Preparation and evaluation of sustained release microballoons of propranolol

*Porwal A, Swami G, Saraf SA.

Department of Pharmaceutics, Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Lucknow (U.P.) 227105, India.

ABSTRACT

Background and the purpose of the study: The purpose of the present investigation was to characterize, optimize and evaluate microballoons of Propranolol hydrochloride and to increase its boioavailability by increasing the retention time of the drug in the gastrointestinal tract.

Methods: Propranolol hydrochloride-loaded microballoons were prepared by the non-aqueous O/O emulsion solvent diffusion evaporation method using Eudragit RSPO as polymer. It was found that preparation temperature determined the formation of cavity inside the microballoon and this in turn determined the buoyancy. Microballoons were subjected to particle size determination, micromeritic properties, buoyancy, entrapment efficiency, drug loading, in vitro drug release and IR study. The correlation between the buoyancy, bulk density and porosity of microballoons were elucidated. The release rate was determined in simulated gastric fluid (SGF) of pH 1.2 at 37±0.5 °C.

Results: The microballoons presented spherical and smooth morphologies (SEM) and were porous due to presence of hollow cavity. Microballoons remained buoyant for >12 hrs for the optimized formulation. The formulation demonstrated favorable in vitro floating and release characteristics. The encapsulation efficiency was high. In vitro dissolution kinetics followed the Higuchi model. The drug release from microballoons was mainly controlled by diffusion and showed a biphasic pattern with an initial burst release, followed by sustained release for 12 hrs. The amount of the drug which released up to 12 hrs was 82.05±0.64%. Statistical analysis (ANOVA) showed significant difference (p < 0.05) in the cumulative amount of drug released after 30 min, and up to 12 hrs from optimized formulations.

Conclusion: The designed system for propanolol would possibly be advantageous in terms of increased bioavailability and patient compliance.

Keywords: Floating drug delivery system, O/O emulsion Solvent diffusion/evaporation method, Eudragit RS PO, Buoyancy.

INTRODUCTION

The preferred route for the administration of most drugs is gastrointestinal tract. Most of the orally administered dosage forms have several physiological limitations, such as gastrointestinal (GI) transit time, incomplete drug release from devices and short residence time of the pharmaceutical dosage forms in the absorption region of GI tract. These factors lower the bioavailability of sustained-release dosage forms and even if slow release of drug is attained, the drug released after passing the absorption site is not utilized, thus lowering the efficacy of the drug (1).

To overcome this problem several attempts have been made to develop oral dosage forms having prolonged retention time in the stomach to extend the duration of drug delivery. Several gastrointestinal targeting dosage forms, including intragastric floating, high density, bioadhesive, swelling and magnetic systems have been developed (2-4).

One approach which has been used successfully is floating drug delivery systems (FDDS). While the system floats over the gastric contents, the drug is released slowly at the desired rate. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine (5,6). While both single and multiple unit systems have been developed, a disadvantage of single unit system is the high variability of gastrointestinal transit time, due to its all-or-nothing gastric emptying process. Therefore, a multiple-unit floating system that distributes widely throughout the gastrointestinal tract has been sought. Sato et al. developed a multiple-unit intragastric floating system involving hollow microspheres (microballoons) with excellent buoyant properties using o/w emulsion solvent diffusion method. This gastrointestinal

transit-controlled preparation is designed to float on gastric juice with a specific density of less than 1 for prolonged period (2, 7).

Microballoons are in a strict sense, spherical empty particles without core having internal hollow structure with air inside. Microballoons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs (8). Certain types of drugs can benefit from using gastroretentive devices. These include: 1) Drugs acting locally in the stomach; 2) Drugs that are primarily absorbed in the stomach; 3) Drugs which are poorly soluble at an alkaline pH; 4) Drugs with a narrow window of absorption; 5) Drugs absorbed rapidly from the GI tract; and 6) Drugs that degrade in the colon (9).

Propranolol hydrochloride (PH), a non-selective beta-adrenergic blocker, has been widely used in the treatment of hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmias. Its short biological half-life (3-5 hrs) necessitates the need to administer the drug in two or three doses of 40 to 80 mg per day. Such frequent drug administration may reduce patient compliance and therapeutic efficacy (10). The bioavailability of PH after oral administration is approximately 30%. Co-administration with food appears to enhance bioavailability (11). The development of gastroretentive controlled-release dosage forms thus would clearly be advantageous. Researchers have formulated oral controlled-release products of PH by various techniques. Since, its site of absorption is the stomach, a dosage form that is retained in the stomach would increase the absorption, improve drug efficiency, and decrease dose requirements. Thus, the aim of the present investigation was to characterize, optimize and evaluate microballoons of PH for oral controlled drug delivery (11, 12).

