Panacea Journal of Pharmacy and Pharmaceutical Sciences 2015:4(3);654-679

International Journal

PJPPS

Panacea Research Library

http://prlpublisher.com/journal/index.php/pjpps/index

Panacea Journal of Pharmacy and Pharmaceutical Sciences

ISSN: 2349 7025

Original Research Article **Volume 4 Issue 3**

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF ATENOLOL

Ashok Tripathi*, Harish Chandrawanshi, Mukesh Patel, Arvind Dangi, Dr. D. P. Chatterjee

Mittal Institute of Pharmacy, Bhopal (M.P.)

Article history:

Received: 28th July 2015

Received in revised form: 18th August 2015

Accepted: 21st August 2015

Available online: 25th September 2015

Corresponding author:

Ashok Tripathi

Email:

ashoktripathi35@gmail.com

***Present address*:**

Mittal Institute of Pharmacy, Bhopal (M.P.)

These authors have no conflict of interest to declare.

Abstract:

Floating microspheres prepared with enteric coated polymer successfully by the solvent diffusion method. Upon incorporation of the hydrophilic polymer such as HPMC in the shell of microspheres, the amount of drug release form microspheres could enhance. In vitro data obtained from floating microspheres of show Atenolol excellent float ability, good buoyancy and prolonged drug release. Floating microspheres different size and drug content could be obtained by varying formulation variable. Diffusion found to be the main release mechanisms. Thus the prepared floating microspheres may prove to be potential candidate for multiple-unit delivery device adaptable to any intra gastric condition.

The formulations were evaluated for various Micromeritic and characteristic studies. It increases the bioavailability dosage form with prolonged effect, hence improve the patient compliance.

Ideal property of floating microspheres includes high buoyancy and sufficient release rate of drug. It is necessary to selected appropriate balance between buoyancy and release rate drug from all developing floating microspheres. F4formulation showed the best appropriate balance between buoyancy and release rate drug, which can be considered as a best fit floating microspheres.

The designed system F4 floats in the stomach and prolonged the gastric residence time (GIT) providing sustained release action, in addition floating microspheres enable to increase the absorption rate, as it gradually sank in the stomach and arrived at the absorption site. The developed formulation overcomes the drawback limitation of sustained release preparation. Therefore multiple units floating system i.e., floating microspheres will be possibly beneficial for sustained action.

Key words: Microsphere Polymer, Atenolol, floating microspheres

Introduction:

Oral route of drug administration is the most convenient and widely accepted route of most therapeutic agents. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs.

Controlled release drug delivery systems that can be retained in stomach for long time are important for drug that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having site specific absorption limitation.

Normal gastric residence time usually range between 5 minutes and 2 hours. Migrating Myoelectric complex by four phase 1 period of no contraction (40-60 minutes), phase 2 period of intermittent contraction (20-40 minutes), phase 3 period of regular at contraction at the maximal frequency that travel dist as distally also knows as housekeeper wave (10-20 minute) and phase 4 period of transition between phase 3 and phase 1(0-5minute).

Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric retention improves bioavailability, reduces drug waste and improve solubility for drug that are less soluble in a high PH environment. It has application also for local drug delivery to the stomach and proximal small intestine. Slowed motility of the gastrointestinal tract by concomitant administration of drug or pharmaceutical excipients also increase gastric retention of drug these efforts results in GRDS that were designed in large part, based on the approaches

Development of a successful oral controlled release drug delivery dosage form requires

An understanding of three aspects:

1. The Anatomic and physiologic characteristic of gastrointestinal tract (GIT)

2. Physiochemical, pharmacokinetic and Pharmacodynamic characteristic of the drug and

3. Dosage form characteristics

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state therefore; this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative examples of such drugs.

Floating drug delivery system (FDDS):

Floating drug delivery systems (FDDS) were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. non-effervescent and effervescent systems, have been used in the development of FDDS. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. These considerations have led to the development of oral floating dosage forms possessing gastric retention capabilities. Thus when a drug possesses a narrow absorption window design of

sustained release preparation requires both prolongation of gastrointestinal transit time of dosage forms and controlled drug release.

Material and instrument

Material used

The flowing material was used for the research work. The entire chemical used was of best quality available.

Material used for research work

S.No	Chemical Used	Manufacturer
1	Atenolol IP	Ipca Laboratories ltd
2	HPMC	Yarrow chem. Products Mumbai
3	Ethyl cellulose	**Asha Cellulose (India) Pvt. Ltd,mumbai**
4	Acetone	**Satish Chemical India**
5	Ethanol	**PAB Organics Private Limited,Guj.**
6	Liquid paraffin	**Dwarkesh Pharmaceutical pvt ltd**
7	Spam-80	**Mohini Organics Pvt. Ltd.**
8	n-hexane	**Avani Petrochem pvt ltd**
9	Methanol	**A.B.Enterprises**
10	0.1 n HCI	**R.L Chemical**

Instrument used

The instrument used for research work were as follows

Instrument research work

Table -2

S.No.	Instrument	Manufacturer
1	Uv spectrophotometric 1800	LABINDIA Analytical Instrument.
2	Usp type dissolution	LABINDIA Analytical Instrument.
3	Optical microscopic	Optica microscopic

4	Electronic balance	Shimadzu, Japan
5	Stirrer	REMI, India
6	Sieve	Excel Enterprises, Kolkata.

EXPERIMENT WORK

Experimental work

Preformulation study

- **Spectrophotometer Analysis of Atenolol**

100 mg of Atenolol is weight accurately and transfer to a 100 ml volumetric flask. And dissolve in minimum quantity of ethanol and make final volume with ethanol up to 100 ml. so as to obtain stock solution of 1000 µg/ml. From this stock solution, dilution of 10µg/ml is made with ethanol, and the sample is scan between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer. Atenolol exhibit λmax at 225.5 nm.

