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DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING BEADS OF SIMVASTATIN

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ABSTRACT

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. Simvastatin is a Hypolipidemic used to control elevated cholesterol or hypercholesterolemia. The primary uses of Simvastatin are for the treatment of dyslipidemia and the prevention of cardiovascular disease. Percentage yield of different formulation was determined by weighing the Floating beads after drying. The percentage yield of different formulation was in range of 63.4±0.3–76.1±0.4%. The maximum percentage yield was found in formulation F3, 76.1±0.4 as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 64.85±0.25 - 75.45±0.47% w/w. The maximum drug entrapment was found in formulation F-3 (75.45±0.47). The results of measurement of mean particle size of optimized formulation F3 of floating beads was found to be 322.2 nm. Results of zeta potential of optimized formulation F3 of floating beads was found -23.4 mV. From the experimental study result, it was concluded that optimized batch F3 showed good entrapment efficiency and releases drug slowly and completely for 12 hours as beads remain in floating condition throughout dissolution study that assures prepared formulation remain floated in stomach without its early passing to lower GIT side. This will help to increase the residence time of Simvastatin in stomach i.e. in absorption window and achieve sustained release thereby increase the bioavailability of it.

KEYWORDS: Simvastatin, Gastroretentive, Floating beads, Sustain release.

INTRODUCTION

Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach

without affecting the gastric emptying rate for a prolonged period of time (Yie and Chein, 1992). This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

Micro beads are small, solid and free flowing particulate carriers, on which the drug is coated or encapsulated in the core of beads. Beads can provide controlled/ sustained release properties (Kumar *et al.,* 2017). Furthermore, bioavailability of drugs also has been enhanced. Gastro retentive beads is not just to sustain the drug release, but also to enhances gastric residence of the dosage forms until all the drug is completely released at the desired period. The multi particulate dosage forms have many advantages compared to single unit preparations, such as: Greater flexibility, Dose dumping and incomplete drug release is avoided, Reduction in inter-and intra-subject variability in drug absorption, Increased bioavailability, Increased flow property. Simvastatin, a newer antihyperlipidemic agent, belongs BCS class-II agent. It is a specific inhibitor of HMG CoA. It is a prodrug and is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. It is practically insoluble in water and other aqueous media. The very poor aqueous solubility and wettability of simvastatin give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability. Thus, there is a need to increase rate of dissolution. Hence, the study was carried out to formulate and evaluate sustained floating beads of Simvastatin as a model drug and had an aim those final batch formulation parameters should shows prolong drug release.

MATERIAL AND METHODS

Material

Simvastatin was received as gift sample from pharmaceutical company. Hydroxypropyl methylcellulose (HPMC) was procured from Meditab Specialities Pvt. Ltd., Satara. Ethyl cellulose was purchased from S.D fine chemicals, Mumbai. PVP, $CaCl_2$ and $CaCo_3$ were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Methods

Development of floating beads of simvastatin by ionotropic gelation method

Development of floating beads of Simvastatin by ionotropic gelation method. The beads of simvastatin were prepared by ionotropic gelation technique according to the formula given in

Table 1. Accurately weighed drug was added to 100ml of Distilled Water and stirred on magnetic stirrer. Polymer, $CaCO_3$ and sodium alginate were then added to the solution and stir continuously till uniform polyelectrolyte solution was formed also known as pre alginate solution. Calcium chloride was separately dissolved in 100 ml water and stirred on magnetic stirrer. Pre- alginate solution of drug and polymer was added drop by drop to the $CaCl_2$ solution with the help of 21 G needle. The formed alginate beads were cured at different time interval. The alginate beads were there after dried overnight at room temperature (Zhang et al., 2018).

Table 1: Formulation design of floating beads of Simvastatin.

Formulation Code	Drug (mg)	Sodium alginate (%)	HPMC (mg)	Ethyl cellulose (mg)	PVP (mg)	$CaCl_2$ (%)	$CaCo_3$ (%)
F1	40	2	100	50	10	3	1.5
F2	40	3	-	50	10	3	1.5
F3	40	4	-	50	10	3	1.5
F4	40	2	100	50	10	3	1.5
F5	40	3	-	50	10	3	1.5
F6	40	4	-	50	10	3	1.5

Evaluation tests for floating beads

Determination of Percentage yield

The prepared beads 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 beads (Setia et al., 2018).

Drug Entrapment Efficiency

Beads equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by rushing the beads and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured at suitable wavelength against appropriate blank (Kajale et al., 2016). The amount of drug entrapped in the beads was calculated by the following formula.

$$\textbf{\textit{Drug entrapment Efficiency}} = \frac{Amount\ of\ drug\ actually\ present}{Theoretically\ dug\ loaded\ expected}$$

Measurement of mean particle size

The mean size of the floating beads was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement (Chandrashekar et al., 2015).

Determination of zeta potential

The zeta potential of the drug-loaded floating beads was measured on a zeta sizer (Horiba Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Thakur et al., 2013).

