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Floating microspheres of cimetidine: Formulation, characterization and *in vitro* evaluation

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The present study involves preparation and evaluation of floating microspheres with cimetidine as model drug for prolongation of gastric residence time. The microspheres were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (~ 8 h) and remained buoyant for > 10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres.

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Keywords: floating microspheres, cimetidine, *in vitro* release, bioavailability

Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS) are among the several approaches that have been developed in order to increase the gastric residence time (GRT) of dosage forms (1–3). Both single and multiple unit systems have been developed. 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 (4, 5). Still, the multiple-unit dosage forms may be better suited because they are claimed to reduce the intersubject variability in absorption and lower the probability of dose dumping (6). Such a dosage form can be distributed widely throughout the gastrointestinal tract (GIT), affording the possibility of a longer lasting and more reliable release of the drug from the dosage form (7).

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Both natural and synthetic polymers have been used to prepare floating microspheres. Kawashima *et al.* prepared hollow microspheres or microballoons of ibuprofen by the emulsion-solvent diffusion method using acrylic polymers (8). The microspheres exhibited good *in vitro* floatability and drug release decreased drastically with increasing polymer concentration. Floating microspheres of cellulose acetate loaded with four different drugs were prepared using the solvent diffusion-evaporation method (9). The microspheres remained buoyant for more than 12 hours. Methylcellulose and chitosan micropellets loaded with lansoprazole had a lower density than gastric contents and exhibited better encapsulation efficiencies (10). Other polymer solution systems that have been used to prepare floating microspheres are polycarbonate/dichloromethane (11, 12), cellulose acetate butyrate/Eudragit RL100 mixture in acetone (13) and Eudragit S100/*i*-propanol (14).

Cimetidine (CM) was used as model drug. It is an H_2-antihistaminic drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome and reflux esophagitis (15). It is poorly absorbed from the lower gastrointestinal tract and has a short elimination half life (~ 2 h). The objective of the present study was to develop floating microspheres of CM in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for size, *in vitro* CM release, buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was investigated.

EXPERIMENTAL

Materials and apparatus

CM was obtained as a gift sample from Zydus Cadila Healthcare (India). Sodium chloride was obtained from S.D. Fine Chemicals Ltd. (India). Dichloromethane, hydroxypropylmethyl cellulose (HPMC), ethyl cellulose (EC) and Tween 80 were obtained from Central Drug House (P) Ltd. (India). All other chemicals/reagents used were of analytical grade.

A UV/Vis spectrophotometer (Jasco 7800, Japan) was used for drug analysis.

Preparation of microspheres

Microspheres were prepared by the solvent evaporation technique as employed by Struebel *et al.* (16). CM, HPMC and EC were dissolved in a mixture of ethanol and dichloromethane at room temperature (Table I). This was poured into 250 mL water containing 0.01% Tween 80 maintained at a temperature of 30–40 °C and subsequently stirred at ranging agitation speed for 20 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in vacuum.

Characterization of microspheres

Size and shape of microspheres. – The size of microspheres was determined using a microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular

Table I. Batch specifications of the prepared microspheres

Batch code	Polymer ratio (HPMC/EC)	Temperature (°C)	Solvent ratio (alcohol/DCM)
A1[a]	1:1	30–40	1:1
A2[a]	1:2	30–40	1:1
A3[a]	1:3	30–40	1:1
A4[a]	1:4	30–40	1:1
A5[a]	1:5	30–40	1:1
A6[a]	1:6	30–40	1:1
B1[b]	1:2	30–40	1:1
B2[b]	1:3	30–40	1:1
B3[c]	1:2	30–40	1:1
B4[c]	1:3	30–40	1:1
C1[a]	1:3	30–40	2:1
C2[a]	1:3	30–40	3:1
C3[a]	1:3	30–40	1:2
C4[a]	1:3	30–40	1:3

Stirring rate; a = 300 rpm; b = 500 rpm; c = 1000 rpm

micrometer and stage micrometer. Scanning electron microscopy (SEM) (Philips-XL-20, The Netherlands) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film (~ 200 nm) under reduced pressure (0.133 Pa).

Buoyancy percentage. – Microspheres (0.3 g) were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 mL 0.1 mol L^{-1} HCl containing 0.02% Tween 80 (17). The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

Incorporation efficiency (IE). – To determine the incorporation efficiency, microspheres were taken, thoroughly triturated and suspended in a minimal amount of alcohol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 218 nm.

