Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROBALLOONS OF FUROSEMIDE

Peeush Singhal *, Kapil Kumar, [1] Shubhini A. Saraf

[1]Faculty of Pharmacy Babu Banarasi Das National Institute of Technology and Management Sector-1, Dr. Akhilesh Das Nagar, Faizabad Road, Lucknow, U.P.-227105, India.
*Department of pharmacy Modern Institute of Technology Dhalwala Rishikesh, U.K.-249201, India.
Corresponding author's E-mail: pusmpharma@gmail.com

ABSTRACT

Oral sustained release gastroretentative dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medication that are characterized by narrow absorption window. The purpose of present study was to formulate and develop a new gastroretentative sustained release delivery system of microballoons for furosemide as model drug. Furosemide is a widely used high-ceiling loop diuretic drug with low bioavailability (60-70 %) and shorter half life (1-2 hrs). The microballoons were prepared by using o/w emulsion solvent evaporation method. The effect of various formulation and process variables on the internal and external particle morphology, micromeritic properties, invitro floating behavior (buoyancy), drug loading and invitro release were studied. The microballoons were found to be regular in shape. The microballoons remain buoyant (86.16±2.40) for 12 hrs. The encapsulation efficiency (83.29±2.55 %) was high. The release rate was determined in simulated gastric fluid pH 1.2 at $37\pm0.5^{o}C$. The optimized formulation (F_4) was released approximately 81 % drug after 12 hrs. Invitro drug release followed the Higuchi model with diffusion mechanism and showed a biphasic pattern with an initial burst release. The designed system due to its excellent floating ability and sustained drug release could possibly be advantageous in term of increased bioavailability of furosemide.

Keywords: Gastroretentative dosage forms, furosemide, microballoons, bioavailability, o/w emulsion solvent evaporation method, Higuchi model.

INTRODUCTION

Most of the orally administered dosage forms have several physiological limitations, such as gastrointestinal (GI) transit time, incomplete drug release from devices and/or too short residence time of the pharmaceuticals dosage forms in the absorption region of GI tract. This leads to low 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. To overcome this problem several attempts have been made to develop oral dosage forms capable of having prolonged gastric retention time (GRT) in the stomach to extend the duration of drug delivery. [1]

The gastro retentive drug delivery systems (GDDS) have been developed for prolonged gastric residence time (GRT), extended release devices with reduced frequency of administration and also improved patient compliance. These GDDS included single-unit dosage forms and multiple unit dosage forms.[2] Although single unit sustained dosage forms have been extensively studied, these dosage forms have the disadvantage of a release all or nothing emptying process from the stomach, which cause a high inter individual variability in the absorption of the drug. To overcome such drawbacks, multiple-unit drug delivery systems have been developed, because the multiple-unit particulate systems (such as microspheres) could pass through the gastrointestinal tract (GIT) to avoid the variety of gastric emptying, and thus reduce

interindividual difference in the absorption of the drug. Moreover, release the active ingredients at a sustained release rate in a larger area in the stomach is to reduce high regional concentration and risk of drug burst release compared to the single unit dosage forms. [3]

Approaches to increase the GRT include: (i) Bioadhesive delivery system which adhere to mucosal surface (ii) swellable drug delivery system, which increase in size after swelling and retard the passage through the pylorus and (iii) density controlled delivery systems , which either float or sink in gastric fluids.[4] Floating drug delivery system (low density system) first described by Davis (Davis, 1968), are low-density systems that have sufficient floating properties in the stomach for a prolonged period of time. Moreover, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. So far, hollow microspheres as a new oral solid dosage form are considered as one of the most promising floating drug delivery systems. They possess the unique advantages of multiple unit systems and better floating properties as a result of the central hollow space inside the microspheres.[5]

Floating drug delivery is of particular interest for drugs which (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment.[6]

