Formulation and evaluation of oil entrapped gastroretentive floating gel beads of loratadine

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A gastro retentive controlled release system of loratadine was formulated to increase the residence time in stomach and to modulate the release behaviour of the drug. Oil entrapped floating microbeads prepared by the emulsion gelation method were optimized by 2^3 factorial design and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (m/V) of oil (mineral oil or castor oil) and 0.45 mol L^{-1} calcium chloride solution as the optimized processing conditions for the desired buoyancy and physical stability. *In vitro* drug release in the fed state conditions demonstrated sustained release of loratadine for 8 h, which best fitted the Peppas model with $n < 0.45$. The ethyl cellulose coating on microbeads optimized by 2^2 factorial design resulted in a controlled release formulation of loratadine that provided zero-order release for 8 h.

Keywords: loratadine, gastroretentive, factorial design, ethyl cellulose coating, zero-order release

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed only in a particular portion of GIT or are absorbed to a different extent in various segments of GIT. An absorption window exists because of physiological, physicochemical or biochemical factors. Recent scientific and patent literature reveals increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches is to control the gastric residence time using gastroretentive dosage forms (GRDDS) that can provide newer therapeutic options. GRDDS can improve controlled delivery of drugs by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability (1).

The purpose of designing a floating multiple unit dosage form is to develop a reliable formulation of loratadine that has all the advantages of a floating single unit dosage

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form but is devoid of disadvantages of single unit dosage forms, namely sticking to or being obstructed in the gastrointestinal tract. In spite of all sophisticated formulations, the retention time of the single unit (floating drug delivery system) FDDS depends on many physiological factors and it is a well known fact that early gastric emptying of a monolithic device causes rapid lack of therapeutic efficacy, especially with drugs having an absorption window only in the stomach (2).

Loratadine, a H_1 receptor blocker, is absorbed in the proximal part of the gastrointestinal tract; it is stable in acidic pH, has a narrow therapeutic absorption window in the GI tract and the presence of food enhances its bioavailability (3), meeting the primary criterion for selection of loratadine as the drug candidate to be formulated as a floating multiple unit dosage form.

The low methoxy polysaccharide, pectin, with the degree of esterification less than 50% can form rigid gels by the action of calcium ions or multivalent cations, which crosslink the galacturonic acid chains of pectin to yield hydrogels that are stable at low pH. In this study, the loratadine-loaded gastroretentive emulsion gel beads of calcium pectinate, were developed using selected oils. The release behaviour of the gel beads capable of floating in gastric fluid was investigated with the aim to achieve a gastroretentive, multiple unit, controlled release formulation of loratadine.

EXPERIMENTAL

Materials

Loratadine was obtained as a gift sample from Arti Pharmaceuticals, India. Low methoxy pectin with the degree of esterification of 35% and ethyl cellulose were obtained from S.D. Fine Chem., India. Light mineral oil and castor oil were obtained from the Central Drug House, India.

Optimization studies for floating gel beads

In the 2^3 factorial design (Table 1) used, three factors, namely, the ratio of polymers (pectin: sodium alginate), percentage of oil (mineral oil/castor oil) and concentration of cross linking agent (calcium chloride) were selected as independent variables while the bead size, shape, buoyancy and non leakage of oil from the beads were the response parameters used for optimization of process variables in preparation of floating gel beads.

Loratadine (1%, m/V) was levigated with sufficient quantity of Tween 20 and the smooth dispersion formed was transferred into a polymer mixture of pectin/sodium alginate (3:1). The mixture was stirred on a magnetic stirrer for 2 h and emulsified with either mineral oil or castor oil separately using Silverson emulsifier (Hicon, India) maintained at 500 rpm for 2 min. The drug loaded emulsion was extruded into 0.45 mol L^{-1} calcium chloride solution maintained under gentle agitation. Loratadine loaded beads containing either mineral oil (CPA$_{MO}$) or castor oil (CPA$_{CO}$) were separated, washed with water and allowed to dry at room temperature for 6 h (4, 5).

