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GASTRIC FLOATING MICROSPHERES OF RANITIDINE HYDROCHLORIDE: FORMULATION AND *IN VITRO* EVALUATION

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ABSTRACT

The present study involves the preparation of ranitidine hydrochloride loaded floating microspheres in order to prolong the gastric retention time. The microspheres were prepared by the solvent evaporation method using ethyl cellulose as polymeric material and a mixture of ethanol and dichloromethane (1:1) as solvent system. The prepared microspheres were evaluated for flow properties based on parameters such as angle of repose, Hausner's ratio and Carr's index. The effect of processing and formulation variables such as stirring speed and drug-to-polymer ratio on the mean particle size, percentage yield, entrapment efficiency and *in vitro* buoyancy profile were also studied. The mean particle size increased at higher polymeric concentration. Findings also indicated that prepared floating microspheres exhibit excellent buoyancies in simulated gastric fluid.

Key words: Floating microspheres, Ranitidine hydrochloride, *In vitro* buoyancy profile, Solvent evaporation method.

INTRODUCTION

Numerous technological developments have been utilized globally to prolong the residence time of dosage forms in the stomach[1]. Various approaches are explored to retain the dosage form in the stomach as a way of increasing the gastric residence time (GRT), including floatation systems; high-density systems; mucoadhesive systems; magnetic systems; unfoldable, extendible, or swellable systems; and superporous hydrogel systems[2,3]. Floating drug delivery systems are among the several approaches that have been developed to increase the GRT of dosage forms. These systems are gaining popularity due to several therapeutic advantages and patient compliance benefits[4, 5]. Both single and multiple unit floating systems can be designed. The single-unit floating systems are more popular but have a disadvantage owing to their 'all-or-nothing' emptying process, leading to high variability of the gastrointestinal transit time[6,7]. In contrast, multiple-unit particulate dosage forms (e.g., microspheres) have the advantages that they pass uniformly through the gastrointestinal tract (GIT) to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing the intersubject variability in absorption and risk of local irritation[8].

The objective of present investigation was to prepare gastric floating microspheres of ranitidine hydrochloride as a model drug to reduce frequency of administration, increase bioavailability of drug and

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subsequently improve patient compliance. Ranitidine hydrochloride is a H_2 receptor antagonist used in the treatment of gastric ulcers, gastroesophageal reflux disease and Zollinger-Ellison syndrome. However, due to its short half life and low bioavailability, traditional immediate-release ranitidine hydrochloride dosage forms need to be administered three times a day. It exhibits lower bioavailability when given in conventional dosage forms due to diminished absorption and degradation in the lower part of the GIT. Colonic metabolism is also partly responsible for poor bioavailability of ranitidine hydrochloride, thereby, favouring gastroretentive delivery[9-13].

In this study, ranitidine hydrochloride loaded floating microspheres were prepared by the solvent evaporation method and characterized for their particle size, flow properties, percentage yield, drug entrapment efficiency and *in vitro* buoyancy profile.

EXPERIMENTAL

Preparation of floating microspheres

The composition of different formulations of ethyl cellulose floating microspheres is shown in Table 1. Floating microspheres were prepared by using solvent evaporation technique. In this technique, drug and polymer were weighed and co-dissolved at room temperature into a mixture of ethanol (Eth) and dichloromethane (DCM) (1:1, solvent ratio) with vigorous agitation to form uniform drug-polymer dispersion. This dispersion was then slowly poured into the continuous medium consisting of liquid paraffin containing Span 80 as a surfactant. The system was stirred using an overhead propeller agitator at varying speed and room temperature over a specific period of time to ensure complete evaporation of the solvent. The liquid paraffin was decanted and the floating microspheres formed were separated by filtration through a Whatman filter paper, washed thrice with n-hexane, air dried for 24 hr and subsequently stored in the desiccator until further investigation[14-19]. The drug-to-polymer ratio and stirring speed were varied in formulations F1 to F9.

