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Research Article

**FORMULATION AND EVALUATION OF ATENOLOL
FLOATING MICROSPHERES**

L. Satyanarayana* and N. Sandeepthi

Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar,
Medchal Dist.

Abstract:

The purpose of present work was to formulate and evaluate atenolol tartrate floating microspheres. Floating microspheres concept was applied to increase the gastric residence of the dosage form. The Floating microspheres were prepared by emulsification solvent diffusion technique. The best batch exhibited excellent floating time as well as release at desired time. The particle size was controlled by changing polymer concentration, rpm and temperature. Polymers used for the preparation were Ethyl cellulose and HPMC. This approach suggested the use of floating microsphere to avoid the side effects.

Keywords: Microspheres, Atenolol tartrate, Ethyl cellulose, HPMC.

Corresponding Author:

L. Satyanarayana,

Professor,

Dept. of Pharmaceutics

Omega College of Pharmacy,

Edulabad, Ghatkesar, Medchal, Telangana, INDIA.

E-Mail: satyadna_1@yahoo.co.in

Mobile: +91 94401 27725

QR code



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INTRODUCTION:

Floating systems are the low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for a prolonged period. While the system floats over gastric contents, the drug release slowly at the desired rate, which results in the increased gastro-retention time and reduces fluctuation in the plasma drug concentration. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micrometer. The Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature [1]. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, less

bioavailability and extensive first pass metabolism [2,3].

Atenolol is a selective β -1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. Biological half life of is 3-7 hours of atenolol following oral administration favours development of a sustained release formulation [4].

In the present investigation floating microsphere of atenolol tartarate were prepared by solvent diffusion method using two different polymer hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC). The aim of the work was for drug releases in controlled manner for prolonged period, bioavailability enhancement.

MATERIALS AND METHODS:**Preparation of Floating Microspheres**

The floating microspheres were prepared by using the emulsion solvent diffusion method. In this method, weighed amount of drug (Atenolol Tartarate), EC and HPMC were dissolved in a mixture of Dichloromethane (DCM): Ethanol (ETN) (1:1) at room temperature. This solution was poured into 100ml distilled water containing 0.1% Tween 80 maintained at a temperature of 300-400C. The resultant emulsion was stirred with a propeller type agitator at 1000 rpm for 1 hr to allow volatile solvent to evaporate. The resultant microspheres were filtered and dried. FM1 to FM12 were the batches prepared using different levels of ethyl cellulose, HPMC conc., stirring speed and temperature as shown in Table 1.

Design of Experiment**Table 1: Formulation of Atenolol Tartarate Floating Microsphere**

Batch Code	Ethyl cellulose concentration (grams)	Speed(rpm)	Temperature °C	HPMC concentration (grams)
FM 1	1	1000	30	1
FM 2	2	1000	30	1
FM 3	3	1000	30	1
FM 4	4	1000	30	1
FM 5	1	800	30	1
FM 6	1	1200	30	1
FM 7	1	1400	30	1
FM 8	1	1000	45	1
FM 9	1	1000	60	1
FM 10	1	1000	30	2
FM 11	1	1000	30	3
FM 12	1	1000	30	4

*For all batches inner phase was dichloromethane:ethanol(1:1) and

*Inner phase (dichloromethane: ethanol)to external phase(water)solvent ratio was 1:10

Evaluation of atenololtartarate floating microspheres

1. Particle size determination

The particle size can be determined by using an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 particles with the help of a calibrated oculometer.

2. Bulk density

Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.

3. Tapped density

The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as 1000 taps using tapped density apparatus.

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{volume of microspheres after tapping}}$$

4. Compressibility Index and Hausner Ratio

Compressibility index and hausner ratio was calculated from the values of bulk density and tapped density by using following formulas:

$$\% \text{ compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. Angle of Repose

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as

$$\tan \theta = 2H/D$$

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

6. Entrapment Efficiency

Microspheres containing of drug should be crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was

filtered then assayed by UV-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

7. Yield of Microspheres

The prepared microspheres 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 microspheres.

$$\% \text{ Yield} = \left(\frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \right) \times 100$$

8. Floating Behavior

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

9. In-vitro Release Studies

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at $37 \pm 1^\circ$ at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a $0.25 \mu\text{m}$ membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

RESULTS AND DISCUSSION:

Table 2: Evaluation parameters

Batch code	Particle size (μ m)	Bulk density	Tapped density	% compressibility	Angle of repose (θ)
FM 1	130.5 \pm 3.21	0.55 \pm 0.01	0.60 \pm 0.15	8.33 \pm 0.06	17 ⁰ 7 ¹ \pm 0.21
FM 2	172.7 \pm 3.0	0.65 \pm 0.01	0.70 \pm 0.11	7.142 \pm 0.07	19 ⁰ 3 ¹ \pm 0.12
FM 3	210.3 \pm 2.5	0.82 \pm 0.01	0.90 \pm 0.10	8.88 \pm 0.05	23 ⁰ 2 ¹ \pm 0.10
FM 4	240.6 \pm 1.5	0.90 \pm 0.01	0.99 \pm 0.01	9.09 \pm 0.04	26 ⁰ 5 ¹ \pm 0.09
FM 5	223.2 \pm 1.0	0.89 \pm 0.01	0.95 \pm 0.12	6.31 \pm 0.06	28 ⁰ 1 ¹ \pm 0.06
FM 6	114.8 \pm 3.3	0.44 \pm 0.02	0.53 \pm 0.23	16.98 \pm 0.02	16 ⁰ 7 ¹ \pm 0.32
FM 7	97.1 \pm 3.7	0.30 \pm 0.03	0.40 \pm 0.20	25.1 \pm 0.05	15 ⁰ 3 ¹ \pm 0.45
FM 8	174.4 \pm 2.7	0.67 \pm 0.01	0.72 \pm 0.17	6.94 \pm 0.08	19 ⁰ 9 ¹ \pm 0.10
FM 9	200.5 \pm 1.6	0.80 \pm 0.01	0.90 \pm 0.11	11.11 \pm 0.02	21 ⁰ 4 ¹ \pm 0.01
FM 10	120.9 \pm 2.4	0.47 \pm 0.03	0.59 \pm 0.32	20.33 \pm 0.01	17 ⁰ 1 ¹ \pm 0.25
FM 11	113.2 \pm 3.5	0.43 \pm 0.02	0.52 \pm 0.22	17.30 \pm 0.03	16 ⁰ 5 ¹ \pm 0.36
FM 12	100.9 \pm 2.9	0.37 \pm 0.01	0.45 \pm 0.30	17.77 \pm 0.05	16 ⁰ 1 ¹ \pm 0.40

Particle size

The particle size decreased from 223.2 to 97.1 μ m with increase in speed from 800 to 1400 rpm at 1 % EC conc. And increases the particle size from 130.5 to 240.6 μ m with increases the EC conc 1 to

4%, decreases the particle size from 120.9 to 100.9 μ m increase in the HPMC conc 2 to 4%, increases the particle size from 174.4 to 200.5 μ m increases the temperature 45⁰, 60⁰.

Table 3: Evaluation parameters

Batch Code	Entrapment	Percentage Yield	%Floating	% Cumulative
	Efficacy (% w/w)	(% w/w)	Capacity	Drug Release
FM 1	61.3 \pm 2.0	80.0	77.4 \pm 2.5	78.7 \pm 1.2
FM 2	63.5 \pm 0.9	72.0	85.3 \pm 1.0	69.7 \pm 1.0
FM 3	82.7 \pm 1.0	69.0	90.3 \pm 2.3	57.5 \pm 0.9
FM 4	85.2 \pm 1.2	61.0	94.0 \pm 1.0	49.6 \pm 2.0
FM 5	81.6 \pm 3.0	80.0	95.3 \pm 1.0	85.8 \pm 1.5
FM 6	89.2 \pm 1.2	82.0	70.1 \pm 1.6	79.5 \pm 1.2
FM 7	94.0 \pm 1.0	88.6	63.3 \pm 1.6	65.5 \pm 2.0
FM 8	62.8 \pm 1.2	45.6	67.5 \pm 1.0	67.5 \pm 2.0
FM 9	54.5 \pm 1.1	37.6	73.2 \pm 1.0	60.4 \pm 0.7
FM 10	89.3 \pm 0.8	73.5	83.5 \pm 1.9	81.8 \pm 1.2
FM 11	85.3 \pm 0.8	65.8	72.1 \pm 0.8	88.2 \pm 2.2
FM 12	81.4 \pm 1.0	59.4	65.6 \pm 0.8	95.4 \pm 0.7