Table I. Independent variables and dependent responses for the 2^3 full factorial design of loratadine floating beads

Formulation code		Pectin/sodium alginate (*m/m*)	Oil (%, *m/V*)	Calcium chloride solution (mol L^{-1})	Oil leakage	Shape and flow property	Physical state after floating for 12 h
CPA$_{MO}$	CPA$_{CO}$						
F1	F9	2.5:1.5	15	0.275	yes	spherical and aggregated	intact
F2	F10	2.5:1.5	25	0.275	yes	spherical and aggregated	intact
F3	F11	2.5:1.5	15	0.450	no	spherical and free flowing	intact
F4	F12	2.5:1.5	25	0.450	yes	spherical and aggregated	intact
F5	F13	3.5:0.5	15	0.275	yes	spherical and sticky	flattened at the end
F6	F14	3.5:0.5	25	0.275	yes	spherical and sticky	flattened at the end
F7	F15	3.5:0.5	15	0.450	yes	spherical and sticky	flattened at the end
F8	F16	3.5:0.5	25	0.450	yes	spherical but sticky	flattened at the end

Size and morphology

The mean diameter of loratadine floating gel beads was determined by sieving. The collected fractions were weighed and the average particle size was determined. External surface and cross sections of gel beads were studied with a scanning electron microscope (Joel 6100, Japan). The gel beads and their cross sections were coated with gold-palladium under an argon atmosphere using a gold sputter module in a high vacuum evaporator.

Buoyancy

Seventy mL of each test medium (water, 0.1 mol L^{-1} HCl, acid phthalate buffer, pH 3.12 and normal saline) was separately agitated on a magnetic stirrer at 75 rpm and 37 °C and 1 g of the floating beads were incorporated into the test medium (6). The lag time to float and the floating behavior of the beads in each test medium were observed for a period of 12 h.

In vitro *drug release*

In vitro drug release characteristics of loratadine floating gel beads were evaluated in both fasted (0.1 mol L^{-1} HCl, pH 1.25) and fed state (acid phthalate buffer, pH 3.12) conditions. Dissolution of floating beads was carried out in a Modified Rosette Rice test

apparatus (7). A glass beaker was modified at the base by adding an 's' shaped glass tube so that the glass beaker can hold 70 mL of dissolution medium. The medium was stirred at 75 rpm on a magnetic stirrer and maintained at 37 °C. A burette connected to a reservoir was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 mL min^{-1}. Sampling was done at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h when 5 mL aliquots were withdrawn, suitably diluted and analyzed at 282.5 nm and 273.5 nm (UV spectrophotometer, Pharmaspec 1700, Shimadzu, Japan) for fasted and fed states, respectively. The release data was subjected to model fitting using the PCP Disso 2.0 software, Pune, India.

Additionally, an experimental formulation F17 containing 10 mg loratadine and lactose (q.s.) filled in a capsule (# 2) was used as a reference formulation.

Coating of gel beads

2^2 factorial design (Table II) was used to optimize the coating conditions on the selected floating beads. The coating parameters were 5 and 10% (m/V) ethyl cellulose (EC) solution in acetone and coating times of 10 and 20 min. Gel beads (2 g) were placed in a fluidized bed dryer (TG 100, Retsch, Germany) and the coating solution was sprayed on the fluidized beads using a spray gun for a period of 20 min at an air inlet speed of 220 m s^{-1} at room temperature. The beads were dried at room temperature for a period of 24 h until all solvent was evaporated, leaving a film of EC coat on the gel beads.

Evaluation of EC-coated loratadine gel beads

The beads collected at the end of the coating process were weighed and the percentage increase in mass was calculated. *In vitro* drug release of the coated beads equivalent to 10 mg of loratadine was carried out in the fed state conditions and the drug release profile obtained was evaluated for model independent parameters. SEM micrograph (Joel 6100, Japan) of the bisected coated beads was used to calculate the coating thickness.

RESULTS AND DISCUSSION

CPA$_{MO}$ and CPA$_{CO}$ floating gel beads

Experimental results of the 2^3 factorial design demonstrated a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (m/V) of oil (mineral oil or castor oil) and 0.45 mol L^{-1} CaCl$_2$ solution (cross linking agent) as the optimimum processing conditions for the desired dependent responses. Thus CPA$_{MO}$ and CPA$_{CO}$ floating gel beads of loratadine were prepared by the emulsion gelation method wherein homogenized emulsion of either mineral oil or castor oil containing polymer mixture was dropped into 0.45 mol L^{-1} CaCl$_2$ solution; spherical gel beads were formed instantaneously.