Eudragit RSPO as a low-density polymer was used to prepare floating PH microballoons because it has sustained release properties with low water permeability, which results in enhanced floatability. In the present study, floating microballoons of PH were prepared using an O/O emulsion solvent diffusion evaporation technique which is useful for stabilization of drugs and to improve their distribution. This technique is suitable for encapsulating both lipophilic and hydrophilic drugs (8). Another advantage is the possibility of producing microballoons of required size range, porosities, and shapes.

MATERIAL AND METHODS

Propranolol hydrochloride was procured as a gift sample from Kwality Pharmaceuticals, (Amritsar, India). Eudragit® RSPO (Ammonio Methacrylate Copolymer Type B) was also procured as a gift sample from Cadila Pharmaceuticals Ltd., (Ahemdabad, India). Dichloromethane LR was purchased from RFCL limited (New Delhi, India),

and Ethanol AR, light liquid paraffin oil LR and glycerol monostearate were purchased from S D Fine Chem limited, (Mumbai, India). All other chemicals were of analytical grade.

Preparation of microballoons

Microballoons were prepared by the O/O emulsion solvent diffusion evaporation method. Weighed amounts of PH, Eudragit RSPO and glyceryl monostearate (12.5%w/w) were dissolved in a mixture of dichloromethane (10 ml) and ethanol (10 ml) at room temperature. The resulting solution of PH was then poured dropwise into 200 ml light liquid paraffin oil containing span 20 (0.2% v/v) as a surfactant with constant stirring at 500 rpm employing a 3-bladed propeller type agitator (REMI motors, Mumbai, India) for 2 hrs at various temperatures of 30, 40 and 50°C. Residual organic solvents were evaporated using a rotary evaporator (Buchi rotavapour R II, Switzerland) for 20 min. at 40°C. The resulting microballoons were separated by filtration, freed from liquid paraffin oil by repeated washing with n-hexane (4x50 ml) and finally air dried over a period of 12 hrs (2, 8).

Variation of formulation factors

Different PH: Eudragit RSPO ratios (1:1, 1:2, 1:3, 1:4 and 1:5) were used in order to find out the effect of drug: polymer ratio on physical characterization and buoyancy of microballoons. The effect of stirring speed (250, 500, and 750 rpm), concentrations of span 20 (0.2%, 0.3% and 0.4% v/v), the volume of processing medium (light liquid paraffin oil, 150, 200 and 250 ml) and the deaggregating agent (5%, 10%, 15% w/w) on microballoons characteristics were investigated.

Characterization of microballoons
Microballoon morphology

The morphology of the microballoons was studied by scanning electron microscopy (Philips 505, Holland). SEM requires the coating of the dried sample with a conductive material usually gold. 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 a mixture of gold and palladium to a thickness of 200-500 Å under an argon atmosphere using a gold sputter module (POLARON, SEM coating system) in a high-vacuum evaporator at 1.4KV voltage, 18 mA current and 10^{-2} mbar pressure. The coated samples were then randomly scanned and photomicrographs were taken with SEM. To investigate the internal morphology, the hollow microspheres were dissected with a blade (13, 14).

Micromeritic Properties

Microballoons were characterized for micromeritic properties such as particle size, bulk density, true

density and porosity (13, 15).

Particle size analysis
Particle size measurements were carried out on an image analysis system. An optical microscope connected with a digital camera (YOKO CCD Camera, Taiwan) was used to produce pictures of the microballoons. The particle size distribution of each formulation was measured by determination of the diameter of 100 randomly selected microballoons using the MEDICAL PRO software (16).

Bulk density, True density and Porosity
Bulk density was calculated from the formula given below (17):

$$\text{Bulk density } P_b = \frac{\text{Mass of microballoons}}{\text{Bulk volume of microballoons}}$$

True density (P_t) was determined by using a Helium air densitometer (No. 1305, Shimadzu, Japan). Porosity was calculated as follows:

$$\text{Porosity } \varepsilon = [1 - P_b/P_t] \times 100$$

Interaction studies
The IR spectra were recorded for PH, Eudragit RSPO, physical mixture and drug-loaded microballoons using KBr pellets by FTIR-8400s (Shimadzu, Japan). The scanning range was 4000 cm^{-1} - 400 cm^{-1}.