Table 1: Formulation design of ethyl cellulose (EC) floating microspheres

Formulation code	Drug : EC	Stirring speed (rpm)	Solvent system (Eth : DCM)
F1	1:1	500	1:1
F2	1:1	700	1:1
F3	1:1	900	1:1
F4	1:2	500	1:1
F5	1:2	700	1:1
F6	1:2	900	1:1
F7	1:3	500	1:1
F8	1:3	700	1:1
F9	1:3	900	1:1

Particle size analysis

The particle size of the microspheres was measured using an optical microscope and the mean particle size was calculated by measuring particles with the help of a calibrated ocular micrometer[20].

Measurement of flow properties

Angle of repose (θ) of different formulation, which measures the resistance to particle flow, was determined by using a fixed funnel method and calculated as follows:

$$\tan \theta = \frac{2H}{D} \quad \ldots(1)$$

where 2*H*/*D* is the surface area of the free standing height of the microspheres heap, which is formed on a graph paper after making the microspheres flow from the glass funnel[20].

Hausner's ratio of the microspheres was calculated by using following formula[21]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots(2)$$

The Carr's index of microspheres was determined by following equation[21]:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \ldots(3)$$

Percentage yield

The yield was calculated by dividing the weight of the collected microspheres by the weight of all the non-volatile components used for the preparation of microspheres and expressed in the terms of percentage[22].

$$\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100 \quad \ldots(4)$$

Drug entrapment efficiency

Accurately weighed amount of drug loaded microspheres were crushed in a glass mortar and pestle, and then the powdered microspheres were dissolved in a simulated gastric fluid. The resulting mixture was also continuously shaken by the magnetic stirrer for 24 hr to extract the drug from microspheres completely. The solution was filtered and an aliquot was assayed spectrophotometrically for ranitidine hydrochloride. Each formulation was examined in a triplicate manner. Drug entrapment efficiency was determined by using the following equation[23,24]

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad \ldots(5)$$

***In vitro* buoyancy test**

In vitro floating test was performed by spreading the floating microspheres on a simulated gastric fluid containing the surfactant in USP type II dissolution test apparatus. The media was agitated at 37 ± 0.5°C. After specific intervals of time, both the fractions of microspheres (floating and settled microspheres) were collected separately. The microspheres were dried and weighed. Buoyancy percentage of the floating microspheres was calculated by using formula[25].

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_s} \times 100 \quad \ldots(6)$$

where, Q_f and Q_s are the weights of floating and settled microspheres, respectively. All the determinations were made in triplicate.

RESULTS AND DISCUSSION

Preparation of floating microspheres

Ranitidine hydrochloride floating microspheres were prepared by using the solvent evaporation method. Ethyl cellulose was selected as a polymer for the preparation of floating microspheres owing to its film forming, release rate controlling ability, non-toxicity, non-irritancy, stability at gastrointestinal pH, compatibility with drug and good mechanical strength property. It has also been found that the kind of mechanical device utilized for stirring also influenced the size of particles formed. The magnetic stirrer often provided larger particles along with sticky masses owing to its comparatively lower stirring speed when compared to the propeller agitator, which has higher stirring speed. Therefore, discrete and free flowing microparticles were formed by employing propeller agitator.

Particle size analysis

Microspheres were prepared by using a gradually increasing concentration of ethyl cellulose with a fixed concentration of ranitidine hydrochloride in order to assess the effect of polymer concentration on the size of microspheres. The data revealed that particle size was highly influenced by polymer concentration. The mean particle size of the microspheres significantly increased with the increase in polymer concentration and found in the size range of 117.91 ± 3.239 µm to 294.34 ± 2.119 µm as presented in Table 2. This might be due to the increase in viscosity of the medium at a higher polymer concentration resulting in enhanced interfacial tension. In addition, shearing efficiency is also diminished at higher viscosities, resulting in the formation of larger particles. The particle size of formulation **F1** containing 1:1 drug: polymer ratio was found to be 138.43 ± 4.195 µm, in case of **F4** with 1:2 drug: polymer ratio was 190.49 ± 1.963 µm and in **F7** with 1:3 drug: polymer ratio was 294.34 ± 2.119 µm. In all these formulations, stirring speed has been kept constant i.e. 500 rpm.

