

Full Length Research Paper

Engineering Propranolol Hydrochloride-Loaded Microballoons for Gastroretentive Floating Drug Delivery

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Accepted 20 September, 2025

The purpose of this research was to prepare floating microballoons consisting of (i) calcium silicate as porous carrier; (ii) propranolol hydrochloride (PRH), an oral anti-hypertensive agent; and (iii) Eudragit S as polymer, by solvent evaporation method and to evaluate their gastro-retentive and controlled release properties. The effect of various formulation and process variables on the particle morphology, micromeritic properties, *in-vitro* floating behavior, percentage drug entrapment, and *in-vitro* drug release was studied. The gamma scintigraphy of the optimized formulation was performed in albino rabbits to monitor the transit of floating microballoons in the gastrointestinal tract. The propranolol hydrochloride-loaded optimized formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters of propranolol hydrochloride from floating microballoons. The microballoons were found to be regular in shape and highly porous. Microballoons formulation CS4, containing 200 mg calcium silicate showed the best floating ability (89 ± 4% buoyancy) in simulated gastric fluid as compared with other formulations. Release pattern of propranolol hydrochloride in simulated gastric fluid from all floating microballoons followed Higuchi matrix model and Peppas-Korsmeyer model. Prolonged gastric residence time of over 6 h was achieved in all rabbits for calcium silicate based floating microballoons of propranolol hydrochloride. The enhanced elimination half life observed after pharmacokinetic investigations in the present study is due to the floating nature of the designed formulations.

Key words: Propranolol hydrochloride, calcium silicate, gastroretentive floating drug delivery, microballoons, gamma scintigraphy.

INTRODUCTION

Floating drug delivery is of particular interest for drugs that (i) act locally in the stomach, (ii) are primarily absorbed in the stomach, (iii) are poorly soluble at an alkaline pH, (iv) have a narrow window of absorption, and (v) are unstable in the intestinal or colonic environment (Singh and Kim, 2000).

To provide good floating behavior in the stomach, the

density of the device should be less than that of the gastric contents ($\approx 1.004 \text{ g/cm}^3$). Srivastava et al. (2005) reported cimetidine loaded floating microspheres of hydroxypropyl methylcellulose and ethyl cellulose. The prepared microspheres exhibited prolonged drug release ($\sim 8 \text{ h}$) and remained buoyant for $>10 \text{ h}$. Sato et al developed hollow microspheres or microballoons (MB) of riboflavin, aspirin, salicylic acid, ethoxybenzamide, and indomethacin using Eudragit S100 as enteric polymer (Sato et al., 2003). Sato et al. (2003) also reported gamma scintigraphy of riboflavin- containing MB to establish its gastro-retention in human volunteers.

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Simultaneously, pharmacokinetic examination of riboflavin release from MB was conducted in fasted and fed human subjects. Streubel et al. (2002) used polypropylene foam powder as porous carrier for the development of verapamil HCl loaded floating microparticles. Jain et al. (2005) developed and reported *in-vitro* characterization of calcium silicate (CS) based floating microspheres of repaglinide. The developed formulation was also evaluated for the microballoons gastro-retentive behavior and pharmacokinetic parameters by gamma scintigraphy and blood plasma studies, respectively (Jain et al., 2006). CS was first used as a floating and sustained release carrier for the development of floating microballoons by Jain et al. (2005).

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. It is used as antihypertensive, antianginal and antiarrhythmic. Propranolol is reported to be of value in cardiovascular disorders, many of which are associated with central nervous system.

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver, and on average, only about 25% of propranolol reaches the systemic circulation. Approximately 90% of circulating propranolol is bound to plasma proteins. Propranolol is extensively metabolized with most metabolites appearing in the urine. Peak plasma concentrations occur about 1 to 4 h after an oral dose. $t_{1/2}$ of propranolol is 3 to 4 h. Thus, propranolol has relatively short half-life. Consecutively, for an optimum effect, the administration of propranolol hydrochloride as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day.

Therapy with immediate release propranolol hydrochloride tablets typically requires 40 to 160 mg as daily dose given in three to four divided doses. The presence of food increases the bioavailability. The secretory transporter P-glycoprotein (P-gp) located on the epithelium cells is responsible for low and variable bioavailability of various compounds such as propranolol. Although P-gp appears to be distributed throughout the gastrointestinal tract (GIT), its levels are higher in more distal regions (stomach < jejunum < colon). Absorption through P-glycoprotein prolongs the drug exposure to CYP3A4.

Because of its short half-life, dosing frequency, and gastric side effects at high concentration, PRH was considered to be a potential candidate for floating controlled release formulations. PRH, which has a characteristically porous structure with many pores and a

large pore volume, has a sustained-release property. It has floating ability due to the air trapped within its pores when covered with a polymer (Yuasa et al., 1996).