Process yield
The prepared microballoons were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microballoons (18).

$$\% \text{ Yield} = \frac{\text{Actual weight of the product}}{\text{Total weight of excipient and drug}} \times 100$$

Entrapment Efficiency (E.E.) and drug loading
Microballoons equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microballoons and extracting with aliquots of 0.1N HCl of pH 1.2 repeatedly (3x10ml). The extract was transferred to a 100 ml volumetric flask and the volume was made up to 100ml using 0.1N HCl of pH 1.2. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV-1700 Pharmaspec Shimadzu, Japan) at 289 nm against appropriate blank. The amount of the drug entrapped in the microballoons was calculated by the following formula (18):

$$\text{E.E.} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

$$\text{Drug loading} = \frac{\text{Weight of drug in microballoons}}{\text{Weight of microballoons recovered}} \times 100$$

In vitro buoyancy
Microballoons (100 mg) were spread over the surface of a USP dissolution apparatus (type II) filled with 900 ml simulated gastric fluid of pH 1.2 containing 0.02% Tween 20. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microballoons were recovered separately. The microballoons were air dried and weighed. Percentage buoyancy was calculated as the ratio of the mass of the microballoons that remained floating and the total mass of the taken microballoons (2). Buoyancy was recorded as a function of temperature, drug polymer ratio, stirring time, emulsifier concentration, volume of processing medium and deaggregating agent. Observations are recorded in tables 1 and 2.

In-vitro drug release study
The drug release study was carried out using USP rotating paddle apparatus (Veego, DA-6DR USP Standards) at 37 ± 0.5 ºC and at 100 rpm using 900 ml of simulated gastric fluid of pH 1.2 containing 0.02% Tween 20 as a dissolution medium. Microballoons equivalent to 50 mg of PH were used for the test. Five ml of the sample solution was withdrawn at predetermined time intervals, filtered through filter paper, diluted suitably and analyzed spectrophotometrically using UV-VIS spectrophotometer (Should be eliminated, it has been repeated) at a wavelength of 289 nm. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain the sink condition. All experiments were performed in triplicates (19).

Drug release kinetics
The drug release kinetics was studied by various kinetic models such as Korsmeyer-peppas, Higuchi, first order and zero order plots. The best fit model was confirmed by the value of correlation coefficient near to 1 (10, 20).

Statistical analysis of dissolution data
The mean readings of in vitro release data of Propranolol hydrochloride from microballoons of formulations MB1, MB2, MB3, MB4, and MB5 were statistically analyzed by one-way analysis of variance (ANOVA) with post test (Newman-Keuls Multiple Comparison Test) at two different time intervals 30 min and 12 hrs. Differences between in vitro drug release of formulations were defined as statistically significant when P<0.05. Calculations were performed using GraphPad Prism software.

Stability testing

Microballoons were hermetically sealed in glass bottles and stored for 3 months at 4 ± 0.5ºC, room temperature and 40 ± 1ºC and 75% RH as per ICH guidelines. After every 15 days, one bottle was used for evaluation. The microballoons were evaluated for physical appearance and drug content (21).

RESULTS AND DISCUSSION

PH, due to its hydrophilicity, is likely to be preferentially partitioned into the aqueous medium, leading to low entrapment efficiency, when encapsulated using aqueous phase as the processing medium. The solvent system selected for the present study was a mixture of ethanol and dichloromethane in the ratio of 1:1. Span 20 was used as surfactant for stabilization of emulsification process. Glyceryl monostearate was used as deaggregating agent.

Microballoons prepared at 30°C had porous surface but were so brittle as to crumble upon touching. They also displayed lower buoyancies (25.34 ± 1.23% after 12 hrs) probably due to the easy penetration of simulated gastric fluid of pH 1.2 through the porous surface (Table 1). Microballoons prepared at 40°C were spherical in shape and smoother than those prepared at 30°C. They showed better buoyancy (74.43 ± 3.46%). Microballoons prepared at 50°C showed poor buoyancy due to its non-porous nature which could be due to rapid evaporation of dichloromethane at temperatures beyond its boiling point of 40.2°C. Thus, the optimized temperature for the formulation of microballoons was selected as 40°C.

Microballoons were prepared with different drug: polymer ratio (1:1, 1:2, 1:3, 1:4, 1:5), keeping all other parameters constant at 40°C. The mean particle size of the microballoons increased significantly by decrease in drug polymer ratio (22) and was in the range of 286 ± 4.61 -594 ± 7.46 µm (Table 2A).