Furosemide, a widely used "high-ceiling" loop diuretic drug, is indicated for congestive heart failure, chronic renal failure, and hepatic cirrhosis. Furosemide is absorbed mostly in the stomach and upper small intestine, possibly due to its weak acidic properties (pKa 3.93), and is characterized by a short half-life (1-2 hrs). The narrow absorption window of furosemide leads to its low bioavailability (60-70 %). The narrow absorption window of furosemide in the upper part of the gastrointestinal tract, together with the improved effect of continuous drug input, provides a rationale for developing a gastroretentive dosage form (GRDF) for this drug. Such a dosage form would be retained for prolonged periods of time in the stomach and release the drug in a sustained manner, thus providing the drug continuously to its absorption sites in a controlled manner, extending the absorption phase and increasing the magnitude of the drug effect.[7]

An object of the present investigation was to develop a multiparticulate floating delivery system consisting furosemide as drug and Eudragit RS 100 as sustained release polymer, which is capable of floating on gastric fluid and delivering the therapeutic agent over an extend period of time.

MATERIALS AND METHODS

Materials

Furosemide was obtained as a gift sample from Kwality Pharma Amritsar. Eudragit RS 100 was obtained as gift sample from Kopran pharmaceutical Ltd. Mumbai. Polyvinyl alcohol, ethanol, dichloromethane, monostearine and tween 20 were purchased from SD Fine Chemicals Ltd. All chemicals/reagents used were of analytical grade. A UV/Vis spectrophotometer (Shimadzu 1700 pharma spec) was used for drug analysis.

Preparation of Microballoons

Furosemide (0.1 g), Eudragit RS 100 and monostearin (0.5 g) were dissolved in ethanol: dichloromethane mixture (1:1 v/v, 10 ml) at room temperature. The drug solution was poured slowly as a thin stream into 200 ml of water containing 1.0 % w/v polyvinyl alcohol. The solution was kept at constant temperature while stirring at 300 rpm. The finely dispersed/emulsified droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent.[8] After agitating the mixture for 1 h, the microspheres were filtered, washed several times with water to remove traces of polyvinyl alcohol and dried overnight at 40 °C. During drying, microsphere cavity became hollow resulting in floating drug delivery system. O/w solvent evaporation method has been successfully used to encapsulate lipophilic drugs into micro particles.

Process variables:

Amount of Polymer: 100, 200, 300, 400, 500 mg; Stirring rate: 300, 600, 900 rpm; Temperature of the preparation: 30, 40, 50 °C; Volume of aqueous phase: 150, 200, 250 ml; Concentration of dispersing agent: 0.75, 1.0, 1.5 w/v.

Characterization of Prepared Microballoons

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.[9]

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

Micromeritic Properties

The microspheres were characterized by their micromeritic properties, such as particle size, true density, tapped density, compressibility index and flow properties. Particle size measurements were carried out on an image analysis system. An optical microscope was used to produce pictures of the microballoons. The particle size distribution of each formulation was measured by determination of the diameter of 200-300 particles using the MEDICAL PRO software. The tapping method was used to determine the tapped density as follows:[10]

Tapped density = [Mass of microspheres / Volume of microspheres after tapping] × 100

True density was determined using a benzene displacement method. Porosity[11] (ε) was calculated using the equation:

$$\varepsilon = (1 - Pp / Pt) \times 100$$

Where Pt and Pp are the true density and tapped density, respectively.

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method [12] and calculated as:

$$\text{Tan } \theta = 2H / D$$

Where 2H/D is the surface area of the free standing height of the microspheres heap that is formed on a graph paper after making the microspheres flow from the glass funnel.

Morphology

The morphology of microsphere were studied by scanning electron microscopy (SEM) (Philips 505, Holland) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with platinum film. To investigate the internal morphology, the microballoons were dissected with a blade.