To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying stirring speeds (500-900 rpm). Results indicated that the size of the resulting microspheres decreased with the increase in speed of stirring as shown in Table 2. This may be attributed to the high rotation speed of the propeller provide high shearing force resulting into the breakdown of drug polymer solution into smaller globules. As observed from formulations (**F1** to **F3**) having same drug: polymer ratio (1:1) but prepared at varying stirring speed, particle size was found to be in the range 138.43 ± 4.195 to 117.91 ± 3.239 µm.

Micromeritics studies

Microspheres were evaluated for flow properties by calculating the angle of repose, Hausner's ratio and Carr's index. Results of flow properties of microspheres are summarized in Table 2. Calculated value of angle of repose of microspheres lies in between 28.33 ± 0.531° – 32.45 ± 0.386° indicating good flow properties. The calculated value of angle of repose was compared with that of standard value, which reveals that all the prepared formulations showed good flow characteristics. Results of Hausner's ratio of all the prepared formulations are also shown in Table 2 and compared with that of standard value, which illustrates

that all formulations possesses good flow properties. Findings were also further substantiated by the values of Carr's index, which indicate good flow characteristics of prepared floating microspheres. This also signifies that the formulated microspheres were non-aggregated along with improved micromeritics characteristics. Thus, it is an added advantage while processing the formulation using high-speed packaging equipments. Moreover, the process scale up is also facilitated because of good flow properties.

Table 2: Micromeritics of ethyl cellulose floating microspheres

Formulation code	Angle of repose (θ)	Hausner's ratio	Carr's index	Mean particle size (µm)
F1	32.45 ± 0.386	1.15 ± 0.016	12.67 ± 1.205	138.43 ± 4.195
F2	29.04 ± 0.015	1.13 ± 0.012	11.22 ± 0.896	128.98 ± 7.301
F3	31.51 ± 0.426	1.17 ± 0.017	14.64 ± 1.223	117.91 ± 3.239
F4	30.04 ± 0.031	1.16 ± 0.007	13.68 ± 0.513	190.49 ± 1.963
F5	28.44 ± 1.001	1.17 ± 0.010	14.76 ± 0.746	175.71 ± 1.831
F6	30.30 ± 1.144	1.13 ± 0.011	11.39 ± 0.873	162.33 ± 6.298
F7	28.33 ± 0.531	1.12 ± 0.014	11.08 ± 1.012	294.34 ± 2.119
F8	29.57 ± 1.449	1.16 ± 0.017	13.56 ± 1.277	263.73 ± 3.026
F9	31.05 ± 0.081	1.14 ± 0.015	12.60 ± 1.180	231.55 ± 2.049

Data are expressed as mean ± SD (n=3)

Percentage yield

The percentage yield of various formulations was determined by dividing the weight of prepared floating microspheres by the weight of all the non-volatile components utilized for the preparation of microspheres. The percentage yield of floating microspheres varied from 74.52 ± 0.350% - 89.36 ± 0.282% as depicted in Table 3. From results, it has been observed that the percentage yield of resulting microspheres increased with increase in the concentration of polymer. As observed in the formulations **F1** (77.18 ± 0.166%), **F4** (82.13 ± 0.061%) and **F7** (89.36 ± 0.282%) having drug: polymer ratio of 1:1, 1:2 and 1:3, respectively. At low concentration of the polymer, a portion of the polymer solution may aggregate into a fibre-like structure, as it solidified before forming droplets, or the transient droplets were broken before solidification was complete resulting in low yield. It has also been observed that product yield may depend upon the formation of agglomerates accompanied with sticking of the polymers to the stirrer blade and to the wall of the beaker surface during microspheres formation. The percentage yield decreased, when stirring speed increased from 500 to 900 rpm. At higher stirring speed, the percentage yield decreases as it leads to the break up of microspheres. This was concluded from the results obtained in Table 3. As shown in case of formulations **F1** (77.18 ± 0.166%), **F2** (75.10 ± 0.096%) and **F3** (74.52 ± 0.350%) prepared at varying speed (500-900 rpm).