The drug entrapment efficiency increased initially from 44.16 ± 4.32 to 80.40 ± 1.75 % w/w by the decrease in drug polymer ratio up to 1:4 after which it decreased. A larger particle size was observed at drug: polymer ratio of 1:5 (594.79 ± 7.46 µm). Since drug entrapment, buoyancy and particle size are dependent on factors like stirring speed, emulsifier concentration and deaggregating agent, an increase in polymer concentration may have resulted in a shift in the equilibrium between these factors, which was evident by a reduction in drug entrapment, per cent process yield, per cent drug loading and reduced buoyancy. Thus, the optimized drug: polymer ratio was selected as 1:4.

Microballoons were prepared by keeping all other parameters constant, at three different speeds i.e. 250, 500, 750 rpm. Highest entrapment efficiency was observed with the stirring speed of 500 rpm having desired particle size i.e. 575 ± 6.22 µm and

maximum drug entrapment i.e. 80.40 ± 1.75 % w/w (Table 2B).

Microballoons were then optimized for emulsifier concentrations (0.2%, 0.3% and 0.4% v/v). At 0.2 %v/v concentration of span 20, an average particle size of 575 ± 6.22µm and maximum % drug entrapment efficiency of 80.40 ± 1.75% w/w was obtained (Table 2C). The mean microballoon size, buoyancy and drug entrapment efficiency were also found to decrease by increase in emulsifier concentration. This may be due to the fact that the increase in emulsifier concentration proportionately increases miscibility of ethanol with light liquid paraffin (processing medium), which may increase the extraction of drug into the processing medium. The buoyancy could have decreased due to tightening of polymeric network, leading to microballoon shrinkage with an increase in the concentration of emulsifier (23, 24). Microballoons were then optimized for volume of processing medium (150, 200 and 250 ml). The highest entrapment efficiency was observed with 200 ml of processing medium having desired particle size i.e. 575 ± 6.22 µm and maximum drug entrapment i.e. 80.40 ± 1.75 % (Table 2D). Decrease in volume of processing medium (150 ml) resulted in low drug entrapment and buoyancy which could be due to aggregation of polymer due to its increased concentration. An increase in volume of processing medium (250 ml) resulted in low drug entrapment because as the volume of processing medium increased, collision induced aggregation reduced, yielding smaller microballoons with low buoyancy due to lesser porosity. This could also be the reason for higher drug extraction in to the processing medium resulting in lower entrapment efficiency.

Microballoons were then optimized for different concentrations of deaggregating agent at 40°C. At 10 %w/w concentration of glyceryl monostearate, an average particle size of 612.23 ± 5.56 µm and maximum % drug entrapment efficiency of 80.34 ± 1.34% w/w was obtained (Table 2E). As the concentration of deaggregating agent was increased, the particle size decreased and the drug entrapment increased. However, there was no significant difference when concentration was increased from 10% to 15% w/w.

The average particle size of the optimized batch was found to be 575 ± 6.22 µm (Table 2)**.** The bulk density values ranged from 0.6682 ± 0.024 to 0.4433 ± 0.015 gm/cm^3 while their true densities ranged from 1.0169 ± 0.0035 to 1.0018 ± 0.0031 gm/cm^3.The porosity of all the microballoon formulations was found to be in the range from 34.29 ± 0.45 to 55.72 ± 0.51 (Table 3). The optimized batch showed excellent porosity which is necessary for the longer floatability of microballoons.

The shape and surface morphology of the microballoons were investigated by SEM as shown

Table 1. Effect of temperature on buoyancy.

Formulation (MB0) prepared at temperature	30°C	40°C	50°C
Buoyancy (%) after 12 hours	25.34±1.23	74.43±3.46	16.58±62

Table 2. Effect of various processing parameters on Entrapment Efficiency (E.E.) and buoyancy*.