The objective of the present investigation was to prepare and evaluate floating microballoons consisting of (i) CS as porous carrier; (ii) PRH, an anti-hypertensive drug; and (iii) Eudragit S (ES) as polymer, which is capable of floating on gastric fluid and delivering the therapeutic agent over an extended period of time.

MATERIALS AND METHODS

PRH was generously supplied as a gift sample by IPCA Lab. Ltd., Mumbai. CS and stannous chloride (SnCl) were purchased from Sigma-Aldrich GmbH (Munich, Germany). ES was received as a gift sample from M/s Rohm Chemische GmbH (Fabrik, Germany). Polyvinyl alcohol (PVA) was purchased from Sigma Chemical Co (St Louis, MO). Ethanol, dichloromethane (DCM), and other solvents were purchased from HiMedia Laboratories Ltd (Mumbai, India). Technetium-99 m (as pertechnetate) ($^{99m}\text{TcO}_4$) was obtained from the Nuclear Medicine Department, Jawaharlal Nehru Cancer Hospital and Research Centre (Bhopal, India). All other chemicals were of analytical reagent grade and were used as received.

Preparation of propranolol hydrochloride-absorbed CS

CS (1.0 g) was dispersed in 10 ml ethanolic solution of PRH (80 mg) to prepare slurry. The slurry was ultrasonicated for 10 min in an ice bath at 40% voltage frequency using a probe sonicator (Soniweld, Imeco Ultrasonics, Mumbai, India) to entrap the drug solution inside the pores of porous carrier. The excess ethanolic solution was removed by filtration and then by drying in vacuum, which resulted in PRH absorbed CS powder.

Preparation of floating microballoons

Microballoons were prepared using a modified emulsion solvent diffusion technique (Kawashima et al., 1992). The PRH absorbed CS was added into the polymer solution of ES (1 g) in ethanol and dichloromethane (DCM) (2:1) and sonicated using probe sonicator (Soniweld). The resulting suspension was poured into a 200 ml aqueous solution of PVA (0.75% w/v) in 500 ml beaker at 40°C. The emulsion/suspension was stirred at 500 rpm employing a two bladed propeller type agitator (Remi, Mumbai, India) for 3 h. The microballoons were separated by filtration using Whatman filter paper (No. 41, Whatman, Brentford, UK), washed with water, and dried at room temperature in a desiccator for 24 h. The microballoons of PRH without CS (WC) were also prepared using the same method for comparative study.

Preparation of nonfloating microspheres

Nonfloating microspheres (NFM) were prepared using the procedure reported by Choi et al. (2000). ES (1.0 g) and PRH (80 mg) were dissolved in 10 ml of DCM/ethanol mixture (2:1), followed by addition of 1 ml of aqueous phase containing 0.25% w/v of Tween 80. The initial water/oil (w/o) emulsion was prepared by stirring in the mixture for 220 s. The w/o emulsion was slowly added into 500 ml of corn oil, the second oil phase containing

0.02% w/v of Span 80 as a surfactant, with stirring at 250 rpm at 25°C. The mixture was stirred for 1 h and the hardened microspheres were collected by filtration. The collected microspheres were washed with n-hexane 3 times and soaked in fresh hexane with gentle shaking for 24 h. The microspheres were separated and then dried in an oven overnight at 50°C.

Characterization of the microballoons

Micromeritic properties

Microballoons were characterized for micromeritic properties, such as particle size, true density, tapped density, compressibility index, and flow properties (Martin et al., 1993). The size was measured using an optical microscope, and the mean particle size was calculated by measuring 200 to 300 particles with the help of a calibrated ocular micrometer. The tapping method was used to determine the tapped density and percentage compressibility index as follows:

$$\text{Tapped density} = \frac{\text{Mass of microballoons}}{\text{Volume of microballoons after tapping}} \quad (1)$$

$$\% \text{ Compressibility index} = \left[1 - \frac{V}{V_0} \right] \times 100 \quad (2)$$

Where, V and V_0 are the volumes of the sample after and before the standard tapings, respectively.

True density was determined using a Helium densitometer (No. 1305, Shimadzu, Kyoto, Japan). Porosity (ϵ) was calculated using the following equation:

$$\epsilon = \left[1 - \frac{P_p}{P_t} \right] \times 100 \quad (3)$$

Where, P_p and P_t are the tapped density and true density, respectively. Angle of repose (θ) of the microballoons was determined by the fixed funnel method.

Morphology

The morphology of the microballoons and CS were studied by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the powder on a double sided adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ~300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with an SEM (Jeol JSM-1600, Tokyo, Japan).

Percentage drug entrapment

The PRH content in ES microballoons was determined by dispersing accurately weighed 80 mg formulation in 10 ml of ethanol followed by agitation with a magnetic stirrer for 12 h to dissolve the polymer and extract the drug. After filtration through a 0.25 µm membrane filter (Millipore Corp, Billerica, MA), the PRH content was determined in filtrate using HPLC method

(Koerner et al., 2010). Each determination was made in triplicate.