Determination of Percent Drug Entrapment

The drug content of eudragit RS 100 microspheres was determined by dispersing 50 mg formulation (accurately weighed) in 10 ml ethanol followed by agitation with a magnetic stirrer for 12 hrs to dissolve the polymer and to

extract the drug. After filtration through a 5 μm membrane filter (Millipore), the drug concentration in the ethanol phase was determined spectrophotometrically at 274 nm. Eudragit RS 100 did not interfere under these conditions. Each determination was made in triplicate. The percentage drug entrapment was calculated as follows:[13]

% Drug entrapment = [Calculated drug conc. / Theoretical drug content] × 100

Percentage Buoyancy

Fifty milligrams of the floating microparticles were placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v % Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 12 hrs, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried at 40 ^{o}C overnight until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. [14, 15]

$$Buoyancy\ (\%) = Wf / (Wf + Ws) \times 100$$

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

In-Vitro Release

The drug release study was carried out using USP rotating basket apparatus (Veego, DA-6DR USP Standards) at 37 ± 0.5 °C and at 100 rpm using 900 ml of simulated gastric fluid pH 1.2 containing 0.02 % Tween 20 as a dissolution medium. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through filter paper, diluted suitably and analyzed spectrophotometrically with UV-VIS spectrophotometer (UV-1700 Pharmaspec, Shimadzu) at a wavelength of 274 nm. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample.

Data Analysis of Release Studies

Four kinetic models including the zero order (Equation 5), first order (Equation 6), Higuchi matrix (Equation 7), and Peppas-Korsmeyer (Equation 8) release equations were applied to process the in vitro release data to find the equation with the best fit using PCP Disso v3 software.[16,17]

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

$$\log UR = k_2 t / 2.303 \qquad (6)$$

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

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

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

Statistical Treatment of Dissolution Data

Differences in vitro drug release of furosemide from microballoons and microballoons were statistically analyzed by 1-way analysis of variance (ANOVA) with posttest (Newman-Keuls Multiple Comparison Test) at two different time intervals 0.5 h and 12 hrs. Statistically significant differences between in vitro furosemide releases of formulations were defined as $P < 0.05$. Calculations were performed with the GraphPad-Instat software program (GraphPad Software Inc, San Diego, CA).

Stability

The optimized formulation (F4) was stored in screw capped glass vials in stability chamber at 40±1 ^{o}C and 75±5 % relative humidity, room temperature, and 4±0.5 ^{o}C for 3 months. Samples were analyzed for physical appearance, residual drug content after a period of 15, 30, 45, 60, 75 and 90 days. Initial drug content was taken as 100 % for each formulation. The log % residual drug content vs. time graph was also plotted for the optimized formulation in order to evaluate half-life and shelf life of formulations.

Half-life was evaluated by an equation:

$$T_{10\%} = 0.152 \text{ X } t_{1/2}$$

Shelf life was evaluated by an equation:

$$T_{10\%} = 0.104/K$$

RESULTS AND DISCUSSION

Formation of Microspheres

To increase the gastric retention time (GRT) of the drug, we developed hollow microspheres with excellent floating properties, which can be retained in the upper gastrointestinal tract (GIT) for a longer time for prolonged drug action and improvement of oral drug bioavailability. Several preformulation trials were undertaken for various proportions of dug and polymer by variation of aqueous phase volumes for qualitative and quantitative determination of microballoons characteristics. It was found that Eudragit RS 100 microballoons show desirable high drug content, yield, floatation and adequate release characteristics and hence were suitable for development of a sustained release system.

Floating microspheres were prepared by the emulsification solvent-evaporation technique using Eudragit RS 100 as a polymer. A solution or suspension of Eudragit RS 100 and furosemide in ethanol and dichloromethane was poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitioned into the external aqueous phase and the polymer precipitated around dichloromethane droplets.

The subsequent evaporation of the entrapped dichloromethane led to the formation of internal cavities within the microspheres.