Optimization parameters	Mean Particle size (µm)	E.E. (%w/w)	% Process Yield	Drug loading (%w/w)	Buoyancy (%) after 12 hrs	Inference (Based on E.E. (%w/w) and % buoyancy)
A) Drug: polymer ratio						
1:1 (MB1)	286.14±4.61	44.16±4.32	66.36±4.78	25.21±2.45	34.75±4.62	Very low
1:2 (MB2)	328.25±6.83	66.22±3.12	74.13±3.65	24.64±2.12	46.34±2.95	Very low
1:3 (MB3)	436.33±8.64	70.07±3.45	80.80±3.85	19.01±2.48	73.66±3.88	Low
1:4 (MB4) [#]	**575.21±6.22**	**80.40±1.75**	**90.42±1.25**	**16.13±1.18**	**87.43±1.61**	**High**
1:5 (MB5)	594.79±7.46	76.03±3.45	86.11±3.12	13.74±2.02	84.25±3.20	Good
B) Stirring speed (rpm)						
250 (MBS1)	732.62±8.57	72.73±3.62	81.98±3.75	15.87±1.75	82.54±3.89	Low
500 (MBS2) [#]	**575.21±6.22**	**80.40±1.75**	**90.42±1.25**	**16.13±1.18**	**87.43±1.61**	**High**
750 (MBS3)	189.74±5.57	70.04±5.02	78.95±4.78	15.71±1.66	74.43±3.46	Low
C) Emulsifier conc. (%v/v)						
0.2 (MBE1) [#]	**575.21±6.22**	**80.40±1.75**	**90.42±1.25**	**16.13±1.18**	**87.43±1.61**	**High**
0.3 (MBE2)	454.45±8.54	74.91±3.69	85.60±3.45	15.69±1.13	79.23±3.48	Low
0.4 (MBE3)	387.19±5.62	73.10±3.87	82.41±4.12	15.79±1.77	77.18±2.89	Low
D) Volume of processing Medium (ml)						
150 (MBV1)	752.16±7.35	76.22±2.94	86.03±2.82	15.81±1.23	84.14±3.51	Good
200 (MBV2) [#]	**575.21±6.22**	**80.40±1.75**	**90.42±1.25**	**16.13±1.18**	**87.43±1.61**	**High**
250 (MBV3)	412.89±4.87	71.11±2.68	79.95±3.06	16.30±1.31	78.12±2.91	Low
E) Deaggregating agent (%w/w)						
5 (MBD1)	678.15±7.23	68.74±2.54	75.02±2.55	17.50±1.45	76.16±2.16	Low
10 (MBD2) [#]	**612.23±5.56**	**80.34±1.34**	**90.14±1.19**	**16.15±1.07**	**87.54±1.41**	**High**
15 (MBD3)	594.44±6.74	80.50±2.31	90.11±2.24	15.59±1.23	87.12±1.98	High

*all experiments were performed in triplicate (n=3), [#] optimized formulation

in figures 1a-d which confirms that the drug-loaded microballoons were spherical and had a smooth surface. The characteristic internal structure of the microballoon, a hollow cavity enclosed in a rigid shell was clearly evident (Fig 1). Diffusion of ethanol through the solution, accompanied by simultaneous evaporation of dichloromethane may have resulted in formation of cavity.

There was no drug- excipient interaction, as it was confirmed by IR spectra of pure drug as well as microballoons since similar peaks were obtained in both the cases.

Drug loading and process yield of the optimized batch was found to be 16.13±1.18% w/w and 90.42±1.25 % respectively as it is shown in table 2. The higher drug loading typically results in lower encapsulation efficiency due to higher concentration gradients resulting in the drug diffusing out of the polymer/solvent droplets into the external processing medium.