Gelation occurred due to intermolecular cross-linking between the divalent calcium ions and the negatively charged carboxyl groups of pectin and sodium alginate molecules (8). Pectin helped emulsify the mixture of water and oil phase during the homogenization process and its emulsion stabilization property could be explained by its surfa-

ce-active ability to reduce the interfacial tension between the oil and water phases. Thus, formulations F3 (CPA$_{MO}$) and F11 (CPA$_{CO}$) with spherically shaped beads, uniform size distribution, buoyant behavior in 0.1 mol L^{-1} HCl for 12 h, and non leakage of oil at room temperature (Table I) were selected as optimized formulations.

Morphology

F3 gel beads appeared as white, translucent and rigid, whereas F11 gel beads were off-white, transparent and elastic (Fig. 1). Gel beads containing mineral oil were not significantly smaller in diameter (1.24 ± 0.26 mm) than those incorporating castor oil (1.31 ± 0.13 mm).The surface of F3 (Fig. 1a) floating gel beads appeared smooth and the presence of minor projections on the surface of F3 gel beads may be attributed to the presence of insoluble drug particles in the bead matrix, which was in contrast to F11 beads with a rough surface (Fig. 1b) with honey-comb like texture without projections on the surface. The cross sectional studies of F3 (Fig. 2a) and F11 (Fig. 2b) gel beads showed sponge like structure, corresponding to the egg box where the oil droplets were entrapped. Numerous oil globules of the 0.06 ± 0.03 diameter mm were embedded in the bead matrix pores of both F3 and F11.

Buoyancy and drug content

F3 and F11 were steeped separately in test solutions water, 0.1 mol L^{-1} HCl, acid phthalate buffer, pH 3.12 and normal saline (pH 6.80), of specific gravities 1.007, 1.013, 1.013 and 1.014 g mL^{-1}, respectively. F3 and F11 gel beads floated in all the test media without any lag time and remained buoyant for 12 h without any signs of degradation in test solutions. The factors contributing to the floating appeared to be the porous structure of beads, low relative densities of mineral (0.84 g mL^{-1}) and castor oil (0.98 g mL^{-1}) as compared to that of gastric media (1.004 g mL^{-1}), facilitation of air entrapment by the oils and low true density values of F3 (0.9232 g mL^{-1}) and F11 (0.9456 g mL^{-1}).
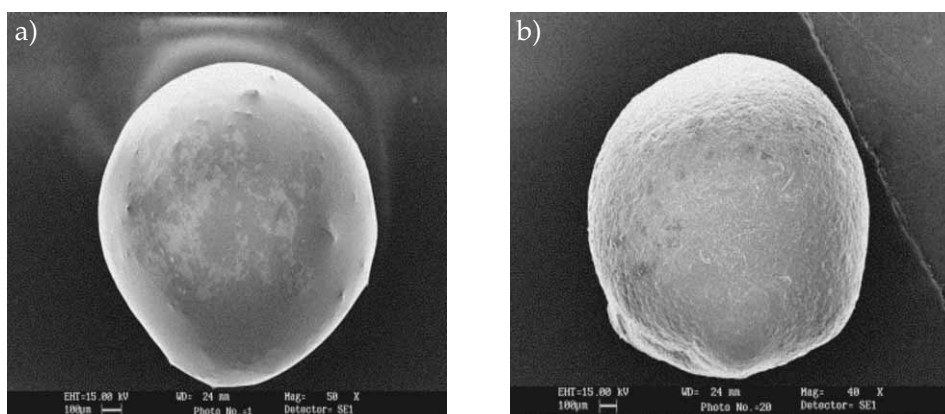

Fig. 1. Scanning electron micrographs of the external surface of loratadine floating beads: a) CPA$_{MO}$ and b) CPA$_{CO}$.