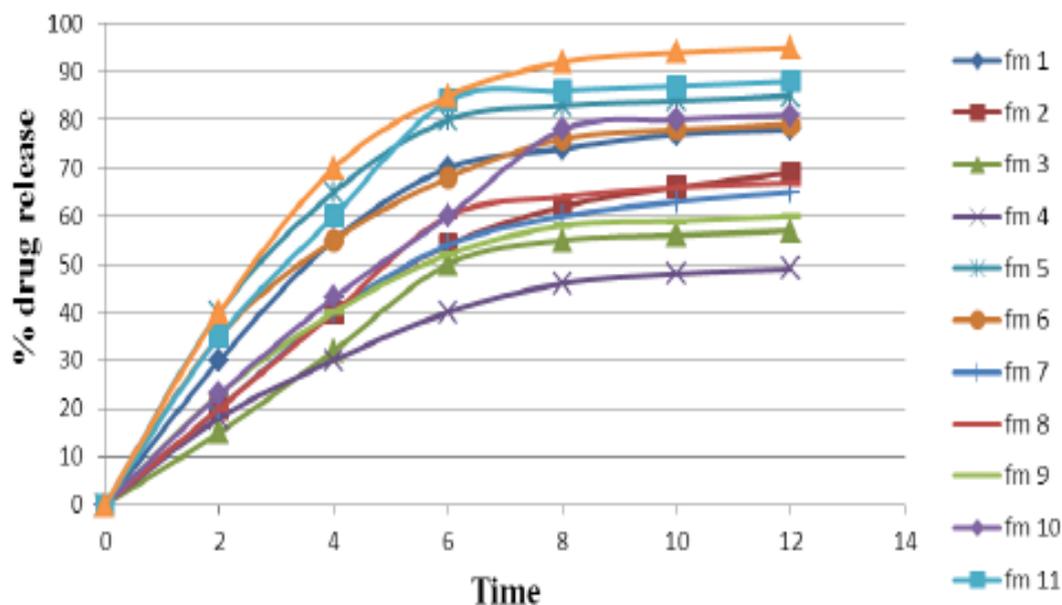


Fig.1: Drug release profile of atenolol tartrate floating microspheres

% Entrapment Efficiency: Formulations showed good % entrapment efficiency with maximum up to 94% as shown in Table 12. The % entrapment efficiency increase from 61 to 85 % for 1 to 4 % EC conc. Increases the % entrapment efficiency from 81 to 94 % with increase in speed from 800 to 1400 rpm., decreases the entrapment efficacy with increasing temperature and HPMC concentration is shown in Table 3.

% Yield of Microspheres: The % yield increased from 61% to 80 % with increase EC conc. Decreases the % yield with increasing HPMC concentration and speed and temperature is shown in Table 3.

% Floating capacity: The purpose of preparing floating microspheres was to extend the GRT of the drug. The microspheres containing EC showed good floating ability for more than 10 hrs due to insolubility of EC polymer in SGF (pH 1.2). With increase in speed as the particle size decreases the % floating capacity also decreases, which indicates that larger the particle size, the longer the floating time shown in Table 3.

% Cumulative drug release: At different EC concentration, when RPM was increased, the drug release after 12 hours from microsphere is increased for each levels of EC concentration. It can also be seen that for different EC concentration the % drug release decreased (78.7 for FM1, 49.6% for FM4). As the RPM increased the particle size increased which leads to decrease in drug release

because release of drug from smaller particle is faster than larger particle as the area available is more for drug release.

CONCLUSION:

Atenolol Tartarate Floating Microspheres was successfully prepared by solvent diffusion method using ethyl cellulose and HPMC in different ratios and with different stirring speeds and different temperatures. The concentration of Ethyl cellulose (EC) had significant impact on drug entrapment efficiency and particle size. HPMC was selected in combination with ethyl cellulose to increase the drug release from microspheres but at the same time drug entrapment efficiency and yield of microsphere decreases with increase in concentration of HPMC. Evaluation of 12 formulations, formulation 5 (EC: 1%, HPMC: 1% and stirring speed: 800rpm) fulfilled maximum requisites because of better drug entrapment efficiency, sustained release of the drug and optimum particle size.

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