapment efficiencies were high for all formulations and maximum for optimized formulation (EC 4).

The drug release rate from microspheres were studied at pH 1.2 or (0.1 N HCL) using the USP type 2 paddle method. The in vitro drug release profile was biphasic with an initial burst release (19.22 %) in 1 hour attributed to surface associated drug, followed by a slower release phase as the entrapped drug

slowly diffuse out into the release medium. 81.33 % drug release after 12 hours there was a sustain release of drug at a constant rate. The absorbed molecules on surface of particle are rapidly desorbed when in contact with the dissolution medium. The diffusion of drug, the erosion and degradation of polymer are the main mechanism for the drug release.

Kinetics model further support the above statement. Zero order, first order, hixon crowell cube root plot, korsmeyer peppas, higuchi plot were applied on optimized formulation. The n value and r² value show that the formulation releases the drug by erosion as well as diffusion and optimized batch follow this release kinetic model (Table 5).

Statistical analysis was carried out by applying one way ANOVA followed by Newman Keuls Multiple Comparison, value obtained (p< 0.05) was considered to be statistically significant. The studied showed that drug release from all formulations was not found to be statistically significant. But on the basis of required size, shape, drug entrapment efficiency of floating microspheres EC 4, drug: polymer ratio (1:4) was found to be optimum batch.

4. CONCLUSION

Ranitidine hydrochloride floating microspheres were prepared successfully using non-aqueous solvent evaporation method. Polymer: drug ratio and stirring speed of the system were important to obtain spherical particles. The yield of preparation and entrapment efficiency were high for all formulations. Ranitidine hydrochloride is water soluble drug which gives a controlled release from ethyl cellulose microspheres. Thus gastroretentive floating microspheres of Ranitidine hydrochloride supposed to remain in the stomach for longer period of time and give controlled release. These formulations can reduce dosing frequency, decrease side effects and improve patient compliance.

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