In vitro percentage of buoyancy for the optimized batch was satisfactory which may be attributed to the low bulk density and optimum porosity of the microballoons (13, 25). Porosity of microballoons increased as cavity volume increased (Fig 2). The buoyancy of the optimized batch was found to be
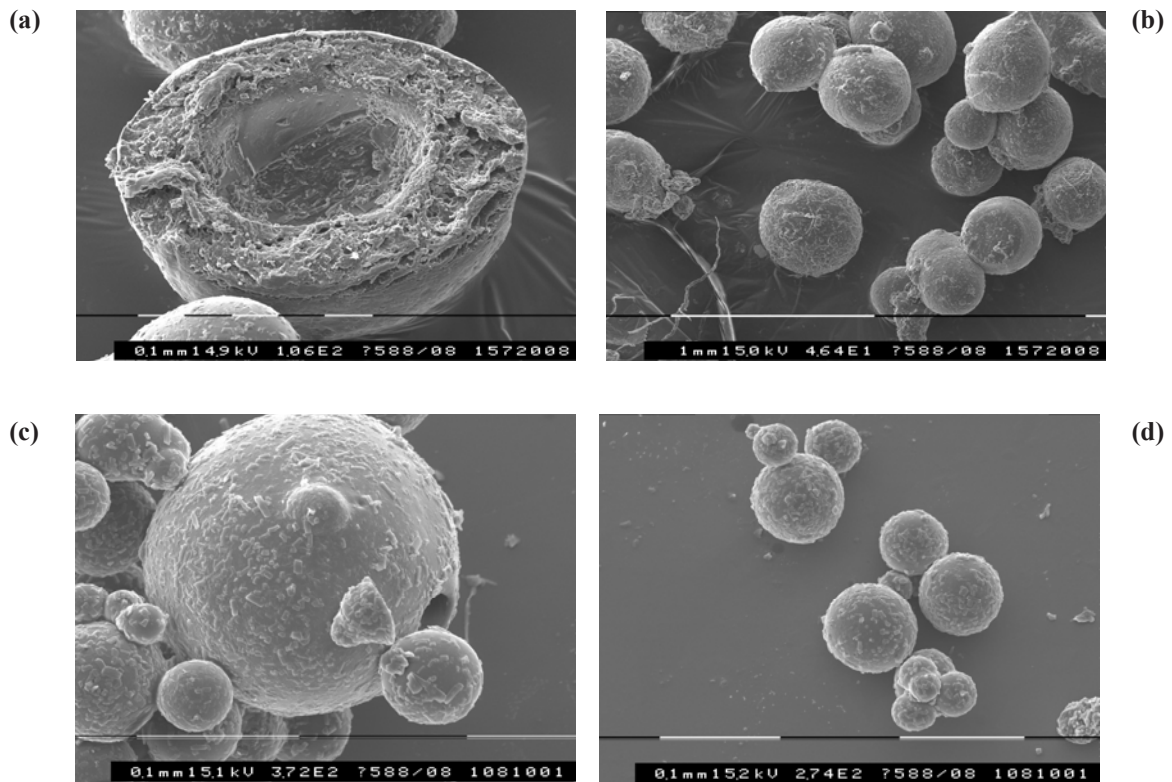
Figure 1. SEM Photomicrographs (a) Cross-section of Microballoons showing hollow structure prepared at 500 rpm, (b) Microballoons prepared at 500 rpm. (c) & (d) Microballoons prepared at 750 rpm.
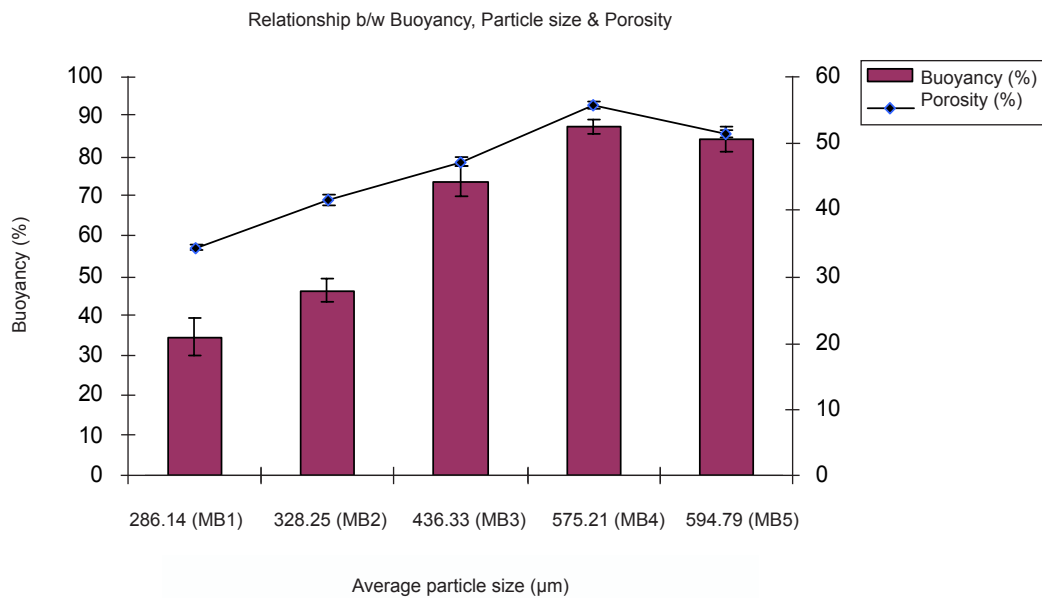

Figure 2. Relationship between Buoyancy, Particle size & Porosity of Propranolol HCl Microballoons prepared at various drug-polymer ratios (n=3)

87.43 ± 1.61 % when the average particle size was $575.21\pm6.22\mu m$.

The microballoons sank completely within 24 to 30 hrs. As the drug diffused out from the microballoon, small pores were formed in the system which allowed surrounding medium to enter and fill up the void spaces, thereby increasing weight.