In vitro *release.* – A USP basket apparatus has been used to study *in vitro* drug release from microspheres (18–20). In the present study, drug release was studied using a modified USP XXIV (17) dissolution apparatus type I (basket mesh # 120, equals 125 μm) at 100 rpm in distilled water and 0.1 mol L^{-1} HCl (pH 1.2) as dissolution fluids (900 mL) maintained at 37 ± 0.5 °C. Withdrawn samples (10 mL) were analyzed spectrophotometrically as stated above. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate.

Linear regression was used to analyze the *in vitro* release mechanism.

Statistical analysis. – Experimental results were expressed as mean ± SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Floating microspheres were prepared by the solvent evaporation method using HPMC and EC (Table I). The SEM photographs showed that the fabricated microspheres were spherical with a smooth surface and exhibited a range of sizes within each batch (Fig. 1). The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range 69,0 ± 3.2 % (batch B3) to 87.7 ± 5.5 (batch A6) (Table II).

Microspheres were prepared using a gradually increasing EC concentration in combination with a fixed concentration of HPMC to assess the effect of polymer concentration on the size of microspheres. The mean particle size of the microspheres significantly increased with increasing ethyl cellulose concentration ($p < 0.05$) and was in the range 237.2 ± 3.3 μm to 387.0 ± 9.8 μm (Table II). The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities (21, 22). This results in the formation of larger particles.

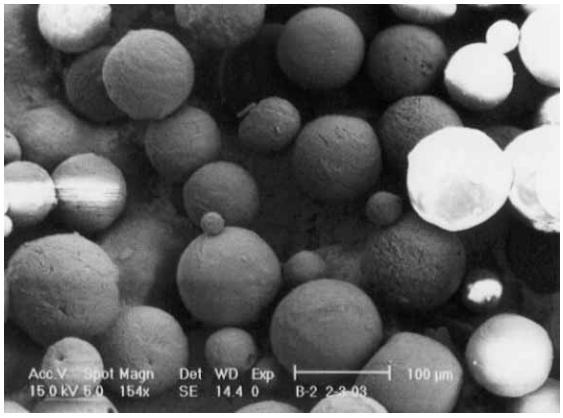
To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds (batches B1–B4). The size of the

Table II. Various formulation parameters for microspheres

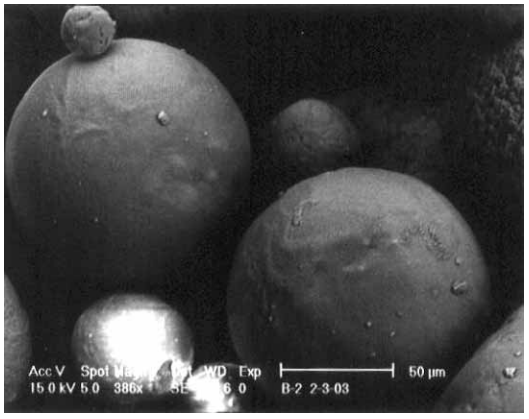
Batch code	Mean particle size[a] (μm)	Incorporation efficiency[b] (%)	Buoyancy[b] (%)
A1	237.2 ± 3.3	52.1 ± 2.3	71.0 ± 2.2
A2	258.0 ± 6.7	55.6 ± 4.8	74.7 ± 4.2
A3	273.5 ± 9.6	57.7. ± 2.7	76.0 ± 3.4
A4	309.5 ± 2.2	57.5 ± 5.5	80.7 ± 4.8
A5	340.7 ± 5.9	58.1 ± 1.8	83.7 ± 2.1
A6	387.0 ± 9.8	60.3 ± 3.8	87.7 ± 5.5
B1	219.0 ± 2.7	57.1 ± 4.9	78.0 ± 1.9
B2	242.0 ± 3.6	58.2 ± 4.7	72.0 ± 2.2
B3	205.1 ± 8.1	56.8 ± 3.8	69.0 ± 3.2
B4	213.4 ± 7.2	58.9 ± 5.3	69.7 ± 3.6
C1	252.0 ± 4.8	53.1 ± 1.9	73.6 ± 3.8
C2	239.0 ± 3.8	52.8 ± 3.8	71.0 ± 1.7
C3	276.5 ± 5.3	62.2 ± 2.1	79.7 ± 3.1
C4	289.5 ± 2.8	63.5 ± 5.2	76.3 ± 1.8