Before optimization of formulation, all the process variables (stirring speed, temperature, volume of aqueous phase and dispersing agent concentration) were optimized. To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds (batches FS1–FS3). The size of the 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 (Table 1).

Preparation at 30^{0}C provided porous microspheres having higher porosity with a surface so rough as to crumble upon touching. The surfaces of microballoons prepared at 40°C were less rough than those of microballoons prepared at 20 or 30°C. At 40°C, polymer and the drug were coprecipitated and the shell was formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. Microballoons prepared at 50°C exhibited no hollow nature. In contrast, microspheres prepared at 50°C demonstrated a single large depression at the surface, which was a consequence of rapid evaporation of dichloromethane (Table 1).

The mean microballoon size and also buoyancy was found to increase with increasing dispersing agent concentration. With 150 ml volume of aqueous phase, drug entrapment and buoyancy was low due to aggregation of polymer due to its increased concentration. With 250 ml of processing medium, drug entrapment was low because as the volume of processing medium increased, the emulsion droplets moved freely in the medium, thus reducing collision induced aggregation and yielding small and uniform microballoons and resulting in low buoyancy. This could also be the reason for higher drug extraction in to the processing medium resulting in lower entrapment efficiency (Table 1).

After optimizing the all parameter, the drug polymer ratio is optimized. All the formulations were formed by using optimized parameters. The mean particle size of the microspheres significantly increased with increasing eudragit RS 100 concentration. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. In case of batch F4 higher drug entrapment efficiency, percent yield and buoyancy (83.29±2.55, 88.12±2.45 and 86.16±2.40 respectively) were achieved. On the basis of these characteristics, the batch F4 is selected as optimized formulation (Table 2).

Table 1: Optimization of process variables

Batch code	Drug: Polymer	Stirring rate (rpm)	Temperature (^{0}C)	Dispersing agent Concentration (w/v)	Volume of processing medium	Mean particle size (µm)	Percent yield	Drug entrapment efficiency (%)	Buoyancy (%)
FS1	1:3	300	40	0.75	200	415.35±5.63	77.89±2.45	72.14±2.35	75.28±2.40
FS2	1:3	600	40	0.75	200	325.99±4.37	73.17±4.51	70.41±2.15	71.16±1.61
FS3	1:3	900	40	0.75	200	288.34±5.92	71.25±2.94	67.12±1.72	67.12±3.46
FT1	1:3	300	30	0.75	200	490.62±4.21	71.34±2.85	64.15±3.56	65.29±3.14
FT2	1:3	300	40	0.75	200	422.83±5.63	74.28±2.45	74.10±2.55	76.13±2.19
FT3	1:3	300	50	0.75	200	348.21±6.73	72.12±2.94	67.03±4.23	68.92±3.25
FD1	1:3	300	40	0.5	200	325.48±3.45	72.83±2.89	70.19±2.21	68.19±2.92
FD2	1:3	300	40	1.0	200	408.27±3.63	73.34±3.21	73.49±2.55	76.21±2.40
FD3	1:3	300	40	1.5	200	475.61±4.22	69.10±3.11	68.10±1.21	78.90±3.15
FV1	1:3	300	40	1.0	150	470.59±5.60	73.12±2.82	67.20±2.20	67.43±2.72
FV2	1:3	300	40	1.0	200	410.35±6.10	77.89±2.45	74.81±2.55	75.28±2.40
FV3	1:3	300	40	1.0	250	319.67±5.28	70.46±3.86	63.75±2.15	64.91±2.91