Floating behavior

Fifty milligrams of the floating microballoons were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 h, the layer of buoyant microballoons was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microballoons were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles:

$$\text{Buoyancy (\%)} = \frac{W_f}{W_f + W_s} \times 100 \quad (4)$$

Where, W_f and W_s are the weights of the floating and settled microparticles, respectively. All the determinations were made in triplicate.

In-vitro release studies

The release rate of PRH from floating microballoons was determined in a United States Pharmacopeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microballoons equivalent to 80 mg drug was filled into a hard gelatin capsule and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37°C ± 1°C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. Five- milliliter samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore). The amount of PRH was determined by high performance liquid chromatography (SLC-10A; UV detector, SPD-10A; Shimadzu Corp.). The operating conditions were as follows: Column, fully porous 5 µm C8 (250 × 4.6 mm); mobile phase, 0.5 g SDS in 18 ml of 150 mM phosphoric acid, 90 ml acetonitrile, 90 ml methanol diluted to 250 ml with water; flow rate, 1.5 ml/min; column temperature, 25°C and wavelength, 290 nm.

Data analysis of release studies

Five kinetic models including the zero order (Equation 5), first order (Equation 6), Higuchi matrix (Equation 7), Peppas-Korsmeyer (Equation 8) and Hixon-Crowell (Equation 9) release equations were applied to process the *in-vitro* release data to find the equation with the best fit using PCP Disso v3 software (Polli et al., 1997; Wu et al., 2002).

$$R = k_1 t \quad (5)$$

$$\log UR = \frac{k_2 t}{2.303} \quad (6)$$

$$R = k_3 t^{0.5} \quad (7)$$

$$R = k_4 t^n \text{ or } \log R = \log k_4 + n \log t \quad (8)$$

$$(UR)^{1/3} = k_5 t \quad (9)$$

where R and UR are the released and unreleased percentages, respectively, at time (t); k_1 , k_2 , k_3 , k_4 and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer, and Hixon-Crowell model, respectively.

Statistical treatment of dissolution data

Differences in *in-vitro* drug release of PRH from CS-based microballoons and microballoons devoid of CS were statistically analyzed by one way analysis of variance (ANOVA) with post test (Dunnnett multiple comparison test). Statistically significant differences between *in-vitro* PRH release of formulations were defined as $P < 0.05$. Calculations were performed with the GraphPad-Instat software program (GraphPad Software Inc, San Diego, CA).

In-vivo scintigraphic study

The optimized formulation (CS4) and nonfloating microspheres (NFM) of 500 mg each, loaded with SnCl and PRH, were placed in a test tube and soaked in 10 ml of normal saline (0.9% NaCl) for 15 min. A small amount of sodium pertechnetate solution equivalent to radioactivity of 40 mBq obtained from a technetium generator and stored in a sterile vial was added to the tube. The suspension was mixed intermittently for 15 min using a vortex shaker (Superfit, Mumbai, India). The supernatant was removed and the labeled microballoons were recovered by filtration through a Whatman filter paper (No. 41) followed by washing thoroughly with deionized water. The microballoons were then allowed to dry in air for 15 min. Twelve, one year old male albino rabbits were used to monitor the *in-vivo* transit behavior of the floating and nonfloating microballoons. These rabbits were divided into 2 groups (Groups I and II). None of them had symptoms or a past history of gastrointestinal (GI) disease. In order to standardize the conditions of GI motility, the animals were fasted for 12 h prior to the commencement of each experiment. CS4 (100 mg) was orally administered in suspension form to animals of Group I and NFM to Group II followed by sufficient volume of drinking water. All 4 legs of the rabbit were tied over a piece of plywood (20 × 20 inch), and the location of the formulation in the stomach was monitored by keeping the subjects in front of a gamma camera (Siemens, Forchheim, Germany). The gamma camera had a field view of 40 cm and was fitted with a medium-energy parallel hole collimator. The

140 keV gamma rays emitted by ^{99m}Tc were imaged. Specific stomach site (anterior) were imaged by E-Cam Single Head gamma camera after definite time intervals and activity counts were recorded for a 5 min period to calculate the counts per minute (cpm). The gamma images were recorded using an online computer system, stored on magnetic disk, and analyzed to determine the distribution of activity in the oral cavity, stomach, and intestinal region. In between the gamma scanning, the animals were freed and allowed to move and carry out normal activities but were not allowed to take any food or water until the formulation had emptied the stomach completely (Atyabi et al., 1996).