- **Preparation of Calibration Curve in Ethanol**:-

A stock solution of Atenolol (100ug/ml) in ethanol is prepared by dissolving 25mg of drug 25 ml in ethanol, To prepared the series of different conc. 20 ,40, 60, 80,100ug/ml were form the stock solution. This solution is taken at 225.5nm using ethanol blank solution.

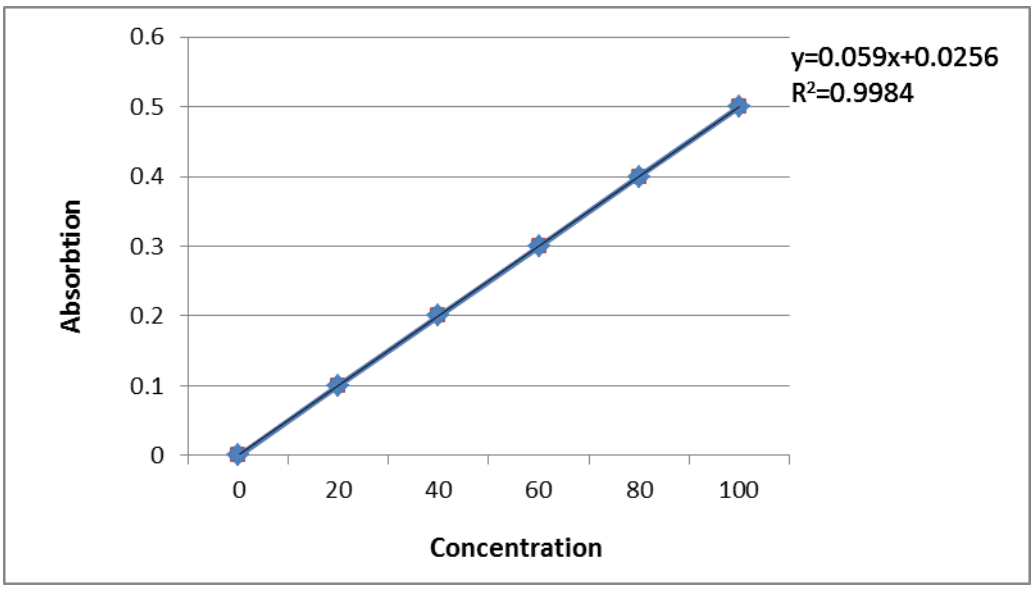

Figure-1 Calibration curve of Atenolol in ethanol

Preparation of calibration curve in 0.1NHCL:-

A stock solution of Atenolol (100ug/ml) in 0.1NHCL is prepared by dissolving 25mg of drug 25 ml in 0.1N Hcl, To prepared the series of different conc. 20 ,40, 60, 80, 100ug/ml form the stock solution. This solution is taken at 225.5nm using 0.1NHCL blank solution.

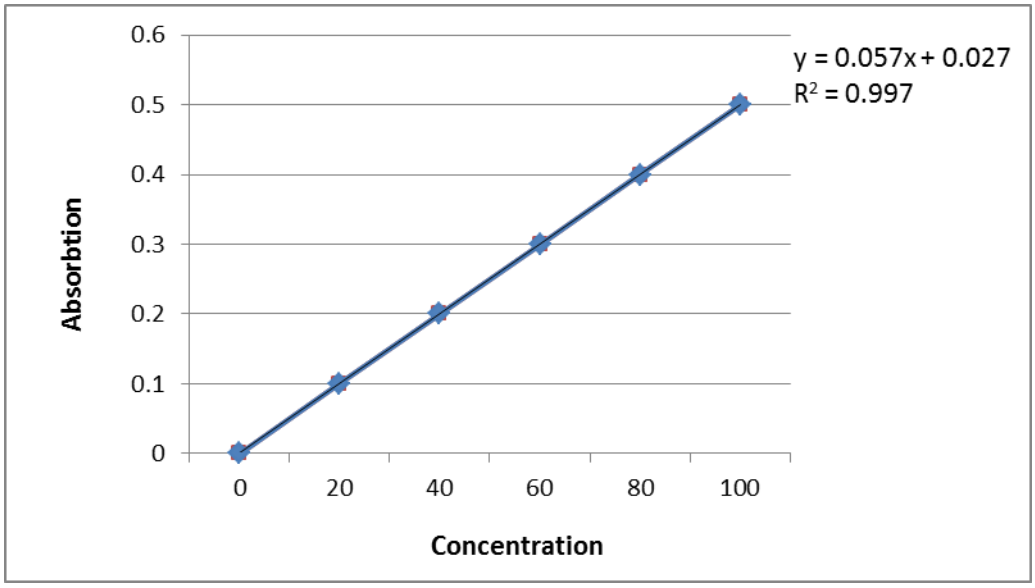

Figure-2 Calibration curve of Atenolol in 0.1N Hcl

Preparation of calibration curve in water:

A stock solution of Atenolol (1000µg/ml) in prepared by dissolving 25 mg of drug 25 ml in water, to prepared the series of different conc. 20, 40, 60, 80, 100µg/ml form the stock solution. This solution taken at 225.5 using water blank solution

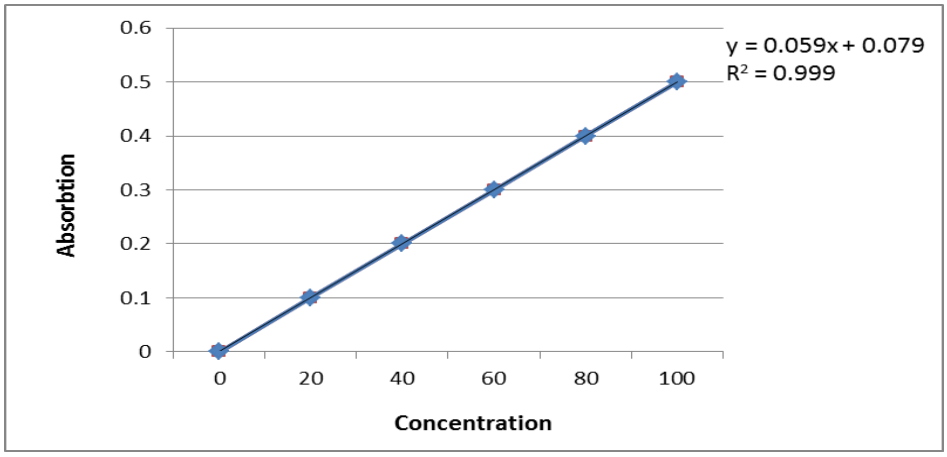

Figure-3 Calibration curve of Atenolol in water

Drug Excipient Compatibilities:

Thin Layer Chromatographic Studies

In order to examine the possibility of interaction between drug and excipient thin layer chromatographic studies were performed. A plate of silica gel G was activated at 105°C for 1 hour and used. The metabolic solution of drug alone, the aqueous solution of hydrotropic solution as well as solubilized product of Atenolol different solution were spotted on the base line with the aid of micro dropper. Then, the plate was left in air for 10 min to dry and transferred to a solvent jar saturated with solvent system composed of mixture of methanol and ammonia solution (99:1 v/v/v). The solvent system was allowed to run for about 4 cm. Finally, the plate was transferred to an oven maintained at temperature 80^{o}C for 5 min and observed then, it was under UV light for visualization of spots. The respective R_F values were determined and recorded.

Melting point

The melting point of determined by open capillary method using thiel'tube. Drug in packed capillary. The average of three values is taken as the melting point of drug.

EVALUATION OF POWDER MIXTURE:

1. Angle of Repose:

The angle of repose of powder was determined by the funnel method. The accurately Weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way

that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

tan θ=h/r

Where, **h** = Height of power cone, and, **r** = Radius of the power cone

2. Poured Density & Tapped Density:

Both poured density and tapped density were determined. A quantity of 2 g of powder from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. Poured & tapped densities were calculated using the following formulas:

Poured Density = Weight of powder/bulk volume of the packing

Tapped Density = Weight of the powder/tapped volume of the packing

3. Carr's Index and Hausner's Ratio:

Compressibility index and Hausner's ratio has become the simple, fast, and popular

Methods of predicting powder flow characteristics. The compressibility index and the

Hausner's ratios were determined by measured both the bulk density and the tapped density of a powder.

The compressibility index and Hausner's ratio was calculated as follows:

Where,

C= Compressibility index,

H= Hausner's ratio,

ρB=Bulk density,

ρT= Tapped density.

6.3 Preparation of floating microspheres of Atenolol

Floating microspheres containing Atenolol was prepared using solvent evaporation method. The drug to polymer ratio to used to prepare a different formulation. The polymer content was mixture of ethyl cellulose and HPMC KM4. The drug polymer mixture is dissolve in mixture of ethanol and acetone (1:1) was dropped in tween-80, the mixture adds the 50 ml liquid paraffin. The solution was stirrer with a propeller- type agitator at 40°C temp. For 1h at 300 rpm. The form floating microspheres passage the sieve and wash with n-hexane and dried at room temperature. The various batch floating microspheres were prepared as follows

Table -3

Formulation of floating microspheres prepared

S.No	Formulation code	Atenolol (mg)	HPMC (mg)	Ethyl cellulose (mg)
1	A1	500	1000	-
2	A2	500	500	500
3	A3	500	700	300
4	A4	500	300	700
5	A5	500	-	1000
6	A6	500	900	100
7	A7	500	100	900
8	A8	500	200	800
9	A9	500	800	200
10	A10	500	600	400
11	A11	500	400	600

Evaluation of Floating Microspheres

- **Particles size analysis:**

Particles size analysis play important role in determine the release characterize and floating properties. The size of floating microspheres was measured by using optical microscopy.

- **Floating behavior of floating microspheres**

100 mg of the floating microspheres were placed in 0.1N Hcl (300 ml) containing 0.01% of tween-80. The mixture was stirrer with paddle at 100rmp. The layer of buoyant microspheres was pipette and separated by filtration at 1, 2, 3, 4, and 6h. The collected the microspheres were dried in desiccators over night. The percentage of microspheres was calculated by using this equation.

$$\% \text{ Floating microsphere} = \frac{\text{weight of floating microsphere}}{\text{Initial weight of floating microspheres}} \times 100$$

- **Drug Entrapment:**

The various formulation of the floating microspheres were subject to drug content 50 mg floating microspheres form all batches were accurately weighed and cursed. The powdered of microspheres were dissolved with 10 ml ethanol in 100 ml volumetric flask and makeup the volume with 0.1N HCL. This resulting solution is than filtrated through whatmann filter paper. After the filtration, form this solution 10ml was taken out and diluted up to100 ml with 0.1N HCL and the absorption was measured at 225.5 nm against 0.1N HCL as a blank

The percentage drug entrapment was calculated as follow

$$\% \text{ Drug entrapment} = \frac{\text{calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

- **Percentage yield:**

The prepared floating microspheres were collected and weight form different formulation. The measured weight was divided by the total amount of all non volatile components which were used for the preparation of the floating microspheres

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total of drug and polymer}} \times 100$$

- **Determination of tapped density:**

It is the ratio between a given mass of floating microspheres and its volume after tapping. Tapped density of floating microspheres was determined by the tapping

method. Accurately weighed quantity of floating microspheres was transferred in to a 10 ml measuring cylinder. After observing the initial volume floating microspheres, the tapping was continued on a hard surface until no further change in volume was noted and the tapped density was calculated according to following formula.

$$\text{Tapped density} = \frac{\text{Mass of floating microspheres}}{\text{Volume of floating microspheres after tapping}} \times 100$$

- **Percentage compressibility index:**

The same tapping method was used to determine percentage compressibility index. The percentage compressibility index was calculated according to following formula.