Mean ± SD, n=3

Table 2: Optimization of formulation

Batch	Drug : Polymer	Average diameter (µm)	Drug entrapment efficiency (%w/w)	Percent yield	Buoyancy (%)	Tapped density (gm/cm^3)	True density (gm/cm^3)	Porosity (%)	Angle of repose
F1	1:1	309.36±3.78	58.40±1.71	50.28±3.12	54.86±4.20	0.40±0.02	1.60±0.2	75.01±2.98	31.5±2.40
F2	1:2	336.87±3.16	62.58±2.80	67.19±3.85	67.47±2.96	0.44±0.04	1.62±0.3	73.45±3.10	30.9±2.19
F3	1:3	415.77±5.57	72.14±2.32	77.88±4.19	75.28±2.43	0.51±0.07	1.68±0.1	72.02±2.54	34.1±1.51
F4	1:4	493.35±5.63	83.29±2.55	88.12±2.45	86.16±2.40	0.53±0.09	1.70±0.2	70.58±2.81	28.3±1.86
F5	1:5	538.46±4.35	74.57±3.35	80.90±4.12	8.31±3.38	0.57±0.06	1.78±0.1	67.93±3.15	33.4±2.25

Mean ± SD, n=3

Table 3: One way ANOVA (Newman-Keuls multiple comparison) test for in vitro drug release of furosemide after 0.5 h.

Newman-Keuls Multiple Comparison Test	Mean Diff.	q	P value
F4 Vs F1	6.330	10.05	P < 0.001
F4 Vs F2	3.240	5.146	P < 0.05
F4 Vs F3	2.070	3.288	P < 0.05
F4 Vs F5	0.820	1.302	P < 0.05

Table 4: One way ANOVA (Newman-Keuls multiple comparison) test for in vitro drug release of furosemide after 12 hrs.

Newman-Keuls Multiple Comparison Test	Mean Diff.	q	P value
F4 Vs F1	12.70	15.36	P < 0.001
F4 Vs F2	7.890	9.543	P < 0.001
F4 Vs F3	3.990	4.826	P < 0.01
F4 Vs F5	2.050	2.480	P < 0.05

Table 5: Shelf life of optimized formulation

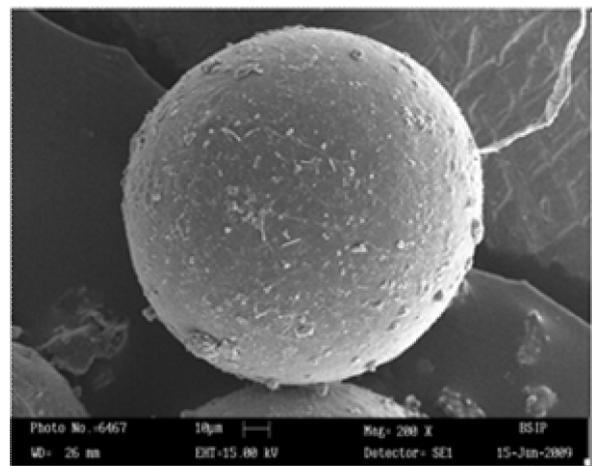| Storage condition	K (day^{-1})	T$_{10\%}$ (days)	t$_{1/2}$ (days)
4±0.5 °C	3.06 x 10^{-4}	344.23	2264.70
Room temperature	3.84 x 10^{-4}	274.30	1804.68

Micromeritic Properties and Morphology

The particle size for all formulations was in the range of 309.36 to 538.46 μm. The tapped density values ranged from 0.40 to 0.57 g/cm^3, while their true densities ranged between 1.60 to 1.78 g/cm^3 of all the formulations, which may be due to the presence of low-density particles in the microspheres. The porosity of all the formulations was found to be in the range of 67.93–75.01 %. All formulations showed excellent flowability as expressed in terms of angle of repose in the range 28°- 34°. The better flow property indicates that the floating microspheres produced are non-aggregated (Table 2). The SEM photographs showed that the fabricated microspheres were spherical with a smooth surface, internal hollow cavity and exhibited a range of sizes within each batch (Fig. 1).
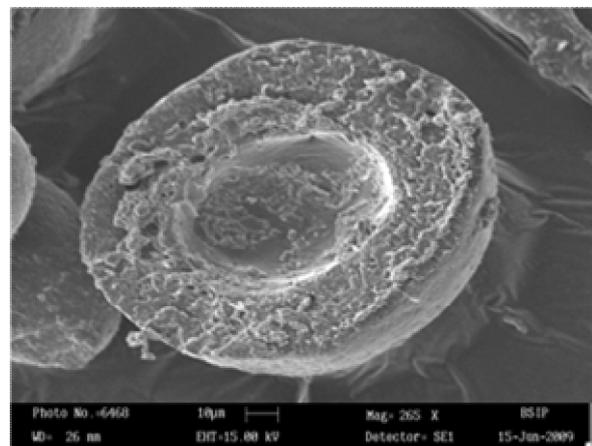
Fig. 1 Scanning electron photomicrograph of optimized batch (F4)