Drug entrapment efficiency

The drug entrapment efficiency of all formulations is depicted in Table 3 and varied from 61.54 ± 0.972% – 82.79 ± 1.921%. Results demonstrated that an increase in the concentration of ethyl cellulose increased the entrapment efficiency of the drug. This may be due to the increase in viscosity at higher polymer concentration restricted the movement of drug from polymer matrix into external phase. In addition, an increase in concentration of ethyl cellulose also resulted in the formation of larger microspheres, which

causes slow diffusion of drug with in polymer droplets, thus entrapping more amount of drug. Moreover, the high entrapment efficiency of drug can also be attributed to its less solubility in the external phase. The entrapped drug may not leach into the surrounding medium, which ultimately resulted into the good entrapment efficiency. However, drug entrapment efficiency decreases with the increase in stirring speed. This may be due to smaller size microspheres formed at higher speed of rotation.

In vitro buoyancy studies

The purpose of preparing floating microspheres was to extend the gastric residence time of the drug. The floating ability test was carried out to investigate the floatability of the prepared microspheres. The microspheres were spread over the surface of simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantified. It was observed that all formulations showed buoyancy percentage of more than 67.52 ± 2.597 % as represented in Table 3.

Table 3: Physicochemical properties of the ethyl cellulose floating microspheres

Formulation code	Percentage yield (%)	Entrapment efficiency (%)	Percentage buoyancy (%)
F1	77.18 ± 0.166	67.55 ± 3.215	72.67 ± 0.901
F2	75.10 ± 0.096	63.03 ± 1.970	70.71 ± 1.131
F3	74.52 ± 0.350	61.54 ± 0.972	67.52 ± 2.597
F4	82.13 ± 0.061	73.42 ± 1.257	80.59 ± 2.150
F5	79.23 ± 0.327	70.50 ± 2.583	77.05 ± 3.025
F6	78.29 ± 0.235	68.53 ± 1.563	74.35 ± 2.419
F7	89.36 ± 0.282	82.79 ± 1.921	87.06 ± 1.010
F8	87.71 ± 0.195	79.38 ± 2.501	85.64 ± 1.159
F9	84.48 ± 0.261	75.45 ± 0.545	82.23 ± 0.883

Data are expressed as mean ± SD (n = 3)

The microspheres containing ethyl cellulose showed good floating ability due to the insolubility of ethyl cellulose polymer in the simulated gastric fluid (pH 1.2). In general, the results also showed a tendency that the larger is the particle size, the longer is the floating time. The microspheres with higher concentration of polymer were more floatable than those with lower concentrations of polymer. Furthermore, all formulations floated for prolonged time over the surface of the medium without any apparent gelation, thus, indicating that prepared microspheres exhibit excellent buoyancies, which may be attributed to the pores and cavities present in them. It is pertinent to mention that the situation of *in vivo* can be quite different and the residence time may vary widely depending on the phase of gastric motility.

CONCLUSION

In the present work, multi-unit floating microspheres of ranitidine hydrochloride were formulated to provide an effective and safe therapy for stomach ulcer. Ranitidine hydrochloride loaded ethyl cellulose floating microspheres were prepared easily and successfully by using the solvent evaporation technique. Developed microspheres showed good physicochemical characteristics. Particle size, entrapment efficiency and production yield were highly influenced by the drug-to-polymer ratio and stirring speed. *In vitro* data obtained for floating microspheres of ranitidine hydrochloride revealed satisfactory buoyant ability.

Therefore, the formulated floating microspheres may prove to be a potential candidate as an oral gastroretentive system for better therapeutic interventions and subsequently facilitates an enormous impact on patient compliance.