Pharmacokinetic studies

The *in-vivo* study was performed as per the guidelines approved by the Committee for the Purpose of Control and Supervision of

Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. The Institutional Animals Ethical Committee of College of Pharmacy, IPS Academy, Indore, approved the protocol for the study. The *in-vivo* studies were conducted in healthy male albino rabbits weighing 2.2 to 2.5 kg. Rabbits were kept for 1 week in an animal house to acclimatize them and fed a fixed standard diet. Twelve rabbits were divided into 2 groups of 6 each and were fasted for 24 h. The first group was fed with Ciplar LA capsule (Cipla Pharmaceuticals) equivalent to 80 mg of PRH, while CS4 equivalent to 80 mg of PRH was fed to the second group of animals. Water was allowed *ad libitum* during fasting and throughout the experiment. The rabbits were not anesthetized during or prior to the treatment and were administered the formulation with an oral cannula. The rabbits swallowed the formulation without any difficulty. Blood samples (2 ml) were collected from the marginal ear vein into heparinized centrifuge tubes just before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h during the study. The blood samples withdrawn as aforementioned were transferred to a series of graduated centrifuge tubes containing 0.4 ml of 2.5% w/v sodium citrate solution. The samples were centrifuged at 2500 rpm for 5 min. The plasma was transferred into another set of sample tubes and frozen until assayed. One un-dosed plasma sample was kept as blank. The sample was filtered through 0.25 μm membrane filter (Millipore). The PRH concentration in blood plasma samples was analyzed using HPLC method.

RESULTS AND DISCUSSION

Micromeritic properties and morphology

The mean particle size of CS powder was $142 \pm 02 \mu\text{m}$, while that of microballoons formulations containing CS in the range of 50 to 280 mg measured 550 ± 05 , 610 ± 08 , 648 ± 12 , 720 ± 10 and $828 \pm 12 \mu\text{m}$. The particle size of microsphere formulation WC was found to be $180 \pm 08 \mu\text{m}$. The tapped density values ranged from 0.43 ± 0.04 to $0.68 \pm 0.06 \text{ g/cm}^3$, while their true density ranged between 1.66 ± 0.12 and $1.94 \pm 0.10 \text{ g/cm}^3$. This significant difference in the densities may be caused by the presence of low-density CS particles in the microballoons.

The porosity of all the microsphere formulations was found to be in the range of 60.6 ± 2.5 to $80.0 \pm 4.0\%$. The compressibility index ranged between 25.0 ± 2.2 and $34.6 \pm 3.1\%$. All formulations showed excellent flowability as expressed in terms of angle of repose ($< 40^\circ$) except formulation CS5, probably because of the higher content of CS. The better flow property of microballoons indicates that the floating microballoons produced are nonaggregated. CS-based Eudragit microballoons were spherical in shape. The porous nature of the CS and the spherical shape of the microballoons are evident from their SEM photomicrographs (Figure 1). A large population of microballoons in the optimized formulation exists in spherical shape, which may be clearly seen in Figure 1.

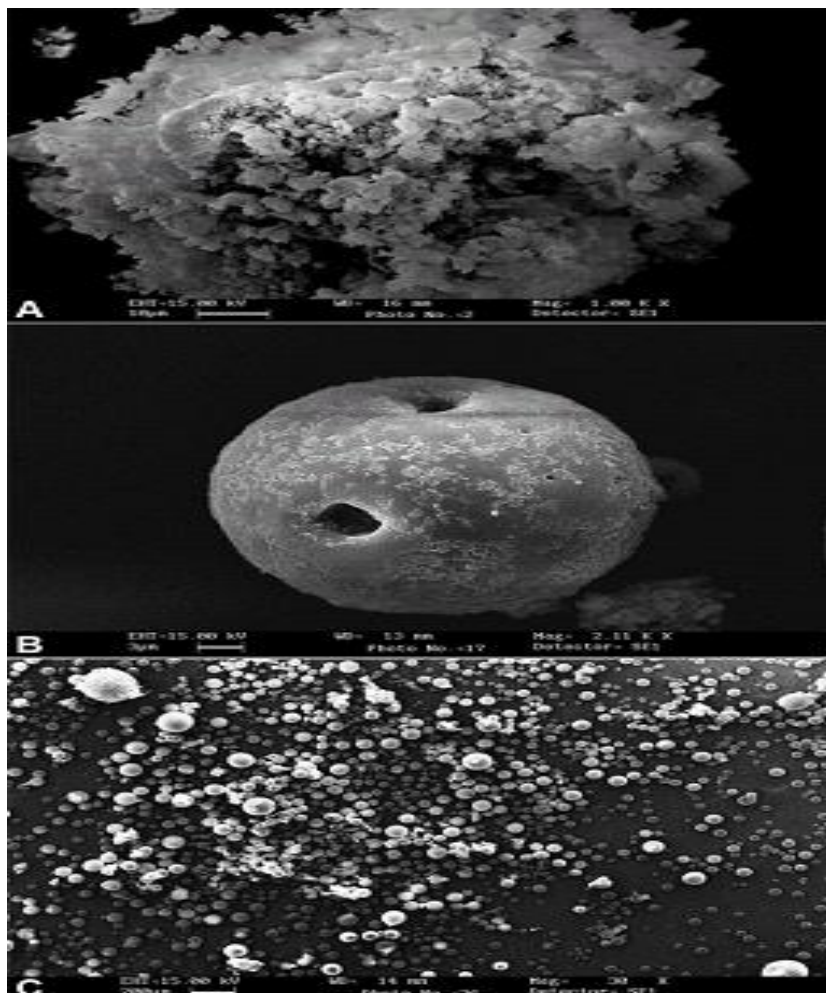


Figure 1. Scanning electron photomicrographs; (A) CS particle, (B) CS based microballoons, and (C) population of microballoons. CS indicates calcium silicate.