(B) shows smooth texture of microballoons

(A) Shows size range of microballoons

(C) Shows cross section view of microballoons.

Percentage Buoyancy and Drug Entrapment

The floating test was carried out to investigate the floatability of the prepared microspheres. The floating ability differed according to the formulation tested and the medium used. The microspheres were spread over the surface of simulated gastric fluid (SGF) and the fraction of microspheres settled down as a function of time was quantitated. All the formulations showed good floating ability. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. The optimized formulation F4 gave the best floating ability (86.16 %) in SGF. Tween 20 (0.02 % w/v), added to SGF, counteracted the downward pulling at the liquid surface by lowering surface tension, because the relatively high surface tension of simulated gastric fluid causes the highest decrease of surface area at the air fluid interface. Floating of microspheres for 12 hrs was considered satisfactory performance.

The percent drug entrapment of furosemide in all the formulations was found to be good at all levels of drug entrapment efficiency. The high entrapment efficiency of repaglinide is believed to be due to its poor aqueous solubility. The optimized formulation gave the higher drug entrapment (83.29 %).

Invitro Drug Release Study and Release Kinetics

In vitro drug release studies were performed in simulated gastric fluid pH 1.2 for 12 hrs. The cumulative release of drug significantly decreased with increasing polymer concentration. The increased density of the polymer matrix at higher concentrations resulted in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microballoons are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. The in-vitro release profile of optimizes batch (F4) was biphasic with an initial burst release (15.86±0.64 %) in 0.5 h attributed to surface associated drug, followed by a slower release phase as the entrapped drug slowly diffused out into the release medium. 81.12±0.94 % drug was released after 12 hrs. The release of furosemide from different formulations followed the order: F1 > F2 > F3 > F4 > F5. The pattern also provides an idea about the effect of Eudragit RS 100 content on drug release from the microspheres (i.e., the higher the Eudragit RS 100 content in microspheres, the lower the drug release) (Fig. 2).

The release mechanism of furosemide from these floating microballoons was also evaluated on the basis of theoretical dissolution equations including zero-order, first-order, Higuchi matrix, and Peppas-Korsmeyer (fig 3 & 4). The calculated regression coefficients of optimized batch (F4) for zero order, first order, Higuchi models and Korsmeyer-Peppas were 0.972, 0.987, 0.992 and 0.990. It was found that the in vitro drug release of furosemide microballoons was best explained by Higuchi's model as the plot showed the highest linearity, followed by

Korsmeyer-Peppas. Desai and Bolton[18] and Khattar et al [19] reported that noneffervescent floating systems obeyed the Higuchi model indicating drug release via a diffusion mechanism (Fig. 3).
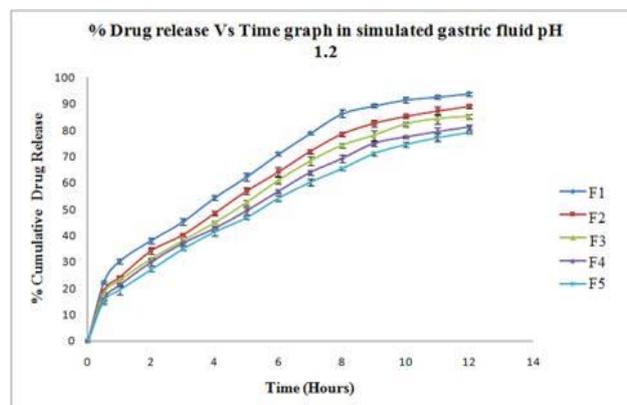
Figure 2: In vitro drug release

