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Research Article

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF PRAZOSIN HYDROCHLORIDE AS A GASTRO RETENTIVE DOSAGE FORM

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ABSTRACT

Prazosin is an antihypertensive drug classifiedas an adrenergic receptor antagonist, alphablocker. It's short half-life and increased dosing frequency suggest the needfor a controlled delivery of Prazosin hydrochloride for better patient compliance.Floating drug delivery system can provide sufficient gastric retention which may help to providesustained release dosage form with enhanced absorption. Different formulation of Prazosin hydrochloride floating microspheres were successfully developed using emulsion solvent diffusion method. The microspheres had good yield and showed high, drugentrapment efficiency. The flow properties of microspheres were within the acceptable range and therefore would be easily filled into capsules. Release properties were satisfactory and the formulations hold promise for further development into drug delivery systems for oral administration of Prazosin hydrochloride.

Keywords: Prazosin hydrochloride, microspheres, HPMC,in-vitro release, stability studies, floating drug delivery system.

INTRODUCTION

The oral route is commonly used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance[1].

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems.Gastro retentive floating drug delivery systems have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time[2]. Whenever the system is floating on gastric contents, the drug is released slowly at a desired rate from the system. It is also suitable for local drug delivery to the stomach and proximal small intestines[3].

These microspheres having a size less than 200 µm, free flowing powders and remain buoyant over gastric contents and for prolonged periods.The drug is released slowly from the floating system at the desired rate, resulting increased gastric retention and reduced fluctuations in plasma drug concentration[4].

Prazosin Hydrochloride is an α-adrenergic blocking agent used to treat hypertension and benign prostatic hyperplasiapheochromocytoma, Raynaud's syndrome, prostatic hypertrophy, and urinary retention[5]. Accordingly, Prazosin Hydrochloride is a selective inhibitor of the α-1 subtype of alpha adrenergic receptors. In the human prostate, Prazosin Hydrochloride antagonizes phenylephrine (α-1 agonist)-inducedcontractions, in vitro, and binds with high affinity to the α-1c adrenoceptor, which is thought to be the predominant functional type in the prostate[6].

The objective of this study is to develop a simple uncomplicated and easy to manufacture floating

microspheres thatis capable of delivering Prazosin Hydrochloride at a prolong release rate of delivery[7].

a. It has short half life (4-5 hrs).

b. It has low bioavailability(40-60%)[8].

c. The frequent dosing, which results in unacceptable patient compliance.

d. It produces side effects such as postural hypotension[9].

Thus, its short half-life and increased dosing frequency suggest the needfor a controlled delivery of Prazosin Hydrochloride for better patient compliance.

MATERIALS AND METHODS

Prazosin hydrochloride was received as gift sample from Sun Pharmaceuticals, Gujarat, HPMC K100 (Cipla, Mumbai), Methyl cellulose (Asia private ltd.Goa), Chitosan (Central Institute of Fisheries, Cochin). All other chemicals were of analytical grade.

Development of floating microspheres of Prazosin hydrochloride by emulsion solvent diffusion method:

The floating microspheres were prepared by emulsion solvent diffusion method[10]. Briefly the drug and polymer ratio are used as shown in table-1 were mixed in ethanol by using blending solvent dichloromethane and heavy liquid paraffin. The slurry was introduced into 250 ml beaker containing 0.2% Span 80 while being stirred at 750 rpm by mechanical stirrer for 1hr at room temperature. The floating microspheres were collected by decantation while the non-floating microspheres were discarded along with polymer residues and washed thrice with n-hexane. The collected microspheres were dried overnight in an oven at 40 ± 2^{0}C and stored in a desiccators containing calcium chloride as a desiccant. Ethanol is a good solvent for the polymers and the drug. The polymers precipitate as the solvents evaporate during the formulation process to form porous microspheres.

Evaluation parameters of floating microspheres of Prazosin hydrochloride

Yield of microspheres: The prepared microspheres with a size range of 251 µm 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[11].