% compressibility index = {1-V/V0}

Where V and V0 are the volume of the sample after and before the standard tapping respectively.

- **Angle of repose:**

The flow property of floating microspheres is usually assessed y determining the angle of repose of the floating microspheres. It is the maximum the angle that can be obtain between the free floating surface of floating microspheres heap and horizontal plane. The angle of repose of floating microspheres was determined by fixed funnel method. The floating microspheres were allowed to fall freely through a funnel unit apex a conical pile just touch the tip of the funnel

- **In-vitro release studies:**

The drug release rate form floating microspheres was carried out using the USP type II dissolution paddle assembly. A weight amount of floating microspheres equivalent to 100 mg drug were dispersed in 900ml of 0.1N HCL (PH 1.2) maintained at 37°C and stirrer in 100rpm. 1 ml sample was withdraw at predetermined interval and filtered and equal volume of dissolution medium was replace in the vessel after each withdraw to maintain sink condition, the collect sample were suitably diluted with 0.1N HCL and analyzed

spectrophotometrically at 225nm to determine the concentration of drug present in the dissolution medium.

- **Shape and surface characterization of floating microspheres of scanning electron microscopy:**

Form the formulated batch the floating microspheres formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using electron microscopy. Sample was fixed in carbon tape and fine gold shuttering was applied in a high vacuum evaporator. The acceleration voltage was set at 30KV during scanning electron microscopy was used surface morphology.

RESULTS AND DISCUSSION

Results and Discussion

Table4: Calibration curve of Atenolol in ethanol

S.No	Concentration µg/ml	Absorption at (255nm)
1	20	0.149
2	40	0.255
3	60	0.359
4	80	0.501
5	100	0.604

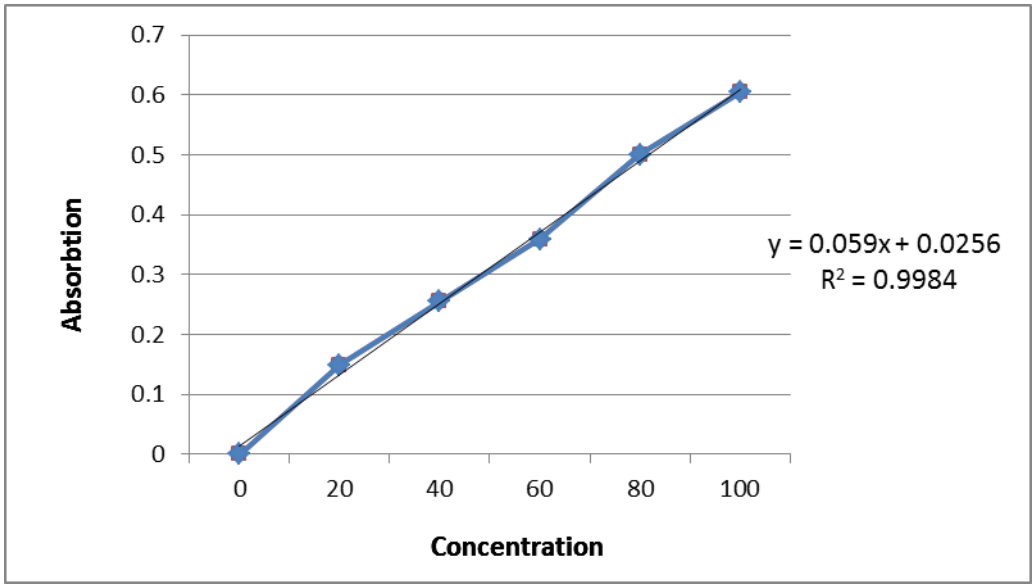

Figure-4 Calibration curve of Atenolol in ethanol

Table -5 Calibration curve of Atenolol in 0.1N Hcl

S.No.	Concentration µg/ml	Absorption nm
1	20	0.145
2	40	0.267
3	60	0.389
4	80	0.490
5	100	0.618