F3 exhibited the highest drug loading value of 4.79 ± 0.02 mg per 100 mg whereas F11 showed the least value of 4.67 ± 0.01 mg per 100 mg of gel beads. Percentage entrapment efficiency was found to be the highest in F3 (67.5 ± 1.2%. This may be attributed to the highly porous nature of the gel bead matrix, which allowed considerable drug loading while F11 (57.2 ± 1.6 %) supported by fewer pores, as visualized in SEM photographs (Fig. 2b), showed lower drug entrapment values. Thus, it is suggested that more porous the matrix, the higher will be the entrapment values, since higher porosity provides larger avenues for entrapment.

In vitro *drug release*

In vitro drug release study of loratadine gel beads was carried out both in the fasted state, pH 1.25, and in the fed state, pH 3.12, for a period of 8 h. In the fasted state, gel beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) was followed by a slower, gradually declining drug release phase after one hour extending up to 8 h (Fig. 3). F3 and F11 released 80.4 ± 2.0% and 76.0 ± 1.5% loratadine, respectively, within one hour, followed by a sustained release profile for 8 h. Experimental capsule (F17) formulation containing 10 mg of loratadine, when dissolved under similar conditions, released more than 83% of the drug within 1 h but could not sustain the release over the following 7 h, but rather exhibited a rapid first-order decline. This release behavior substantiates the use of loratadine emulsion gel beads as a drug delivery system for modifying the release characteristics of the drug.

Under simulated fed state conditions, loratadine gel beads did not exhibit a burst release and sustained drug release was observed. The cumulative amount of drug released in a sustainable manner, from F3 and F11 was 79.0 ± 1.0% and 73.5 ± 1.2%, respecti-
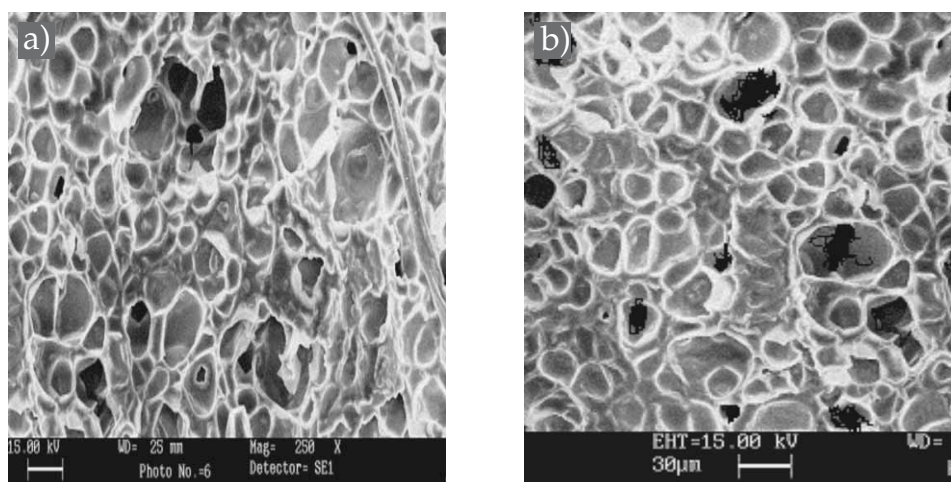

Fig. 2. Scanning electron micrographs of the internal structure of loratadine floating beads: a) CPA$_{MO}$ and b) CPA$_{CO}$.

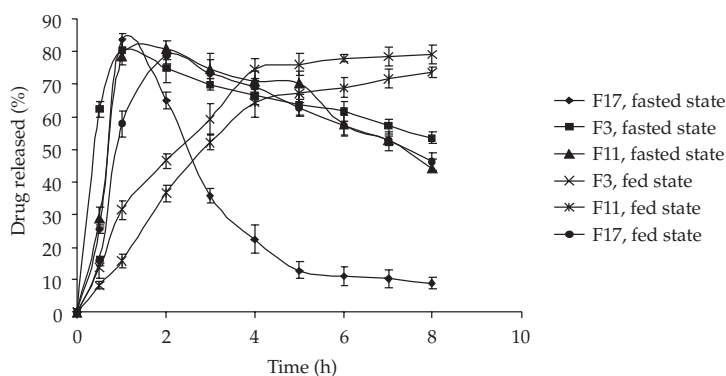Fig. 3. Drug release profiles of experimental formulation, F3, F11 and F17 in fasted and fed states (mean ± SD, *n* = 3).

vely, at the end of 8 h (Fig. 3). Absence of burst effect in fed state may be correlated to the chemical nature of the drug. Being basic in character, it readily dissolves at lower pH values of the fasted state, but as the pH increases (fed conditions) the solubility reduces. The dissolution profiles obtained in the fed state indicate concomitant administration of meals as an essential aspect to obtain the desired controlled release of the gastroretentive formulation of loratadine. The two-way analysis of variance (ANOVA) revealed a significant difference between the *in vitro* drug release profiles of loratadine in the fed and fasted states at a 95% confidence interval ($p < 0.05$).