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REFERENCES

1. B. N. Singh and K. H. Kim, J. Control. Release, **63(3)**, 235-259 (2000).
2. R. Talukder and R. Fassihi, Drug Dev. Ind. Pharm., **30(10)**, 1019-1028 (2004).
3. R. Pahwa, S. Bisht, V. Kumar and K. Kohli, Curr. Drug Deliv., **10(3)**, 286-298 (2013).
4. S. Arora, J. Ali, A. Ahuja, R. K. Khar and S. Baboota, AAPS PharmSciTech., **6(3)**, E372–E390 (2005).
5. K. Adibkia, S. Hamedeyazdan and Y. Javadzadeh, Expert Opin. Drug Deliv., **8(7)**, 891-903 (2011).
6. A. A. Deshpande, C. T. Rhodes, N. H. Shah and A. W. Malick, Drug Dev. Ind. Pharm., **22(6)**, 531-539 (1996).
7. A. K. Srivastava, D. N. Ridhurkar and S. Wadhwa, Acta Pharm., **55(3)**, 277-285 (2005).
8. P. Bhadouriya, M. Kumar and K. Pathak, Curr. Drug Deliv., **9(3)**, 315-324 (2012).
9. S. M. Grant, H. D. Langtry and R. N. Brogden, Drugs, **37(6)**, 801-870 (1989).
10. R. N. Brogden, A. A. Carmine, R. C. Heel, T. M. Speight and G. S. Avery, Drugs, **24(4)**, 267-303 (1982).
11. K. Florey, Analytical Profiles of Drug Substances, Vol. XV. Academic Press, London (1986) p. 535.
12. M. F. Williams, G. E. Dukes, W. Heizer, Y. H. Han, D. J. Hermann, T. Lampkin and L. J. Hak, Pharm. Res., **9(9)**, 1190-1194 (1992).
13. A. W. Basit and L. F. Lacey, Int. J. Pharm., **227(1-2)**, 157-165 (2001).
14. P. B. Donnell and J. W. McGinity, Adv. Drug Deliv. Rev., **28(1)**, 25-42 (1997).
15. Y. S. Gattani, D. A. Bhagwat and A. P. Maske, Asian J. Pharm., **2(4)**, 228-231 (2008).
16. V. Pandit, R. S. Pai, V. Yadav, K. Devi, B. B. Surekha, M. N. Inamdar and S. Sarasija, Drug Dev. Ind. Pharm., **39(1)**, 117-127 (2013).
17. D. Karthikeyan, M. Karthikeyan and C. Ramasamy, Acta Pharma. Sci., **52**, 101-104 (2010).
18. D. S. Jones and K. J. Pearce, Int. J. Pharm., **118(2)**, 199-205 (1995).
19. S. Haznedar and B. Dortunc, Int. J. Pharm., **269(1)**, 131-140 (2004).
20. P. J. Sinko, Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th Ed., Lippincott Williams and Wilkins, Philadelphia (2006) p. 558.
21. B. R. Rane, N. A. Gujarathi and J. K. Patel, Drug Dev. Ind. Pharm., **38(12)**, 1460-1469 (2012).
22. S. K. Sahoo, A. A. Mallick, B. B. Barik and P. C. Senapati, Trop. J. Pharm. Res. **4(1)**, 369-375 (2005).

23. P. K. Choudhury, M. Kar and C. S. Chauhan, Drug Dev. Ind. Pharm., **34(4)**, 349-354 (2008).

24. Y. Javadzadeh, S. Hamedeyazdan, K. Adibkia, F. Kiafar, M. H. Zarrintan and M. Barzegar-Jalali, Pharm. Dev. Technol., **15(4)**, 329-338 (2010).

25. P. Goyal, S. Gill, U. D. Gupta, G. Rath, R. K. Narang and A. K. Goyal, Artif. Cells Blood Substit. Biotechnol., **39(5)**, 330-334 (2011).