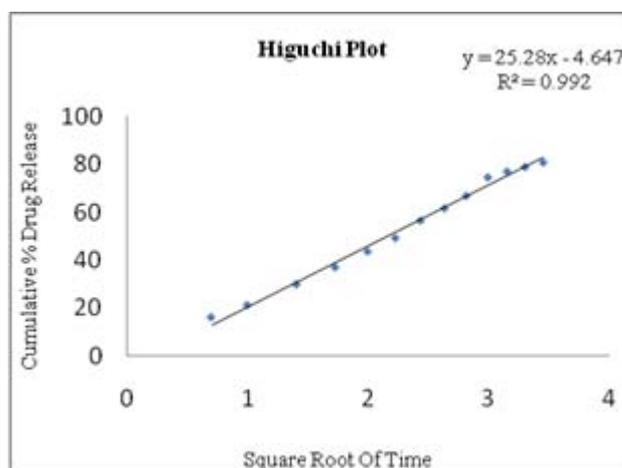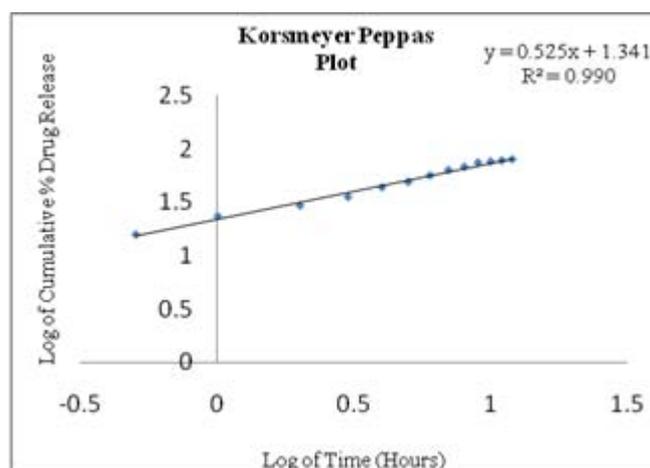**Figure 3:** Higuchi model drug release

Figure 3: Peppas-Korsmeyer model drug release

The means of in vitro release data of furosemide from microballoons of formulations F1, F2, F3, F4, and F5 were statistically analyzed by one-way analysis of variance (ANOVA) with post test (Newman-Keuls Multiple Comparison Test) at two different time intervals 0.5 h and 12 hrs. Statistically significant differences between in vitro

drug release of formulations were defined as P<0.05. Calculations were performed with GraphPad Prism software program. The in vitro release data of formulations F1, F2, F3, F4 and F5 compared by one-way ANOVA (Newman-Keuls multiple comparison) test, the in vitro release in SGF (pH 1.2) from F4 after 0.5 h was found to be significant (P<0.0001) (Table 3). Significant differences ($p < 0.0001$) were also observed for the amount of drug released after 12 hrs from the same formulation F4 (Table 4).

Stability Studies

The $T_{10\%}$ obtained in case of formulation stored at 4±0.5 °C was found to be higher in comparison with the formulation stored at room temperature which indicated that the formulations tend to degrade faster at higher temperatures and humidity (Table 5).

The results of stability studies suggest that for adequate shelf life of optimized furosemide microballoons, it should be stored in cool and dry place.