Percentage buoyancy and drug entrapment

The floating test was performed to investigate the floatability of the prepared microballoons. Good *in-vitro* percentage buoyancy was observed for all the microballoons formulations (Table 1). This characteristic may be attributed to the low tapped density of the microballoons as a result of the entrapment of low density CS within the system (21). Microballoons formulation CS4 containing 200 mg CS showed the best floating ability ($89 \pm 4\%$ buoyancy) in SGF as compared with other formulations. The floating ability of microballoons for 8 h may be considered a satisfactory performance of the prepared formulations. The percentage entrapment of PRH was found to be good at all loading. The high entrapment efficiency of PRH in microballoons may be attributed to its poor aqueous solubility. The extent of loading influenced the particle size distribution of

microballoons. When the loading was high, the proportion of larger particles formed was also high. With 80% drug entrapment, most of the particles were in the size range of 600 to 1200 μm , which is suitable for oral administration. From the experimentally determined yields, it was found that $\sim 35\%$ microballoons did not contain any porous carrier. This may be owing to the difference in particle size of microballoons. Because porous carrier free microballoons and carrier particles are much smaller in size (100 to 200 μm) than the microballoons containing carrier (500 to 800 μm), these were separated during the sieving step.

In-vitro drug release study

Release of PRH from CS-based microballoons was evaluated in SGF (pH 2.0). Since the acrylic polymer

Table 1. Buoyancy and drug entrapment of different floating microballoons*.

Formulation code	CS Content (mg)	Buoyancy (%)	Drug entrapment (%)
WC*	0	70 ± 3	70 ± 2.5
CS1†	50	77 ± 2	78 ± 2.4
CS2†	100	80 ± 4	82 ± 1.4
CS3†	150	83 ± 2	82 ± 3.0
CS4†	200	88 ± 4	84 ± 2.8
CS5†	250	82 ± 5	80 ± 1.4

*CS indicates calcium silicate; WC, floating microballoons of propranolol hydrochloride without carrier; and CS1-5, floating microballoons of propranolol hydrochloride with calcium silicate (n = 3).

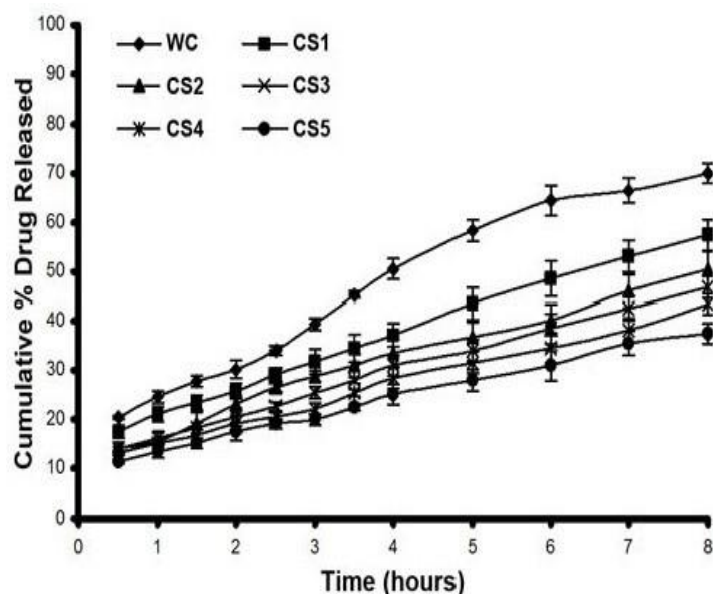


Figure 2. *In-vitro* release of propranolol hydrochloride from various floating microballoons in simulated gastric fluid (pH 2.0) (n = 3). WC indicates floating microballoons of propranolol hydrochloride without carrier; and CS1-5, floating microballoons of propranolol hydrochloride with calcium silicate.

used is not soluble in acidic pH and starts to dissolve above pH 7, microballoons released the PRH only by diffusion in SGF (pH 2.0). The other reason for the slow dissolution rate of drug may be attributed to low solubility of PRH at acidic pH. No burst effect was observed from any of these formulations. The release of PRH from different formulations followed the order: WC>CS1>CS2>CS3>CS4>CS5. The pattern also provides an idea about the effect of CS content on drug release from the microballoons (that is, the higher the CS contents in microballoons, the lower the drug release) (Figure 2). The release mechanism of PRH from these floating microballoons was also evaluated on the basis of

theoretical dissolution equations including zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer, and Hixon-Crowell kinetic models. The regression coefficients and rate constants from *in-vitro* release profiles of PRH in SGF were calculated using PCP Disso Version 3 software (Pune, India) and are reported in Table 2. Release pattern of PRH in SGF (pH 2.0) from all floating microballoons followed Higuchi matrix model and Peppas-Korsmeyer model. Desai and Bolton, (1993) and Khattar et al. (1990) reported that non-effervescent floating systems obeyed the Higuchi model indicating drug release via a diffusion mechanism. When the release data of WC (without CS) was compared with

Table 2. The regression coefficients and rate constants for release of propranolol hydrochloride from floating microballoons in simulated gastric fluid (pH 2.0)*.