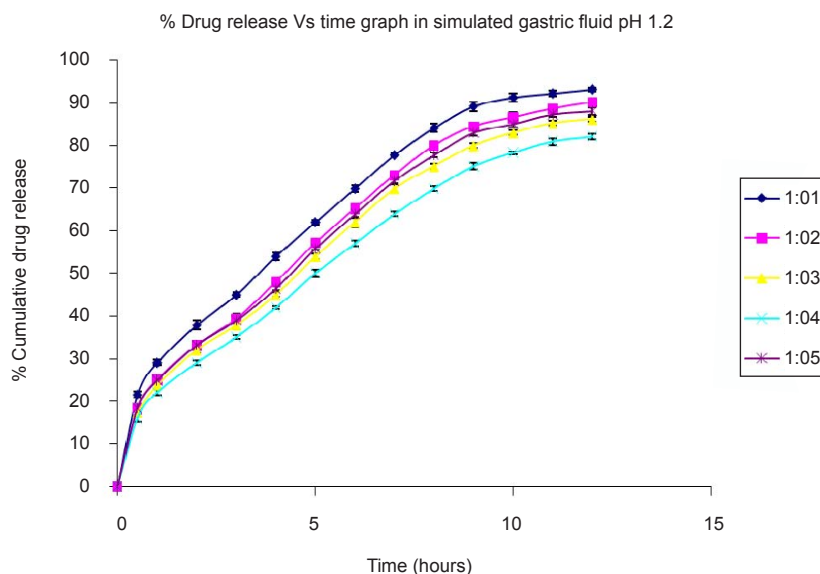In vitro drug release studies were performed in

% Drug release Vs time graph in simulated gastric fluid pH 1.2

Figure 3. In vitro release profile of Propranolol HCl Microballoons in SGF pH 1.2 (n=3) 1:1-1:5 indicates drug polymer ratios.

Table 3. Effect of bulk density and porosity on buoyancy of microballoons*.

Drug: Polymer ratio	Bulk density (gm/cm³)	True density (gm/cm³)	Porosity (%)	Buoyancy (%) after 12 hrs	Inference (porosity (%) and % buoyancy)
1:1 (MB1)	0.6682±0.024	1.0169±0.0035	34.29±0.45	34.75±4.62	Very low
1:2 (MB2)	0.5917±0.019	1.0102±0.0039	41.42±0.84	46.34±2.95	Very low
1:3 (MB3)	0.5294±0.021	1.0016±0.0041	47.14±0.67	73.66±3.88	Low
1:4 (MB4) [#]	**0.4433±0.015**	**1.0012±0.0024**	**55.72±0.51**	**87.43±1.61**	**High**
1:5 (MB5)	0.4865±0.022	1.0018±0.0031	51.43±0.59	84.25±3.20	Good

*All experiments were performed in triplicate (n=3), [#] optimized formulation.

simulated gastric fluid of pH 1.2 for 12 hrs. The cumulative release of drug significantly decreased with increase in polymer concentration (Fig 3).

The in vitro release profile was biphasic with an initial burst release (16.05±0.94%) upto 0.5 hour attributed to surface associated drug, followed by a slower release phase as the entrapped drug slowly diffused into the release medium (Fig 3). Percentage of the drug released up to 12 hrs was 82.05±0.64. There was sustained release of drug at a constant rate.

The calculated regression coefficients for zero order, first order and Higuchi models were found to be 0.976, 0.990, and 0.987 respectively. The in vitro drug release of propranolol HCl microballoons was best explained by first order equation as the plot showed the highest linearity, followed by Higuchi's model. The 'n' value for Korsmeyer-Peppas equation was found to be 0.445 indicating diffusion controlled drug release.

When the in vitro release data of formulation MB4 (drug polymer ratio 1:4) was compared with formulations MB1, MB2, MB3, and MB5 by one-way ANOVA (Newman-Keuls multiple comparison) test, the in vitro release in SGF (pH 1.2) from MB4 after 30 min was found to be significant (P<0.0002). Significant differences ($p<0.0001$) were also observed for the amount of drug released after 12 hrs for the same formulation MB4. MB3 was found to be significantly different from MB1, MB2 and MB5. On the basis of other optimization parameters, MB4 was considered to be the optimized batch.

From the results of stability studies (Table 4) it appears that for adequate shelf life of optimized Propranolol hydrochloride microballoons, they should be stored in cool (4-5ºC) and dry place.

Thus, the prepared microballoons may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

Table 4. Stability Data for propranolol hydrochloride microballoons at different temperatures.