[a] Mean ± SD, $n = 10$.
[b] Mean ± SD, $n = 3$.

a)



b)



c)

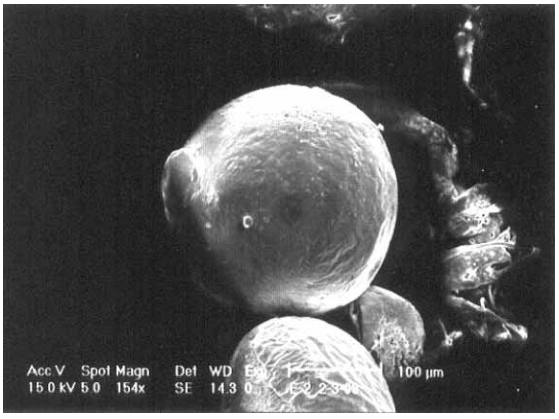


Fig. 1. Scanning electron microphotographs of floating microspheres (batch A3): a) the size range of microspheres; b) and c) smoothness of the surface of spherically shaped microspheres.

resulting microspheres decreased with increasing agitation but the increase was not statistically significant. It may be inferred that the agitation speed in the studied range was not able to break up the bulk of the polymer into finer droplets (23).

In vitro CM release studies were performed in 0.1 mol L^{-1} HCl for 8 h. The cumulative release of CM significantly decreased with increasing ethyl cellulose concentration ($p < 0.05$, Fig. 2). The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. CM release was higher in the case of microspheres prepared at a higher agitation speed but the difference in drug release was not statistically significant (Fig. 3). No significant effect of solvent composition was observed on the *in vitro* release of CM (Fig. 4).

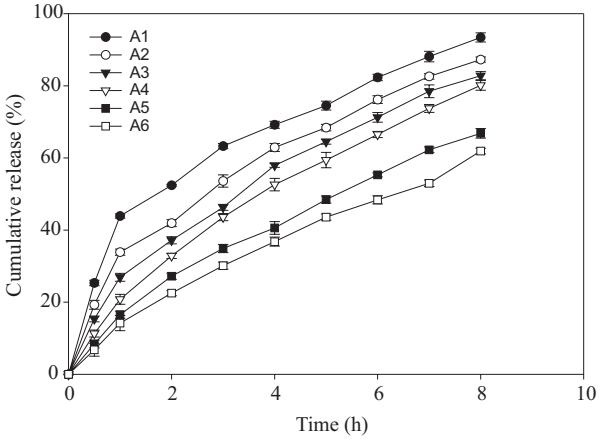


Fig. 2. Effect of polymer concentration on *in vitro* release of CM from floating microspheres (bars represent mean ± SD; $n = 3$, codes in Table I).

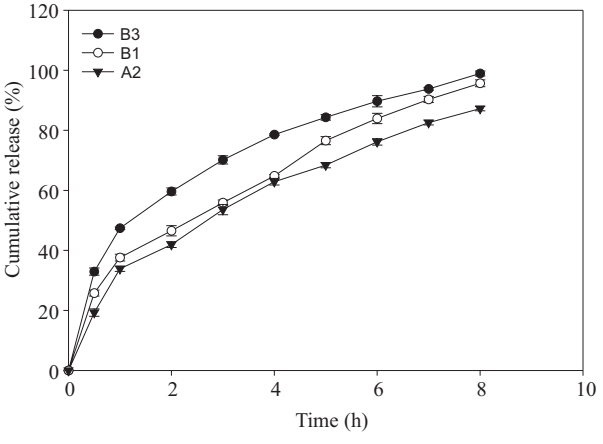


Fig. 3. Effect of the stirring rate during microsphere preparation on *in vitro* release of CM from floating microspheres (bars represent mean ± SD; $n = 3$, codes in Table I).

The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order and Higuchi release models (24–26). The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release.

The drug dissolution rate of diffusion-controlled systems in biological fluids is affected by the variability of pH and hydrodynamic conditions of the GI tract. Hence, a comparison was made in order to see the effect of different dissolution media on drug release. The solubility of CM in distilled water and 0.1 mol L^{-1} HCl at 37 °C was reported to be 11.4 and 250 mg mL^{-1}, respectively (27). This lower aqueous solubility might have result in a marked decrease in drug release. Significantly lower cumulative drug release ($p < 0.05$) was observed in distilled water compared to that in 0.1 mol L^{-1} HCl (Fig. 5).