Calibration curve of Atenolol in 0.1N Hcl

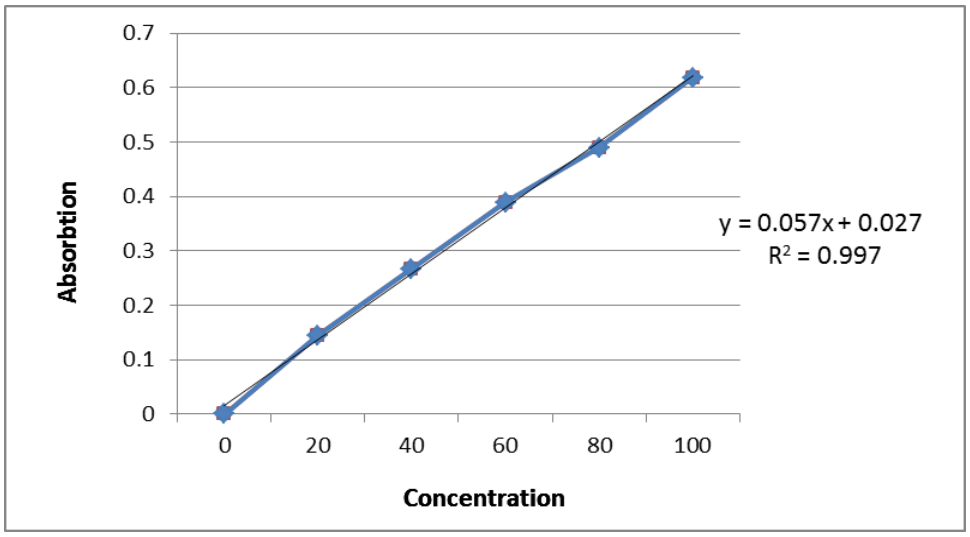

Figure-5 Calibration curve of Atenolol in 0.1N Hcl

Table-6 Calibration curve of Atenolol in water

S.no	Concentration µg/ml	Absorption nm
1	20	0.203
2	40	0.312
3	60	0.434

4	80	0.556
5	100	0.676

Calibration curve of Atenolol in water

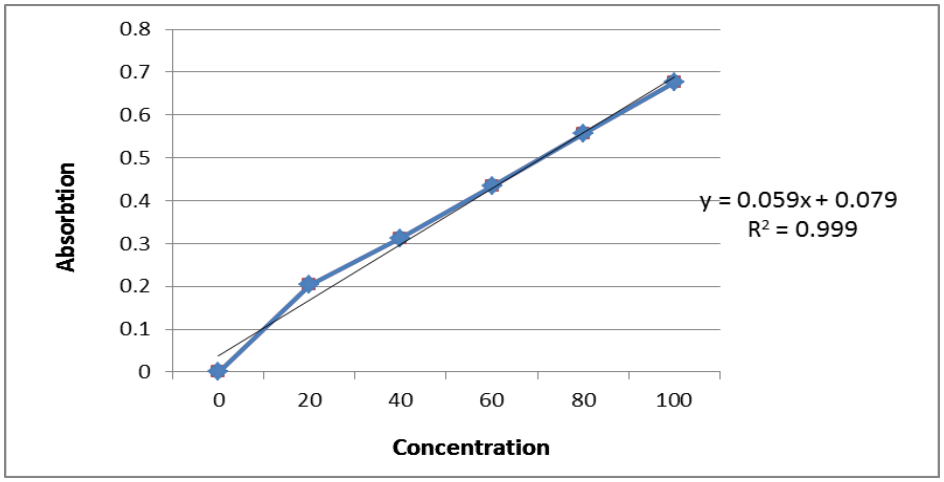

Figure-6 Calibration curve of Atenolol in water

Thin layer chromatography results: In order to examine the possibility of interaction between drug and excipient thin layer chromatographic studies were performed. A plate of silica gel G was activated at 105°C for 1 hour and used. The metabolic solution of drug alone, the aqueous solution of hydrotropic solution as well as solubilized product of Atenolol different solution were spotted on the base line with the aid of micro dropper. Then, the plate was left in air for 10 min to dry and transferred to a solvent jar saturated with solvent system composed of mixture of methanol and ammonia solution (99:1 v/v/v). The solvent system was allowed to run for about 4 cm. Finally, the plate was transferred to an oven maintained at temperature 80^{o}C for 5 min and observed then, it was under UV light for visualization of spots. The respective R_F values were determined and recorded.

Table- 7 Thin layer chromatograph results

S.no	**Atenolol and polymer**	**0 day (Rf)**	**14 day (Rf)**
1	Atenolol	0.5	-
2	Atenolol+ HPMC	0.51	0.5
3	Atenolol+ EC	0.46	0.43
4	Atenolol+HPMC+EC	0.48	0.46

Solubility

Soluble in ethanol, methanol

Sparingly soluble in water

Slightly soluble in acetone

7.2 Evaluation of floating microspheres

- **Particles size analysis:**

Particles size was determined by optical microscopy method. It play important role in floating ability and release drug form microspheres. If size of microspheres is less than 500µ release rate of drug will be high and floating ability will reduced, while microspheres ranging between 500µ-1000µ, the floating ability will be more and release rate will be sustained manner.

The mean particles size of floating microspheres was in range 609-874µm show in table**.**

Table -8 Mean particles size of different batch of floating microspheres

S.No.	**Formulation code**	**Mean particles size µm**
1	A1	874±5
2	A2	854±5
3	A3	836±5
4	A4	794±5
5	A5	776±5
6	A6	769±5
7	A7	754±5
8	A8	**7**34±5
9	A9	698±5
10	A10	643±5
11	A11	609±5

Percentage yield

Percentage of different formulation was determined by weighing microspheres after drying. The percentage yield of different formulation was in range of 54.82-95.86% as show table

Table -9 Percentage yield of different formulation of floating microspheres

Formulation code	Percentage yield (%)
A1	95.86±10
A2	93.98±10
A3	91.09±10
A4	82.87±10
A5	78.53±10
A6	76.47±10
A7	71.56±10
A8	69.31±10
A9	66.03±10
A10	56.84±10
A11	54.35±10

Tapped density

Tapped density was determined by tapping method. The tapped density of value of different microsphere range form 0.234- 0.523 gm/cm as show table. The density value of microspheres were less than the density of gastric fluid, thereby, it will have good buoyancy property in the stomach.

Table -10 Tapped density of different formulation of floating microspheres in Atenolol

S.No	Formulation code	Tapped density(gm/cm)
1	A1	0.234±0.05
2	A2	0.245±0.05
3	A3	0.256±0.05
4	A4	0.267±0.05
5	A5	0.279±0.05
6	A6	0.298±0.05
7	A7	0.374±0.05
8	A8	0.398±0.05
9	A9	0.432±0.05
10	A10	0.489±0.05
11	A11	0.523±0.05

Percentage compressibility index

The determined by same tapping method and its range is 7.89- 19.43% as show in table. The percentage compressibility index value less than 20 for all formulation suggested excellent flow property.

Table – 11% Compressibility index for different formulation of floating microspheres

S.No	Formulation code	% compressibility index
1	A1	7.89±0.5
2	A2	8.39±0.5
3	A3	9.77±0.5
4	A4	10.46±0.5
5	A5	11.63±0.5
6	A6	12.49±0.5
7	A7	14.56±0.5
8	A8	16.04±0.5
9	A9	17.68±0.5
10	A10	18.34±0.5
11	A11	19.43±0.5

Angle of repose

Angle of repose of microspheres was determined by funnel fixed method. Angle of repose of microspheres was in range of 23°.67- 39°.87 as show in the table. All formulation show excellent flow ability as represented in term of angle of repose (<40°).