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of Product}} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Measurement of particle size: The particle size was measured by microscopic technique. In this method suspension of floating microspheres was prepared using castor oil. A drop of suspension was mounted on a slide and observed under optical microscope about 600 particles were measured with the help of the eye piece micrometer. The microspheres were uniformly spread on a slide. The particle size of the microspheres was measured, along the longest axis and the shortest axis (cross shaped measurement). Average of these three readings was given as mean diameter of particles. The particle size was calculated by multiplying the number of division of the ocular disc occupied by the particle with calibration factor. All the microspheres in a field were counted[12].

Determination of sphericity of the microspheres: To determine the sphericity, the tracings of prepared microspheres (45 magnifications) were taken on a black paper using camera lucida[13].

Circulatory factor (S) was calculated using,

$$S = \frac{P^2}{12.56 \times A} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where A is area (cm2) and, P is the perimeter of the circular tracing

Measurement of bulk density: Bulk density is determined by pouring pre-sieved microspheres into a graduated cylinder via a large funnel and measure the volume and weight. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres[14].

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Measurement of tapped density: In this method floating microspheres were transferred to a measuring cylinder and tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres[15].

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}} \quad \ldots\ldots\ldots\ldots (4)$$

Determination of Carr's (compressibility) index[16]

This parameter was calculated from bulk density (the ratio of weighed quantity of microspheres to its volume), DP, and tapped density as follows

$$\text{Compressibility index} = \frac{(DT - DP)}{DTx100} \quad \ldots\ldots\ldots (5)$$

Determination of Hausner's ratio[17]

Hausner's ratio of microspheres was determined by comparing tapped density to bulk density using the equation[14].

$$\text{Hausner,s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots\ldots\ldots (6)$$

Values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr).

Measurement of angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation[18].

$$\theta = tan^{-1}\frac{h}{r} \quad \ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Where, θ - angle of repose, h - height of granules above the flat surface, r - radius of the circle formed by the granule heap.

Determination of drug entrapment efficiency

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was madeup using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank[19].

The amount of drug entrapped in the microspheres was calculated by the following formula:

$$DEE = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} X100 \quad \ldots\ldots\ldots (8)$$

Assessment of in-vitro buoyancy

Microspheres (200mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres[20].

$$\text{Buoyancy}(\%) = \frac{WF}{WF + WS} X100 \quad \ldots\ldots\ldots\ldots\ldots (9)$$

Where WF and WS are the weight of floating and settled microspheres respectively

In-vitro drug release studies

A USP basket apparatus has been used to study in-vitro drug release from microspheres. In the present study drug release was studied for 10 hrs using a modified USP XXIV dissolution apparatus type I (basket) at 100 rpm in distilled water and 0.1 mol L-1 HCL (pH 1.2) as dissolution fluids (900ml) maintained at 37±1^{0}C. Samples were withdrawn at periodical intervals and analyzed spectrophotometrically at 247 nm. The volume was replenished with the same amount of fresh medium to maintain the sink condition. All experiments were performed in triplicate. Cumulative percentage drug release was calculated using an equation obtained from a standard curve[21].

Stability study

Stability studies carried out by storing the prepared microspheres at various temperature conditions like refrigeration on (2-8^{0}C) room temperature (25±0.5^{0}C) and elevated temperature (45±0.5^{0}C) for a period of 12 weeks. Drug content and variation in the average vesicle diameter were periodically monitored. ICH (International Conference on Harmonisation) guidelines suggests stability studies for dry niosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity[22].

RESULTS AND DISCUSSION

Different floating microspheres formulations of Prazosin hydrochloride were prepared by using different polymers i.e. HPMC, chitosan, PVP K30, in different ratio by emulsion solvent diffusion method.