CONCLUSION

Microballoons with ethyl Eudragit RS 100 were successfully prepared by the oil in water (o/w) emulsion solvent evaporation method. The prepared microballoons remain floating for more than 12 hrs in the simulated gastric fluid, and exhibited excellent sustained release of drug (more than 12 hrs). Microballoons of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Microballoons prepared in this study provide a promising gastroretentive drug delivery system to deliver drugs with sustained release in order to improve oral drug bioavailability for many kinds of drugs. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

REFERENCES

1. Kale RD, Tayade PT, A Multiple Unit Floating Drug Delivery System of Piroxicam Using Eudragit Polymer, Indian J Pharm Sci, 69 (1), 2007,120-123.

2. Wei Y, Zhao L, In vitro and in vivo evaluation of ranitidine hydrochloride loaded hollow microspheres in rabbit, Arch. Pharm. Res., 31, 2008, 1369-1377.

3. Shweta A, Javed A, Alka A, Roop K K, Sanjula B, Floating Drug Delivery Systems: A Review, *AAPS Pharm Sci Tech,* 6, 2005, 372-390.

4. Stithit S, Chen W, Price J C, Development and characterization of buoyant theophylline microspheres with near zero order release kinetics, *J. Microencapsul,* 15, 1998,725-737.

5. Jain SK, Awasthi AM, Jain NK, Agrawal GP, Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization, J. Control. Release 107, 2005, 300-309.

6. Singh BN, Kim KH, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Release, 63, 2000, 235– 259.

7. Klausner EA, Lavy E, Stepensky D, Cserepes E, Barta M, Friedman M, Hoffman A, Furosemide Pharmacokinetics and Pharmacodynamics following Gastroretentive Dosage form Administration to Healthy Volunteers, J Clin Pharmacol, 43, 2003,711-720.

8. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Hollow microspheres for use as a floating controlled drug delivery system in the stomach, J. Pharm. Sci., 81, 1992, 135– 140.

9. Patel A, Ray S, Thakur RS. In vitro evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride, DARU, 2, 2006, 57-64.

10. Gattani YS, Kawtikar PS, Sakarkar DM, Formulation and evaluation of Gastro retentive Multipaticulate Drug delivery system of Aceclofenac, Int. J. of ChemTech Res., Jan- March, 2009, 1-10.

11. Martin A, Physical Pharmacy, Ed 4, Lea Febiger, Philadelphia, 1993, 431– 432.

12. Ritschel WA, Thompson GA, Lucker PW, Wetzelsberger K, Biopharmaceutic evaluation of Etofylline clofibrate and its drug formulation, Arzneim.-Forsch/ Drug Res., 30, 1980, 2020– 2023.

13. Whitehead L, Collett JH, Fell JT, Amoxicillin release from a floating dosage form based on alginates, Int.J.Pharm, 210, 2000, 45-49.

14. Yamamoto H, Sato Y, Kawashima Y, Takeuchi H, In vitro evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, European Journal of Pharmaceutics and Biopharmaceutics, 57, 2003,235–243.

15. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H, Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, European Journal of Pharmaceutics and Biopharmaceutics, 55, 2003, 297–304.

16. Polli JE, Rehki GS, Augsburger LL, Shah VP, Methods to compare dissolution profiles and a rationale for wide dissolution specification for metoprolol tartrate tablets, *J Pharm Sci.*, 86, 1997,690-700.

17. Wu PC, Tsai MJ, Huang YB, Cheng JS, Tsai YH, In vitro and in vivo evaluation of potassium chloride sustained release formulation prepared with saturated polyglycolyed glycerides matrices, *Int J Pharm*, 243, 2002,119-124.

18. Desai S, Bolton S A, floating controlled-release drug delivery system: in vitro-in vivo evaluation, *Pharm Res,* 10, 1993, 1321-1325.

19. Khattar D, Ahuja A, Khar RK, Hydrodynamically balanced systems as sustained release dosage forms for propranolol hydrochloride, *Pharmazie,* 45, 1990,356-358.

****