Table 12 Angle of repose of different formulation of floating microspheres

S.No	Formulation code	Angle of reposes
1	A1	23°.67±5
2	A2	24°89±5
3	A3	25°39±5
4	A4	27°.89±5
5	A5	29°.68±5
6	A6	31°.87±5
7	A7	33°65±5
8	A8	34°23±5
9	A9	35°.54±5
10	10	37°41±5
11	A11	39°87±5

Drug entrapment

The drug entrapment efficiency of different formulation was in range of 41.18- 76.19% as show in table. the drug entrapment efficiency slightly decrease with increase HPMC content and decrease ethyl cellulose ratio in microspheres. This is due to the permeation

characteristics of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of floating microspheres.

Table 13 Drug entrapment of different formulation of floating microspheres

S.No	Formulation code	Drug entrapment (% w/w)
1	A1	76.19±10
2	A2	70.59±10
3	A3	66.23±10
4	A4	64.76±10
5	A5	62.01±10
6	A6	60.54±10
7	A7	58.90±10
8	A8	56.67±10
9	A9	50.23±10
10	A10	48.72±10
11	A11	41.14±10

Floating behavior of floating microspheres

Floating microspheres were disperse in 0.1N Hcl containing tween-80 simulate gastric fluid. Floating ability of different formulation were found of be differed according to ethyl cellulose and HPMC ratio, F1 to F5 formulation show best ability in 6 hours. F6 to F12 show the less floating ability as show in the table.

Table -14 Percentage buoyancy of different formulation

Formulation code	1 hour	2 hour	4 hour	6 hour
F1	98.41±5	97.08±5	95.23±5	91.49±5
F2	98.11±5	96.58±5	92.17±5	87.34±5
F3	99.02±5	95.92±5	88.23±5±5	585. 02±5
F4	98.87±5	95.45±5	85.30±5	78.45±5
F5	98.72±5	92.89±5	78.49±5	72.87±5
F6	98.45±5	91.49±5	73. 63±5	70.56±5

F7	98.12±5	86.87±5	66.21±5	68.13±5
F8	88.65±5	75.49±5	65. 10±5	66.23±5
F9	78.34±5	72.05±5	56.04±5	57.87±5
F10	74.11±5	71.44±5	54.98±5	47.81±5
F11	70.32±5	69.23±5	52.23±5	38.14±5

SUMMARY

Summary

The present study of floating microspheres of Atenolol prepare by solvent diffusion method by using ethyl cellulose and HPMC as a polymer. If size of floating microspheres is less than 500 µm release rate of drug will be high and floating ability will reduce, while floating microspheres ranging between 500 µm – 1000 µm, the floating ability will be more and release rate will be sustained manner. Mean particles size range for all formulation was varied from 609 to 879 µ due to change drug and polymer ratio.

Drug entrapment for all formulation was is range found is range 41.32 to 76.19% w/w and its efficiency slight decrease with increase the HPMC content. When distribution coffeicency was high efficiency of drug entrapment in to microspheres was evaluated. This phenomenon was due to the lack of retention of drug with low distribution coefficient in the emulsion droplet aqueous solution during the process, which led to reduced entrapment of drug in to microspheres.

Tapped density values for all formulation were less than that of gastric fluid suggested that its exhibit good buoyancy. Buoyancy of the floating microspheres decrease with increase drug release. The floating ability pattern different according to the formulation test and medium used.F4 gave the best floating ability in all medium. As evidenced by the percentage of particles float at different time interval. This can mainly due to its low bulk density value opting before and after tapping. All formulation showed excellent flow ability as represent in the term of angle of repose (<40) due to the different polymer ratio. Angle of repose in range of (25°. 39°, 37°.72) all formulation show excellent flow ability (<40°).

Shape of floating microspheres was found to be spherical by SEM study. Small cavity represent a surface, which may due to solvent evaporation process, the microspheres were float long time over the surface of the dissolution medium without any apparent gelatin which is responsible for floating ability. Surface morphology surface of formulation F4 exhibited a smooth surface of floating microspheres.

Ideal property of floating microspheres include high buoyancy and sufficient release of drug in 0.1N HCL percent drug release rate of F1, F2, F3, formulation in 12 hours. This is slow and incomplete drug release.

In Odour the increase the percent drug release rate, the ratio of decrease and increase respectively. Formulation F5, F6, F7 formulation show high rate release in 10 hours and F8, F9, F10 formulation show high rate release in 12 hours and less buoyancy. Formulations F4 show best rate release and best buoyancy 99.12% in 12 hours. This considered as best formulation. Form the formulated batch the floating microspheres formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using electron microscopy. Sample was fixed in carbon tape and fine gold shuttering was applied in a high vacuum evaporator. The acceleration voltage was set at 30KV during scanning electron microscopy was used surface morphology.

CONCULSION

Drug absorption in the GIT is a highly variable process, prolonging gastric retention of the dosage form and extended the time of drug absorption. Floating microspheres prepared with enteric coated polymer successfully by the solvent diffusion method. Upon incorporation of the hydrophilic polymer such as HPMC in the shell of microspheres, the amount of drug release form microspheres could enhance. In vitro data obtained from floating microspheres of show Atenolol excellent float ability, good buoyancy and prolonged drug release. floating microspheres different size and drug content could be obtained by varying formulation variable. Diffusion found to be the main release mechanisms. Thus the prepared floating microspheres may prove to be potential candidate for multiple- unit delivery device adaptable to any intra gastric condition.

The formulations were evaluated for various Micromeritic and characteristic studies. It increases the bioavailability dosage form with prolonged effect, hence improve the patient compliance.

Mean particles size for all formulations were varied. Due to change drug and polymer ratio. Drug entrapment efficiency slightly decreases with increase the HPMC content. Tapped density value for all formulation were less than of that of gastric fluid, suggests that good buoyancy. Angle of repose (<40°) for all formulation shows excellent flow ability.