Various release kinetic models were applied to elucidate the mechanism of drug release from the floating gel beads in the fed state. Drug release from the optimized formulations F3 and F11 followed the Higuchi ($R = 0.9841$, $n = 0.38$) and Peppas models ($R = 0.9827$, $n = 0.31$), respectively, suggesting a diffusion based mechanism of drug release as the diffusion exponent values were less than 0.45 (9). As characteristic behavior, mineral oil containing gel beads exhibited a faster release the drug while the beads containing castor oil showed a relatively slow drug release, which may be due to higher specific gravity and viscosity of castor oil and to greater partitioning of the drug to castor oil compared to mineral oil.

Nonenteric polymer ethyl cellulose was selected for coating of gel beads due to its stability in gastric pH and based on the reports on the use of ethyl cellulose for coating on floating micro particles to modify the drug release (10). F3, which exhibited the highest diffusion exponent in fed state conditions, was selected for coating. The desirable dependent response was zero-order release from EC-coated formulation in the fed state. Fig. 4 shows the comparative drug release profiles of EC-coated loratadine floating gel beads (F3C1 to F3C4). The release of loratadine from formulation F3C1 gel beads was the highest, amounting to 64.1 ± 1.7%, whereas formulation F3C4 exhibited the lowest drug release of 34.5 ± 2.0% at the end of 8 h. It is generally known that the mode of drug release from gel beads coated with a water insoluble membrane/polymer (reservoir type), is penetration of liquid, dissolution of the drug to form a saturated solution (as long as undissolved drug is present) and partitioning of drug into the polymeric mem-
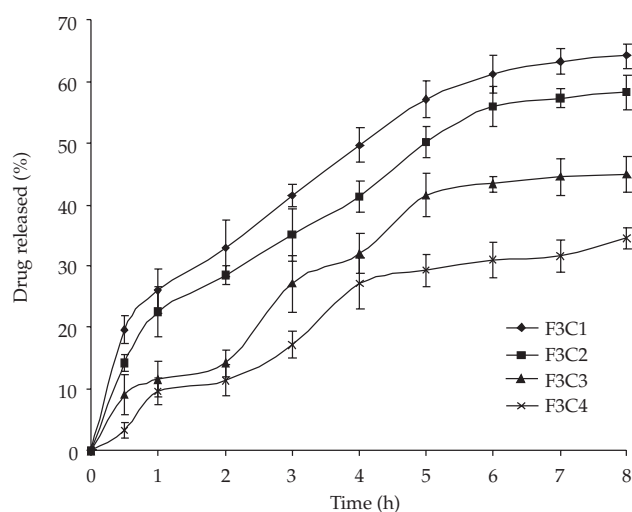
Fig. 4. Drug release profile of ethyl cellulose coated F3 floating gel beads in theb fed state (mean ± SD, n = 3).

brane, resulting in drug diffusion through the membrane (11). A similar mechanism can be suggested for the release of loratadine from the floating gel beads.

Dissolution independent parameters for coated beads are tabulated in Table II. Of all the coated formulations, F3C1 (higher level of EC concentration and higher level of coating time) exhibited maximum dissolution efficiency of 49.8% after 480 min with least $t_{50\%}$ of 4.03 h and a dissolution profile that best fitted zero-order release with R value of 0.9744 was optimized as the gastroretentive controlled-release formulation of loratadine. On the other hand, F3C4 (lower level of EC concentration and lower level of coating time) exhibited the least dissolution efficiency of 22.1% after 480 min with least $t_{50\%}$ of 11.45 h. Other coated beads exhibited intermediate values. Thus both the EC concentration and the time of coating at higher levels were optimized as the coating variables to obtain the desired response.