Formulation	Zero-order model		First-order model		H-M model		P-K model		H-C model	
	r	k ₁	r	k ₂	r	k ₃	r	k ₄	r	k ₅
WC	0.8762	10.6842	0.9799	-0.1641	0.9902	24.6715	0.9782	24.5398	0.9589	-0.0469
CS1	0.8523	8.4173	0.9564	-0.1140	0.9931	19.4937	0.9807	20.7807	0.9313	-0.0342
CS2	0.8652	7.3073	0.9488	-0.0939	0.9953	16.9078	0.9868	17.0995	0.9270	-0.0287
CS3	0.8674	6.7540	0.9457	-0.0849	0.9924	15.6110	0.9787	16.3321	0.9249	-0.0261
CS4	0.8629	6.1582	0.9362	-0.0755	0.9898	14.2356	0.9736	15.1140	0.9163	-0.0235
CS5	0.8563	5.5036	0.9247	-0.0657	0.9924	12.7386	0.9807	13.4997	0.9053	-0.0206

*H-M, indicates Higuchi matrix; P-K, Peppas-Korsmeyer; H-C, Hixon-Crowell; r, indicates correlation coefficient; k₁-k₅, rate constants of zero-order, first-order; WC, floating microballoons of Propranolol hydrochloride without carrier; and CS1-5, floating microballoons of Propranolol hydrochloride with calcium silicate.

Table 3. One-way ANOVA (Dunnnett multiple comparison test) for *In-vitro* release of propranolol hydrochloride in simulated gastric fluid (pH 2.0)*.

Comparison	Mean difference	Q	P Value
WC vs CS1	9.003	1.821 [†]	P > .05
WC vs CS2	13.833	2.788 [‡]	P < .05
WC vs CS3	16.133	3.252 [§]	P < .01
WC vs CS4	18.583	3.746 [§]	P < .01
WC vs CS5	21.267	4.287 [§]	P < .01

*ANOVA indicates analysis of variance; Q, parameter obtained with P when performing ANOVA; WC indicates floating microballoons of propranolol hydrochloride without carrier Control-WC; and CS1-5, floating microballoons of propranolol hydrochloride with calcium silicate. [†], Non-significant; [‡], significant; [§], very significant.

formulations containing CS by one-way ANOVA (Dunnnett multiple comparison test), the difference in *in-vitro* release in SGF from CS2 was found to be significant (PG < 05) and very significant (P < 01) from CS3, CS4, and CS5 (Table 3).

Gamma scintigraphy

The optimized formulation (CS4) had shown good *in-vitro* buoyancy and controlled release behavior and hence was finally selected for *in-vivo* study (that is, gamma scintigraphy), and the results were compared with NFM prepared using the identical polymers. Gamma images of the ^{99m}Tc-labeled CS4 and NFM are shown in Figures 3 and 4. Examination of the sequential gamma scintigraphic images during the study clearly indicated that the CS4 remained buoyant and uniformly distributed in the gastric contents for the study period of 6 h. Prolonged gastric retention time (GRT) of more than 6 h was achieved in all the rabbits for the CS4, which remained buoyant in the stomach for the entire test period. In contrast, NFM showed gastro-retention of less

than 2 h. After swallowing, the floating microballoons adopted a floating position on top of the stomach content. This might be because of the presence of porous low density CS and a hollow cavity inside the microballoons. A measurable number of counts of ^{99m}Tc tagged CS4 for the 6-hour study period showed very good gastro- retentive propensity as the administered microballoons remained floating and distributed in the stomach contents for the 6-hour study period. In case of NFM, the radioactive counts decreased considerably after 2 h (Figure 5). Gamma scintigraphy was performed for 6 h, corresponding to the half-life of ^{99m}Tc. (Saha, 1979).