Drug release pattern was evaluated in 0.1N HCL release rate of F1, F2, F3, formulation were found to be slow and incomplete in dissolution medium. In order to increase the release rate of drug the ratio of ethyl cellulose and HPMC is increase.

Ideal property of floating microspheres includes high buoyancy and sufficient release rate of drug. It is necessary to selected appropriate balance between buoyancy and release rate drug from all developing floating microspheres. F4formulation showed the best appropriate balance between buoyancy and release rate drug, which can be considered as a best fit floating microspheres.

The designed system F4 floats in the stomach and prolonged the gastric residence time (GIT) providing sustained release action, in addition floating microspheres enable to increase the absorption rate, as it gradually sank in the stomach and arrived at the absorption site. The developed formulation overcomes the drawback limitation of sustained release preparation. Therefore multiple units floating system i.e., floating microspheres will be possibly beneficial for sustained action.

When it is been formulated in large scale, formulation will be economical, due to its easy of preparation and good buoyancy due to the polymer used in formulation.

REFERENCE

1. Bhosale UV. Kusum Devi, Jain N, Swamy P. Effect of polymer concentration and viscosity grade of Atenolol release from gastric floating drug delivery system. Indian J.Pharm .Educ.Res. 2010 July-sep; 44(3):267-72.

2 K. Deepa, M.Karthikeyan, Cefpodoxim Proxetil floating microspheres formulation and in–vitro evaluation , Indian journal 2009:5(2), 69-72.

2.Yuveraj Singh tanwar, pushpendra Singh Naruka, Garmia, Rani Ojha. Development and evaluation floating microspheres of varapamil hydrochloride, Indian journal of Pharmaceutical science 2007: 43,78-82.

3. Gohel, Parikh, Shital Bariya, Sustained release floating microspheres of acyclovir, internation journal drug development and research, 2011: 3,80-84.

4. Singh Bandana, Kanoujia Jovita, Manisha pandey, Saraf Shubhini, formulation and evaluation floating microspheres of Famotidine , international journal of pharmatech. Research 2010 :2, 414-420.

5. Najmuddin M, Sachin S, Asgar A, Patel V and Khan T. Formulation andInvitro Evaluation of Floating Microspheres of Ketoprofen Prepared by Emulsion Diffusion Method. International Journal of Pharmacy And Pharmaceutical Research. 2010; 2:13-19.[5]

6. Srivastava Anand Kumar, Ridhurkar Devendra Narayanrao, Wadhwa Saurabh, Floating microspheres of cimetidine: Formulation, characterization and in vitro evaluation, Acta Pharm, 2005, 55, 277–285.

7. Patel Asha, Ray Subhabrata and Thakur Ram Sharnagat, In Vitro Evaluation and Optimization of Controlled Release Floating Drug Delivery System of Metformin Hydrochloride, DARU, 2006, 14(2), 57-63.

8. S.B. Gholap , Banarjee S.K. ,D.Gaulkurad , S. L. Jadhav Hollow microspheres review , Acta Pharma,2010:43,322-329.

9. Suddhasattya Dey, Dhiraj Kumar, D Sandeep Kumar, S. A. Sreenivas and V. Rahul, formulation and in vitro evaluation of floating microspheres Nateylinide ,international Journal and bioscience, 2008:50,147-156.

10. Sunit KS, Abdul AM and BB barik. Formulation and In-Vitro Evaluation of Eudragit Microspheres of Staudinger, Tropical Journal of Pharmaceutical Research. 2005; 4 (1) : 369-375.

11 Patel V, Patel N. Self correcting monolithic floating matrix tablet of dipyridamole: influence of formulation variables. International Jouranl of pharmaceutical sciences. 2009 Nov. 06:210-25.

12. Nagesh, Venkatesh J. S. ,Santosh, Raj M., Jagadish, Sindhu Patil, Floating Drug Delivery system of Levofloxacin formulation and evaluation, Indian Pharma Sci & res 2011:3(6), 1265-1269.

13. Behera BC, sahoo SK, Dhal S, barik BB and Gupta BK.Characterization of Glipizide Loaded Polymethacrylate Microspheres Prepared by Emulsion Solvent Evaporation Method. Tropical Journal of Pharmaceutical Research. 2008;7(1):879-885.

14. Hemangi Patil. S, Moreshwar Patil. P, Bharat Tekade. W, Vinod Thakare. M and Vijay Patil, Formulation and in vitro Evaluation of Floating Microsphere of Acyclovir. Arch Pharm Science & Res. 2009; 1: 194-198.

15. Zhenqiu Yang , Baozhen Song, Qiaoxia Li, Honglei Fan and Fan Ouyang, Preparation of microspheres with microballoons inside for floating drug-delivery systems. Journal of Applied Polymer Science. 2004; 94(1):197-202.

16. Sunil Jain. K, Govind Agrawal. P and Narendra Jain .K , Evaluation of porous carrier-basedfloating orlistat microspheres for gastric delivery. AAPS Pharm Sci Tech.2008; E 54-E 62.

17. Umamaheshwari R.B.; Jain S.; Bhadra D.; Jain N.K.Floating microspheres bearing acetohydroxamic acid for the treatment of Helicobacter pylori.Journal of Pharmacy and Pha. rmacology.2003; 12(55):1607-1613. 33.

18.Kumar R. Development and in-vitro evaluation of sustained release floating matrix tablets of metformin Hydrochloride. International Journal of pharmaceutical sciences. 2010 July 13;1(8):96-100.

19 Yang L, Eshraghi J, Fassihi R. A new intragastric delivery system for the treatment of Helicobacter Pylori associated gastric ulcer: in-vitro evaluation. Journal of controlled release. 1998 April 12;57:215-22.