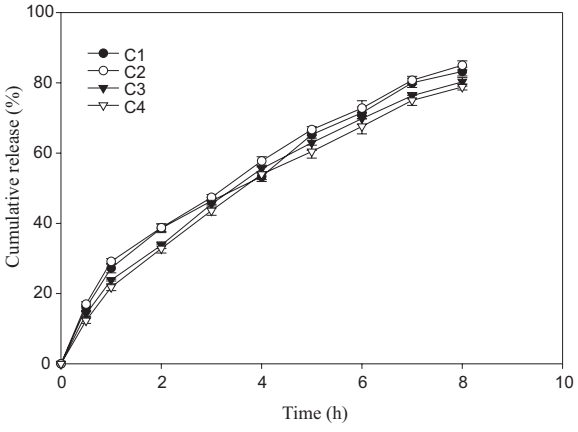


Fig. 4. Effect of solvent composition on *in vitro* release of CM from prepared microspheres (bars represent mean ± SD; $n = 3$, codes in Table I).

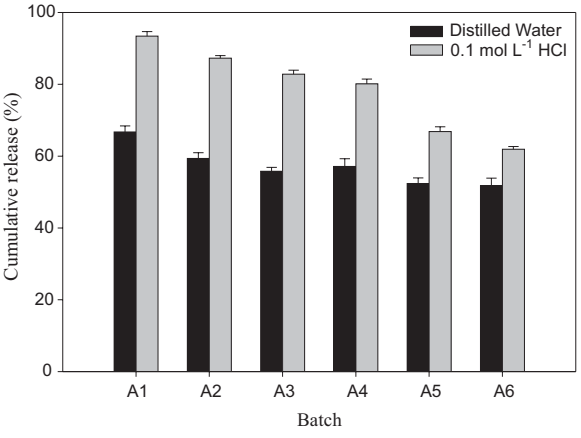


Fig. 5. *In vitro* release of CM from floating microspheres in distilled water and 0.1 mol^{-1} HCl (pH 1.2) after 8 h (bars represent mean ± SD; $n = 3$, codes in Table I).

CONCLUSIONS

In vitro data obtained for floating microspheres of cimetidine showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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REFERENCES

1. P. R. Seth and J. Tossounian, The hydrodynamically balanced system HBS^{TM}: A novel drug delivery system for oral use, *Drug Dev. Ind. Pharm.* **10** (1984) 313–339.
2. A. J. Moes, Gastroretentive dosage forms, *Crit. Rev. Ther. Drug Carrier Syst.* **10** (1993) 143–195.
3. A. A. Deshpande, C. T. Rhodes, N. H. Shah and A. W. Malick, Controlled-release drug delivery systems for prolonged gastric residence: an overview, *Drug Dev. Ind. Pharm.* **22** (1996) 531–539.
4. L. Whitehead, J. T. Fell, J. H. Collett, H. L. Sharma and A. M. Smith, Floating dosage forms: an in vivo study demonstrating prolonged gastric retention, *J. Control. Rel.* **55** (1998) 3–12.
5. R. Talukder and R. Fassihi, Gastroretentive delivery systems: a mini review, *Drug Dev. Ind. Pharm.* **30** (2004) 1019–1028.
6. N. Rouge, J. C. Leroux, E. T. Cole, E. Doelker and P. Buri, Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules, *Eur. J. Pharm. Biopharm.* **43** (1997) 165–171.
7. Y. Sato, Y. Kawashima, H. Takeuchi and H. Yamamoto, In vivo evaluation of riboflavin-containing microballoons for floating controlled drug delivery system in healthy human volunteers, *J. Control. Rel.* **93** (2003) 39–47.
8. Y. Kawashima, T. Niwa, H. Takechi, T. Hino and Y. Itoh, Hollow microspheres for use as floating controlled drug delivery systems in the stomach, *J. Pharm. Sci.* **81** (1992) 135–140.
9. K. S. Soppimath, A. R. Kulkarni, W. E. Rudzinski and T. M. Aminabhavi, Microspheres as floating drug-delivery systems to increase gastric retention of drugs, *Drug Metab. Rev.* **33** (2002) 149–160.
10. K. Muthusamy, G. Govindarazan and T. K. Ravi, Preparation and evaluation of lansoprazole floating micropellets, *Ind. J. Pharm. Sci.* **67** (2005) 75–79.
11. B. C. Thanoo, M. C. Sunny and A. Jayakrishnan, Oral sustained-release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluid, *J. Pharm. Pharmacol.* **45** (1993) 21–24.
12. N. J. Joseph, S. Lakshmi and A. Jayakrishnan, A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits, *J. Control. Rel.* **79** (2002) 71–79.
13. S. Stithit, W. Chen and J. C. Price, Development and characterization of buoyant theophylline microspheres with near zero order release kinetics, *J. Microencaps.* **15** (1998) 725–737.
14. J. H. Lee, T. G. Park and H. K. Choi, Development of oral drug delivery system using floating microspheres, *J. Microencaps.* **16** (1999) 715–729.
15. U. Gladiziwa and U. Klotz, Pharmacokinetics and pharmacodynamics of H2 receptor antagonists in patients with renal insufficiency, *Clin. Pharmacokinet.* **24** (1993) 319–332.