Pharmacokinetic studies

In addition to the developed floating formulation that had shown the best *in-vitro* dissolution and floating behavior, the optimized formulation CS4 was also evaluated for its pharmacokinetic parameters. For comparison, the marketed preparation of PRH (Ciplar LA capsule) was used in the study. In the present study, the peak plasma concentration (C) remained nearly unchanged, as evident

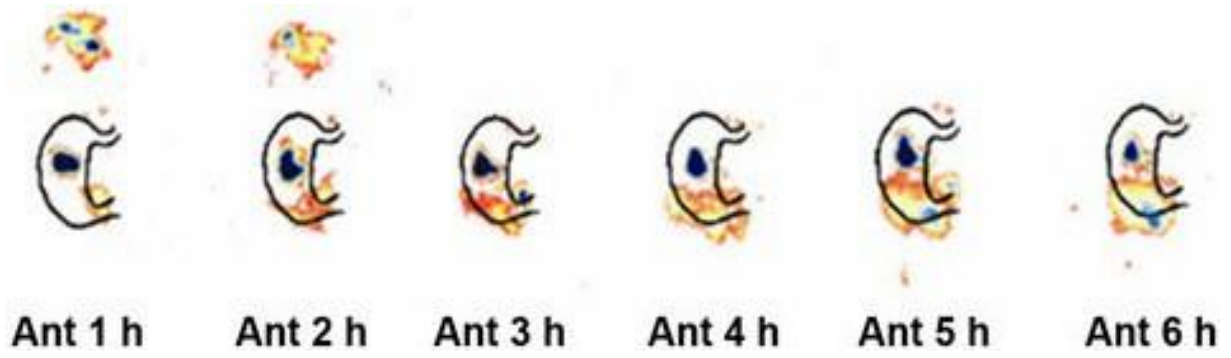


Figure 3. Gamma scintigraphic images of CS4 in albino rabbits. Ant indicates anterior position.

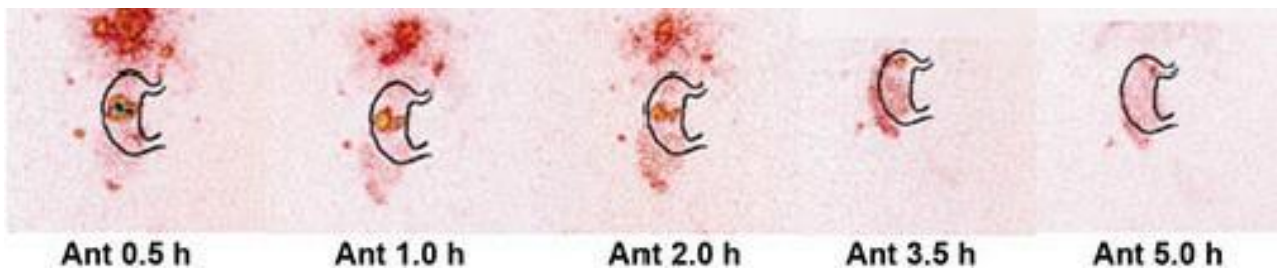


Figure 4. Gamma scintigraphic images of nonfloating microspheres in albino rabbits. Ant indicates anterior position.

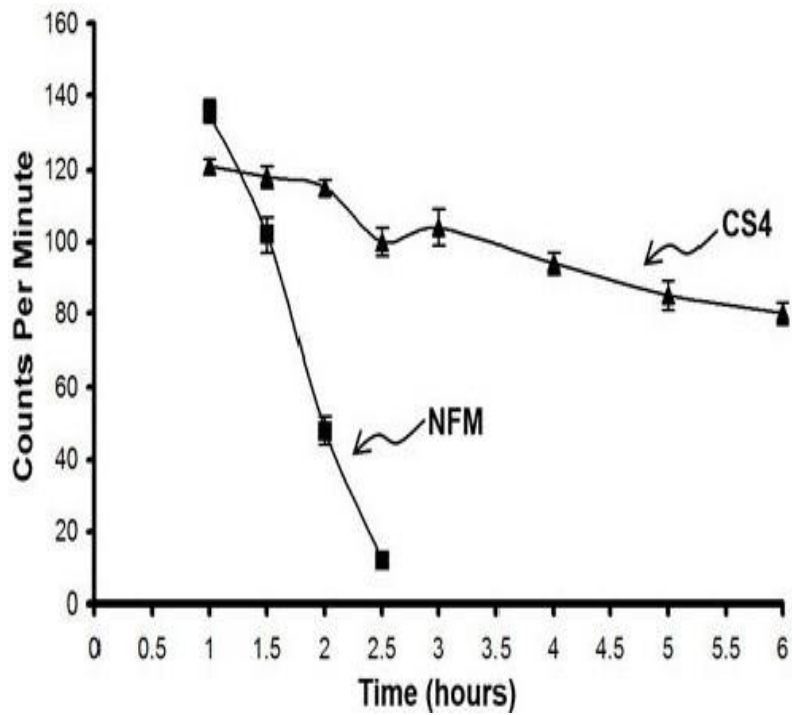


Figure 5. Counts per minute of ^{99m}Tc -tagged optimized floating formulation (CS4) and non-floating microspheres (NFM) ($n = 6$).

Table 4. Pharmacokinetic parameters of propranolol hydrochloride formulations after oral administration in rabbits (n = 6).