Table 1: Composition of floating microspheres formulations of Prazosin hydrochloride

Batch code	Eudragit S100 (mg)	HPMC K4M(mg)	Chitosan (mg)	EC (mg)	Span 80 (mg)	Di-chloromethane :Ethanol ::1:1	Heavy Liquid Paraffin (ml)
MS1	100	200	-	-	3	-	50
MS2	-	-	200	-	3	-	50
MS3	300	-	-	200	-	10	-
MS4	400	200	200	200	-	10	-

Prazosin hydrochloride incorporated in each batch = 200 mg

Table 2: Characterization of floating microspheres formulations of Prazosin

Batch Code	Particle Size (µm)	Bulk Density(g/cm3)	Tapped Density (g/cm3)	Hausner,s ratio	Carr's Index
MS1	238.51±0.34	0.140±0.12	0.212±0.05	1.451±0.012	31.09±0.032
MS2	237.23±0.24	0.137±0.24	0.212±0.08	1.525±0.013	32.80±0.041
MS3	226.12±0.34	0.152±0.16	0.193±0.15	1.253±0.013	28.21±0.043
MS4	230.37±0.17	0.143±0.17	0.190±0.09	1.331±0.016	22.38±0.022

Table 3: Characterization of floating microspheres formulations of Prazosin hydrochloride (Mean±S.D, N=3)

Batch Code	Sphericity	Yield (%)	Entrapment Efficiency (%)	Angle of Repose	% Buoyancy
MS1	1.01±0.03	60.34±0.061	74.52±0.014	14.67±0.054	68.23±0.081
MS2	1.03±0.05	66.41±0.085	78.64±0.021	13.89±0.102	71.46±0.032
MS3	1.12±0.1	65.46±0.102	80.37±0.018	12.32±0.062	70.84±0.125
MS4	1.08±0.09	90.23±0.043	86.37±0.019	13.78±0.101	96.21±0.063

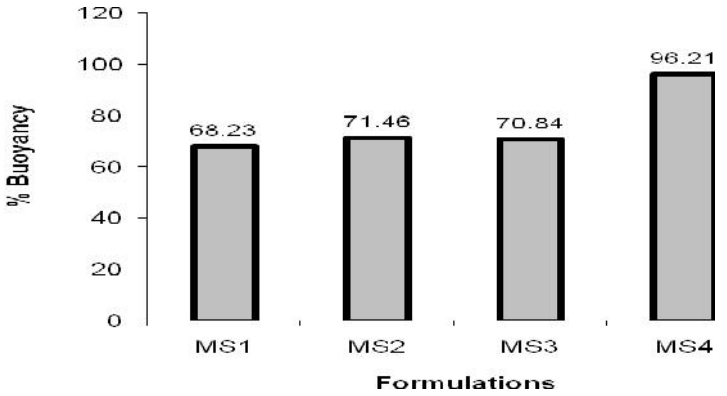

Figure 1: Comparison of % buoyancy of different floating microspheres formulations of Prazosin hydrochloride

The mean particle diameter of the microspheres was between 226.12-238.51 µm. As the polymer concentration increases, the particle size also increases. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency. The densities of floating microspheres were found to be less than the density of gastric fluid (1.004 g/cm3), therefore tended to float over gastric fluid.

The sphericity factor obtained for the microspheres lies in the range of 1.01-1.08. The sphericity value nearer to 1 indicates that the prepared formulations were spherical in nature. The flow properties of all the formulations were found out by measuring the angle of repose and compressibility index. A higher Hausner ratio indicates greater cohesion between particles while a high Carr index is indicative of the tendency to form bridges. The values of angle of repose are within the normal acceptable range of 20 to 40. The porous microspheres thus showed reasonably good flow potential, indicating good flow characteristics of the microspheres. This also implies that the microspheres are non-aggregated.

High incorporation efficiencies are seen with lower concentrations of polymer with the drug. The percentage entrapment efficiency of the microspheres was between 74.52-86.37%. Such data may be due to low solubility of Prazosin hydrochloride in water which facilitates the diffusion of a part of entrapped drug to surrounding medium during preparation of floating microspheres. The percentage yield of the microspheres was between 60.34-90.23%.