16. A. Struebel, J. Siepmann and R. Bodmeier, Multiple units gastroretentive drug delivery systems: a new preparation method for low density microspheres, *J. Microencaps.* **20** (2003) 329–347.
17. *The United States Pharmacopoeia XXIV*, United States Pharmacopoeial Convention, Rockville 2000, pp. 1941–1943.
18. B. N. Singh and K. H. Kim, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, *J. Control. Rel.* **63** (2000) 235–259.
19. R. Dinarvand, S. Mirfattahi and F. Atyabi, Preparation, characterization and *in vitro* drug release of isosorbide dinitrate microspheres, *J. Microencaps.* **19** (2002) 73–81.
20. S. Abrol, A. Trehan and O. P. Katare, Formulation, characterization, and *in vitro* evaluation of silymarin-loaded lipid microspheres, *Drug Deliv.* **11** (2004) 185–191.
21. B. P. Reddy, A. K. Dorle and D. K. Krishna, Albumin microspheres: effect of process variables on the distribution and *in vitro* release, *Drug Dev. Ind. Pharm.* **16** (1990) 1781–1803.
22. T. Ishizaka, Preparation of egg albumin microspheres and microcapsules, *J. Pharm. Sci.* **70** (1981) 358–361.
23. J. H. Ratcliffe, I. M. Hunney Ball, C. G. Wilson, A. Smith and S. S. Davis, Albumin microspheres for intra articular drug delivery: investigation of their retention in normal and arthritic knee joints of rabbits, *J. Pharm. Pharmacol.* **39** (1987) 290–315.
24. P. Costa and J. M. S. Lobo, Modeling and comparison of dissolution profiles, *Eur. J. Pharm. Sci.* **39** (1987) 39–45.
25. J. G. Wagner, Interpretation of percent dissolved-time plots derived from *in vitro* testing of conventional tablets and capsules, *J. Pharm. Sci.* **58** (1969) 1253–1257.
26. E. Schefter and T. Higuchi, Dissolution behavior of crystalline solvated and non-solvated forms of some pharmaceuticals, *J. Pharm. Sci.* **52** (1963) 781–791.

S A Ž E T A K

Plutajuće mikrosfere cimetidina: Priprava, karakterizacija i *in vitro* evaluacija

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U radu je opisana priprava i evaluacija plutajućih mikrosfera za produljeno zadržavanje u želucu. Cimetidin je izabran kao model lijeka. Mikrosfere su pripravljene metodom uparavanja otapala koristeći hidroksipropilmetilcelulozu i etilcelulozu. Optičkom, odnosno pretražnom elektronskom mikroskopijom karakterizirani su oblik mikrosfera i morfologija površine. Kinetika oslobađanja ljekovite tvari *in vitro* evaluirana je pomoću metode linearne regresije. Proučavan je utjecaj brzine miješanja tijekom priprave, koncentracije polimera, vrste otapala i medija za oslobađanje na veličinu mikrosfera, odnosno oslobađanje lijeka. Iz pripravljenih mikrosfera lijek se produljeno oslobađa (~ 8 h), a mikrosfere ostaju plutati više od 10 h. Veće mikrosfere dobivene su upotrebom veće koncentracije polimera. Pokusi *in vitro* ukazuju da je oslobađanje ljekovite tvari kontrolirano difuzijom. Brzina miješanja tijekom priprave nema utjecaj na oslobađanje ljekovite tvari.

Ključne riječi: plutajuće mikrosfere, cimetidin, *in vitro* oslobađanje, bioraspoloživost

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