S/N	Pharmacokinetic parameter	Marketed preparation	Floating microballoons
1	Peak plasma concentration C_{max} (ng/ml)	9.2 ± 0.42	9.2 ± 0.42
2	Time to reach peak plasma concentration t_{max} (h)	4	8
3	Area under the curve AUC_{0-24} (ng.h/ml)	69.0	113.3
4	Absorption rate constant K_a (h^{-1})	0.58	0.54
5	Elimination rate constant K_e (h^{-1})	0.26	0.17
6	Elimination half life $t_{1/2}$ (h)	4.01	6.08
7	Lag time (minutes)	50	45
8	Relative bioavailability	1.0	1.64

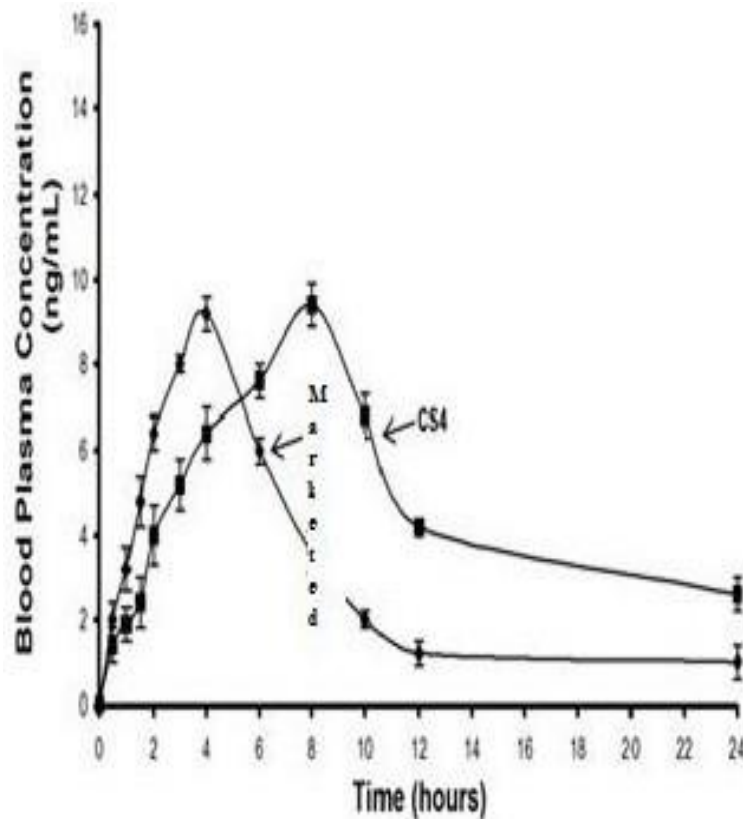


Figure 6. Mean plasma concentration of Propranolol hydrochloride following oral administration of its floating formulation and the marketed product (Ciplar LA capsule).

from the data in Table 4, showing 9.2 ng/ml for the marketed preparation (Ciplar LA capsule) and 9.4 ng/ml for floating microballoons (Figure 6). In addition, the time to reach peak plasma concentration (t_{max}) increased from 4 to 8 h and the area under the curve (AUC) increased from 69.0 to 113.3 ng.h/ml (nearly 1.6 times) for floating microballoons. Elimination half life ($t_{1/2}$) was increased by

~1.5 times (6.08 h) for the CS4 in comparison with the Ciplar LA capsule. The values of C_{max} and t_{max} clearly indicate that the absorption of PRH was not increased from GI tract when given in floating formulations. Absorption from the CS4 took 8 h as compared with 4 h from Ciplar LA capsule to reach the maximum concentration of PRH in blood, indicating delay in

absorption and prolonged localized concentration in the stomach and duodenum, the desired site of action of the drug. The *in-vivo* study of selected floating formulation confirmed its ability to modify the pharmacokinetic behavior of the parent drug in the desired manner. These results clearly indicated the controlled and sustained release of PRH from CS based gastro-retentive floating formulations. It may be concluded that the enhanced elimination half-life observed after gamma scintigraphy in the present study is because of the floating nature of the designed formulations.

Conclusion

The CS-based floating multiparticulate delivery system radiolabeled with ^{99m}Tc can be successfully visualized by scintigraphy to establish gastroretentive performance in the rabbit. The results clearly indicated the controlled and sustained release of PRH from CS based gastroretentive floating microballoons. Further, the microballoons could also be compressed into tablets, filled into capsules, or formulated into oral suspension for reconstitution.

ACKNOWLEDGEMENTS

The authors are very grateful to College of Pharmacy, IPS Academy, Indore, for providing all the necessary facilities to conduct the study. The authors also wish to thank Dr. D. C. Prasad, Jawaharlal Nehru Cancer Hospital and Research Centre, Bhopal, India, and Dr. Praveen Malviya, Indian Institute of Technology (IIT), New Delhi, India, for extending Gamma scintigraphy and SEM facilities, respectively.

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