The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The floating ability test was carried out to investigate the floatability of the prepared microspheres. The mean percentage buoyancy of the microspheres was between 68.23-96.21%. In-vitro buoyancy studies reveal that in spite of stirring the dissolution medium for more than 12 hrs formulations were still continued to float without any apparent gelation, thus indicating that microspheres exhibit excellent buoyancies which can be attributed to the pores and cavities present in them. In general with increase in the amount of polymers there is an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present. The good buoyancy behaviour of the microspheres may be attributed to the hollow nature of the microspheres.

The cumulative percent drug release after 24 hrs of the Prazosin hydrochloride microspheres was 51.4 to 85.114%. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used. The increased density of the polymer matrix at higher concentrations results in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

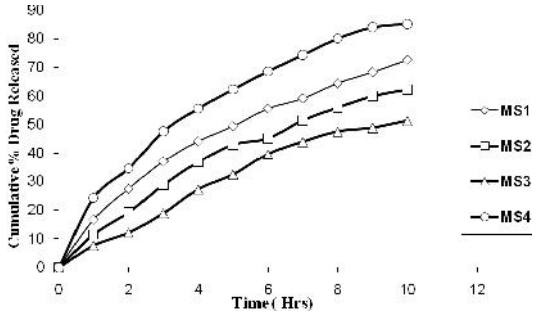

Figure 2: Percentage of drug released from Prazosin hydrochloride floating microspheres of batch MS1 to MS4

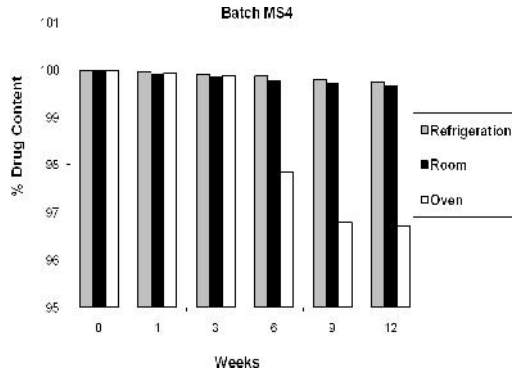

Figure 3: Stability study of Prazosin hydrochloride floating microspheresof batch MS4 at different temperature

Accelerated stability studies for 12 weeks revealed that the floating microspheres formulations were stable at up to 450C. The results showed that floating microspheres formulation was quite stable at refrigeration and room temperatures as not much leakage of drug was found at these temperatures. Therefore, the selected floating microspheres formulations can be stored at either refrigeration or room temperature. The pure drug shows sensitivity to light and moisture.

Statistical analysis

To ascertain drug release mechanism and release rate, the release data were model fitted using PCP Disso V3.0 dissolution software. Experimental results were expressed as mean±SD. Student's t-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p < 0.05$.

CONCLUSION

The present study has been a satisfactory attempt to formulate Prazosin hydrochloride floating microspheres formulations with a view of improving its oral bioavailability and giving a prolonged release of drug. The microspheres had good yield and showed high, drug entrapment efficiency. The flow properties of microspheres were within the acceptable range and therefore would be easily filled into capsules. Release properties were satisfactory and the formulations hold promise for further development into drug delivery systems for oral administration of Prazosin hydrochloride.

Stability studies carried out by storing the prepared floating microspheres of selected batches at various temperature conditions like refrigeration on (2-8^{0}C) room temperature (25±0.5^{0}C) and elevated temperature (45±0.5^{0}C) for a period of 12 weeks. Accelerated stability studies for 12 weeks revealed that the floating microspheres formulations were stable at up to 45^{0}C.

In vitro drug release studies showed that the drug release was more in case of formulations MS4. Prazosin hydrochloride floating microspheres formulations of batch MS4 was concluded as the optimum formulations among the all 12 formulations based on different parameters like, flow properties, buoyancy in-vitro release and stability studies.

However there is need in-vivo study to justify the development of floating microspheres of Prazosin hydrochloride.

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