The sections of EC coated F3C1 gel beads, when observed under a scanning electron microscope revealed uniform coating of ethyl cellulose with coating thickness of 0.12 ±

Table II. *The 2^2 factorial design and model independent parameters of ethyl cellulose-coated F3 beads*

Formulation code	EC concentration (%, m/m)	Time for coating (min)	$t_{50\%}$ (h)	$DE_{480\ min}$ (%)	R	First-order release rate constant (h^{-1})
F3C1	10	20	4.03	49.81	0.9744	0.050
F3C2	10	10	4.83	39.68	0.9345	0.042
F3C3	5	20	8.91	30.43	0.9238	0.034
F3C4	5	10	11.45	22.14	0.9513	0.026

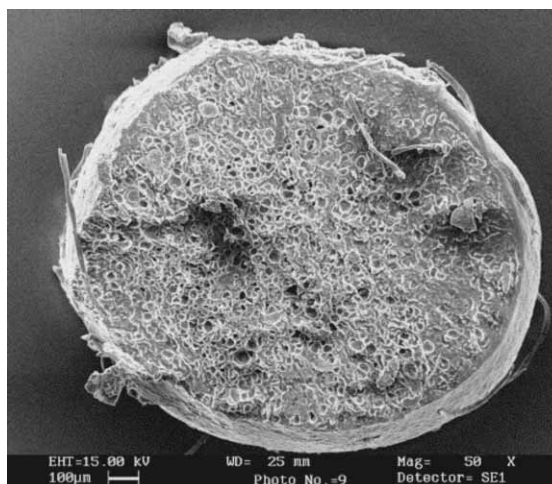*DE* – dissolution efficiancy

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Fig. 5. Scanning electron micrograph of the cross-section of ethyl cellulose coated F3C1.

0.78 mm (Fig. 5) enclosing a highly cross-linked network matrix that could effectively control the release of loratadine for 8 h. Of all the coated formulations, F3C1 which exhibited maximum dissolution efficiency with least $t_{50\%}$ of 4.03 h and a dissolution profile that best fitted zero-order release with R value of 0.9744, was regarded as an optimized gastroretentive controlled release formulation of loratadine. Additionally, the first-order release rate as reported by Saidan *et al.* (12) that may be used to identify the therapeutically efficacious dosage form was determined for the EC-coated gel bead formulations. Formulation F3C1 with the desired release rate value of 0.05 h^{-1} (Table II) calculated using the pharmacokinetic parameters of loratadine for twice daily administration was hence selected as the therapeutically efficacious gastroretentive formulation of loratadine.

CONCLUSIONS

The designed therapeutically efficacious gastroretentive formulation of loratadine combining an excellent buoyant ability and suitable drug release pattern could possibly be advantageous in terms of increased bioavailability of loratadine. The system devoid of disadvantages of a single unit dosage form provided the advantages of ease of preparation and sustained drug release over several hours.

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S A Ž E T A K

Oblikovanje i vrednovanje plutajućih uljnih mikrozrnaca loratadina s produljenim zadržavanjem u želucu

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U radu je opisana priprava plutajućih mikrozrnaca za kontrolirano oslobađanje loratadina metodom želiranja emulzije. Mikrozrnca sadrže ulja, a njihovo zadržavanje u želucu je produljeno. Priprava mikrozrnaca je optimirana 2^3 faktorijalnim dizajnom. Pripravci optimalne sposobnosti plutanja i stabilnosti dobiveni su uz omjer masa pektina i natrijevog alginata 2,5:1,5, udio mineralnog ulja ili ulja kastora 15% (*m/V*) i koncentraciju kalcijevog klorida 0,45 mol L^{-1}. Iz tih se mikrozrnaca loratadin oslobađa *in vitro*

tijekom 8 h, a oslobađanje slijedi Peppasov model ako je *n* < 0,45. Mikrozrnca presvučena etilcelulozom optimirana 2^2 faktorijalnim dizajnom slijede kinetiku nultog reda tijekom 8 h.

Ključne riječi: loratadin, zadržavanje u želucu, faktorijalni dizajn, presvlaka od etilceluloze, kinetika nultog reda

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