***In vitro* buoyancy study**

Beads (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hr. The floating and the settled portions of beads were recovered separately. The beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the beads that remained floating and the total mass of the beads (Rasel et al., 2012).

$$\% \text{ Buoyancy} = \frac{Qfx}{(Qf+Qs}$$

SEM of floating beads

Morphological characterization of the floating beads is done by taking scanning electron micrograph (Model Jeol JSM-5200). Cross-sectional views are obtained by cutting the bead with a razor blade. The samples were coated to 200 Aº thickness with gold- palladium prior to microscopy. A working distance of 20 nm, a tilt of 0º and accelerating voltage of 15 KV were the operating parameters. Photographs were taken within the range of 50- 500 magnifications (Saxena et al., 2016).

***In-vitro* drug release study**

The drug release study from beads is performed using USP dissolution apparatus Type I in 900 ml of 0.1 N HCl dissolution media (pH- 1.2) at 100 rpm and 37°C. 2 ml sample was withdrawn at 1 hr. time interval for 12 hr. and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at

suitable wavelength. The drug release was analyzed by UV spectrophotometer (Singh et al., 2011).

RESULTS AND DISCUSSION

Gastroretentive dosage forms have the potential to improve local therapy with an increase of short gastric residence time and unpredictable gastric emptying time and decrease the variation in bioavailability which is unobserved, in other commercially available preparations. The objective of present work was to develop gastroretentive floating beads formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. Percentage yield of different formulation was determined by weighing the Floating beads after drying. The percentage yield of different formulation was in range of 63.4±0.3–76.1±0.4%. The maximum percentage yield was found in formulation F3, 76.1±0.4 as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 64.85±0.25 - 75.45±0.47% w/w. Results demonstrated that increase in concentration of polymer increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulations. The maximum drug entrapment was found in formulation F-3 (75.45±0.47). The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating beads, The optimized formulation of both batches subjected to further studies. The results of measurement of mean particle size of optimized formulation F3 of floating beads was found to be 322.2 nm. Results of zeta potential of optimized formulation F3 of floating beads was found -23.4 mV. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an ‘r’ value of beads was maximum zero order i.e 0.990 hence indicating drug releases from formulations was found to follow zero order for floating beads.

Table 2: Percentage yield for different formulation.

S. No.	Formulation	Percentage Yield
1.	F1	65.5±0.2
2.	F2	68.8±0.3
3.	F3	76.1±0.4
4.	F4	63.3±0.2
5.	F5	69.8±0.2
6.	F6	63.4±0.3

Table 3: Drug Entrapment for Different formulations.

S. No.	Formulation	Drug entrapment (% w/w) of prepared beads
1	F1	70.23±0.45
2	F2	69.98±0.35
3	F3	75.45±0.47
4	F4	65.58±0.36
5	F5	64.85±0.25
6	F6	67.74±0.41

Table 4: Percentage Buoyancy and floating lag time of floating beads.

Formulation	Floating Lag Time	Percentage Buoyancy
F1	42±3	60.2±0.3
F2	35±2	69.5±0.2
F3	20±4	74.4±0.4
F4	35±2	65.4±0.2
F5	30±3	68.7±0.3
F6	41±2	64.4±0.3

Table 5: Release Study data of formulation F1-F6.

Time	% of Drug Release						
(hr)	F1	F2	F3	F4	F5	F6	Marketed Formulation (Zosta 10 mg)
0.5	25.56	23.25	18.85	11.25	15.56	14.56	33.32
1	36.65	35.65	23.32	20.23	22.23	26.65	65.58
2	48.89	45.58	36.65	33.65	36.65	35.58	98.18
4	65.58	63.32	48.85	45.58	49.98	45.58	
6	88.98	79.98	56.65	56.65	62.25	52.25	
8	98.85	92.26	69.98	62.25	73.32	69.98	
10	98.78	98.85	85.56	75.56	79.98	73.32	
12	99.65	99.12	99.74	85.45	86.65	78.85	

Table 6: Release Kinetics of optimized formulation of beads F-3.

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative% Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	18.85	1.347	77.79	1.891
1	1	0	23.32	1.522	66.75	1.824
2	1.414	0.301	36.65	1.699	50.02	1.699
4	2	0.602	48.85	1.780	39.75	1.599
6	2.449	0.778	56.65	1.845	30.02	1.477
8	2.828	0.903	69.98	1.915	17.75	1.249
10	3.162	1	85.56	1.971	6.55	0.816
12	3.464	1.079	99.74	2.000	0.11	-0.959

Table 7: Comparative study of regression coefficient for selection of optimized Formulation F-4.

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.990	0.665	0.973	0.990

CONCLUSION

In the present study, a satisfactory attempt has been made to formulate gastroretentive floating beads of Simvastatin. From the experimental study result, it was concluded that optimized batch F3 showed good entrapment efficiency and releases drug slowly and completely for 12 hours as beads remain in floating condition throughout dissolution study that assures prepared formulation remain floated in stomach without its early passing to lower GIT side. This will help to increase the residence time of Simvastatin in stomach i.e. in absorption window and achieve sustained release thereby increase the bioavailability of it. Finally the prepared Floating beads of Simvastatin may prove to be potential gastroretentive delivery system for safe and effective controlled release for an extended period of time.

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