S. No.	Sampling interval (days)	% Residual Drug Content Mean±S.D. (n=3)			Physical appearance		
		4±0.5°C	Room temp.	40±0.5°C & 75% RH	4±0.5°C	Room temp.	40±0.5°C & 75% RH
1	15	99.64±0.11	99.38±0.12	-	+	+	-
2	30	99.08±0.07	98.77±0.15	-	+	+	-
3	45	98.67±0.09	98.22±0.11	-	+	+	-
4	60	98.28±0.12	97.61±0.09	-	+	+	-
5	75	97.89±0.06	97.04±0.14	-	+	+	-
6	90	97.51±0.08	96.48±0.08	-	+	+	-

+ No change, - Clump formation

REFERENCES

1. Tayade PT, Kale RD. A multiple unit floating drug delivery system of Piroxicam using Eudragit polymer. Indian J. Pharm. Sci, 2007; 69:120-123.
2. Sato Y, Kawashima Y, Takeuchi H, and Yamamoto H. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Eur. J. Pharm. Biopharm. 2003; 55:297-304.
3. Chawla G, Gupta P, Koradia V, and Bansal AK. Gastroretention: A Means to Address Regional Variability in Intestinal Drug Absorption. Pharm. Tech. 2003; 50-68.
4. Singh BN, and Kim KH. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention. J. Control. Release. 2000; 63**;** 235-259.
5. Arora A, Ali A, Ahuja A, Khar RK, and Baboota S. Floating Drug Delivery Systems: A Review. AAPS PharmSciTech 2005; E372-E390.
6. Deshpande AA. Development of a Novel Controlled-Release System for Gastric Retention. Pharm. Res., 1997; 14: 815-819.
7. Donald LW. Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker Inc. New York, First Indian Reprint 2005; 329-510.
8. Ojha G, Tanwar YS, Chauhan CS, Naruka PS. Floating Microspheres: Development, Characterization and Application. Pharmaceutical Information For You, May 2006 (Online) Available at: www.pharmainfo. net/.../floating-microspheres-development-characterization-and-applications-United *States, Accessed on 14/07/2008*
9. Rocca JG, Omidian H, and Shah K, Progresses in Gastroretentive Drug Delivery Systems. Business Briefing: Pharmatech 2003; 152-156.
10. Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV. Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride, Acta Pharm. 2007; 57: 479-489.
11. http://en.wikipedia.org/wiki/Propranolol; Accessed on 14/07/2008.
12. Hardman JG, Limbird LE, and Goodman GH. The Pharmacological Basis of Therapeutics. McGraw Hill Publications, 10th edition, 2001; 253-254.
13. Jain SK, Jain NK, Agrawal GP. Evaluation of Porous Carrier-based Floating Orlistat Microspheres for Gastric Delivery. AAPS PharmSciTech 2006; 7: E1-E9.
14. Wei YM, Zhao L. In Vitro and In Vivo Evaluation of Ranitidine Hydrochloride Loaded Hollow Microspheres in Rabbits. Archives of Pharmaceutical Research, 2008; 31:1369-1377.
15. Gattani YS, Kawtikwar PS, Sakarkar DM. Formulation and evaluation of Gastro retentive Multiparticulate Drug delivery system of Aceclofenac. Int. J. ChemTech Research, 2009; 1:1-10.
16. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder, Int. J. Pharm., 2002; 241:279-292.
17. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. B.I. Publications Pvt. Ltd., Fifth Edition, 2006; 553-556.
18. Patel A, Ray A, Thakur RS. In vitro evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride. DARU, 2006; 2: 57-64.
19. Srivastava AK, Ridhurkar DN, and Wadhwa S. Floating microspheres of Cimetidine: Formulation, characterization and in vitro evaluation. Acta Pharm. 2005; 55: 277-285.
20. Merchant HA, Shoaib HM, Tazeen J, and Yousuf RI. Once-Daily Tablet Formulation and In Vitro Release Evaluation of Cefpodoxime UsingDandagi PM, Mastiholimath VS, Gadad AP, Iliger SR. Mucoadhesive microspheres of Propranolol hydrochloride for nasal delivery. Indian J. Pharm. Sci., 2007; 69: 402-407.
21. Sharma AK, Keservani RK, Dadarwal SC, Choudhary Y, Ramteke S. Formulation and in vitro

characterization of cefpodoxime proxetil gastroretentive microballoons. DARU, 2011; 19: 33-40

22. Das MK, and Rao KR. Microencapsulation of Zidovudine by Double Emulsion Solvent Diffusion Technique using Ethylcellulose. Indian J. Pharm. Sci., 2007; 69: 244-254.

23. Kamel AHE, Sokar MS, Gamal SSA, Naggar VF. Preparation and evaluation of ketoprofen floating oral drug delivery system. Int. J. Pharm., 2001; 220:13-21.

24. Joseph NJ, Laxmi S, Jayakrishnan A. A floating type oral dosage form for Piroxicam based on hollow microspheres: In vitro and in vivo evaluation in rabbits. J. Control Release, 2002; 79:71-79.