20. S.B. Gholap , Banarjee S.K. ,D.Gaulkurad , S. L. Jadhav Hollow microspheres review , Acta Pharma,2010:43,322-329.

21. Rajeev Garg, G.D. Gupta "gastroretentive floating microspheres of silymarin preparation in vitro evaluation, tropical journal of pharmaceuticals research 2010:9(1):56-66.

22. Ghodake.J.S., Shinde D.A., Kadam A.N "Formulation and evaluation of floating microspheres metformin hydrochloride, international research 2010:2(1):378-384.

23. Vandna Singh, Punita, Amrenara Chaudhury "Preparation on eudragit of floating microspheres of ranitidone hydrochloride 2011:68(6):975-980.

24. Sagar Balase Sanagale, B.V.Jain, Dr. S.D. Bortate "Formulation and evaluation of floating microspheres of felodipines 2011:3(2):11-16.

25. C. Sharon Kumar "Formulation and evaluation of floating microspheres of gabapentine by using solvent evaporation method 2010:1(1):76-79.

26. Biresh Kumar Sarkar, Sandeep Singh Tanwar, Prashant Soni, and Jain" Formulation and characterization and in-vitro evaluation of floating microspheres esomeprazole 2012:1(7):87-92.

27. Sarude, Mittal, Magar, and Shrivastava" Formulation and evaluation floating microspheres of glipizide 2011:3(3):775-783.

28. Bathani Sree Tejaswi, Durgaramanu Sivadasn, Shalini Devi, "Formulation and in-viro evaluation of floating microspheres clathromycin 2011:3(6):90-101.

29. Swapnila VShinde, Rohit Pawar , Hemant, "Domperidone floating microspheres and in-vitro evaluation, journal of pharmacy reaserch 2012 volume 5(4) 2012.

30. Y.S. Tanwar" Floating microspheres and development and characterization and application, Pharma research 2006: 32(2):29-32.

31. P.Puntane S.M.Sarude, M.Mittal, R.M.Magar, and A.D. Shrivastava" Formulation and evaluation floating microspheres of glipizide 2010:3(4):77-82.

32. Gaurang Patel, Ajay Tiwari, Nirav Rabadia,"Floating microspheres as a novel tool of H2 receptor blocker, international research journal of pharmacy 2012:3(2).

33. N. Pandya, M. Pandya, V.H. Bhaskar"Preparation and characterization in vitro of poruse carrier- based floating microspheres for gastric delivery. J young pharm 2011:3(2).

34. Nilamgiri Gawain , Garima Joshi, Krutika Sawant" Floating microspheres of Valacyclovir Hcl. For optimization and characterization in in-vitro and in-vivo studies, journal of pharmacy & bioailled science 2012 4(5) 8-9.

35. Harsoliya, Patel, Pathan "Formulation of floating microspheres of ritonavir by cross linking technique, international journal research of pharmaceutics and biological articles 2012; 3(1):108-111.

36. Ambati Brahma Reddy, M Karunanidhi, K Sudheer Karna, B Samyuktha Rani 'Effect of SLS on ethyl cellulose containing cyclobenzaprine HCl floating, Research Journal of Pharmaceutical, Biological and Chemical Sciences 2010:1(8):898-1004.

37. Abdul Hasan Sathali.A, Kathiravan.S "Formulation and characterization of floating microspheres of perindopril erbumine, Journal of Pharmacy Research 2012,5(4),1862-1871. 35. . 38. Gohel, R. K. Parikh, Shital Bariya, Sustained release floating microspheres of amoxicillin, international journal drug development and research, 2011: 3,80-84.

39. Ambati Brahma Reddy, M Karunanidhi , K Sudheer Karna, B Samyuktha Rani 'Effect of SLS on ethyl cellulose containing cyclobenzaprine HCl floating, Research Journal of Pharmaceutical, Biological and Chemical Sciences 2010:1(8):898-1004.

40. Abdul Hasan Sathali., Kathiravan.S "Formulation and characterization of floating microspheres of perindopril erbumine, Journal of Pharmacy Research 2012,5(4),1862-1871.

41. Nirav Rabadia, Mr. jay Tiwari, Gaurang Patel, Vishal Virani" Development and evaluation of floating microspheres of Pioglitazone hydrochloride using ethyl cellulose, Der Pharmacia , 2010, 2(5): 261-27 Vol. 3, No.1, pp 76-81,

42. Suresh Fartyal, Sajal Kumar Jha, Manvendra Singh Karchuli, "Formulation and Evaluation of Floating Microspheres of Boswellic acid, Int.J. PharmTech Res.2011, 3(1)

43. Shoufeng Li, et al., "Effect of formulation variables on the Floating properties of gastric floating drug delivery system" Drug Development Industrial Pharmacy by Taylor and Francis, volume 28 , 783 –792

44. Nakagawa T, Ichikondo S, Sasai Y, Kuzuya M. Preparation of floating drug delivery system by plasma technique. Chem Pharm. Bull 2006; 54(4): 514-518

45. Singh B, Kim HN: Floating drug delivery system: an approach to oral controlled drug via gastric retention.J Control Rel. 2000; 63: 235-259.

46. Khatri S, Girdhani D, Pahwa R: Recent advances in floating drug delivery system. The Indian Pharmacist.2007; 6: 17–20.

47. Arora S, Ali J, Ahuja A, Khar RK, Baboota S: Floating Drug Delivery Systems: A Review. AAPS PharmSciTech.2005;6(3) :372-390.

48. Deshpande, A. A., Shah, N.H., Rhodes, C.T., and Malick, W., Development of a novel controlled Release system for gastric retention, Pharm. Res. 1997; 14 (6): 815-9.

49. Shah S.H, Patel J.k, Patel N-Stomach Specific Floating Drug Delivery System: A Review Int. J. Pharm Tech Research (1), 623-633

50. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral drug delivery system. Int J Pharm.2001;220:13Y21

51. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (in vivo).J Control Release. 1991;16:279Y290.