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FORMULATION AND EVALUATION OF SIMVASTATIN GASTRORETENTIVE DRUG DELIVERY SYSTEM USING NATURAL POLYMERS

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ABSTRACT

Gastro retentive drug delivery system is also known as novel drug delivery system. They have controlled delivery of drugs which continuously releasing the drug for a prolonged period of time. These are includes floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying device. The main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times. The objective of this work was to formulate and evaluate floating drug delivery system of simvastatin by using natural polymer to modify its pharmacokinetic profile. The various floating microsphere (FF1 – FF8) was prepared by non aqueous solvent evaporation method by using various concentrations of the natural polymer chitosan and sodium alginate. The prepared microspheres were characterized for various parameters like rheological properties, floating behavior, SEM and entrapment efficiency. Floating microspheres were successfully prepared by modified solvent evaporation technique. Microsphere showed passable flow properties. The % yield of microspheres was up to 65-81 %. Mean particle size was found to be in the range 650-1034µm. Entrapment efficiency of different formulations were in the range of 63.50-86.00%. In dissolution medium the swelling property was found in the range of 14.5-19.9%. The cumulative drug release was observed to be in the range of 34.380-66.363%. On the basis of result, it can be concluded that the microspheres produced from chitosan and sodium alginate by using non-aqueous solvent evaporation method is an excellent delivery system that has good release behavior for actively releasing drug in the stomach due to its gastro-retentive (floating) ability and therefore, this system would provide a safe and effective strategy for treatment of ulcers of the stomach or other diseases of the gut.

KEYWORDS: Gastro retentive drug delivery system (GRRDS), Simvastatin, Polymers, Floating microspheres, Drug release.

INTRODUCTION

Among the different routes of drug administration, the oral route has achieved the most attention, partly due to the simplicity of administration and to the important flexibility in dosage form design. Unfortunately, in most cases, the important variability of the gastrointestinal tract physiology and of its transit time leads to unpredictable bioavailability and non reproducible therapeutic effects [1]. One essential for the successful performance of oral controlled release drug delivery systems is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion [2]. Floating microspheres are gastro retentive drug delivery systems based on a

non-effervescent approach. Hollow microspheres, micro balloons or floating micro particles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. These are free-flowing particles, with size ranging from 1 to 1000 μm. Floating microspheres are prepared by using an emulsion solvent evaporation method. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one [3]. This property results in delayed transit through the stomach. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. The objective of the present work is to formulate the simvastatin gastro retentive drug delivery system using natural polymer i.e. chitosan and sodium alginate to modify its pharmacokinetic profile [4]. Treatment of disease requires maintenance of uniform concentration of drug in blood for a long period of time. Floating microspheres were envisaged as the most promising drug delivery system owing to their slow dissolution in gastric fluid thereby rendering the capability to prolong the release of drug at the site of absorption [5].

MATERIALS AND METHODS

Material

Simvastatin was obtained as gift sample from Aristo Pharmaceuticals Limited, Mandideep, Bhopal (MP), India and was confirmed by IR spectroscopy. Acetone, liquid paraffin, chitosan and sodium alginate were procured form Thomas Baker, Himedia and S. D. Fine Chemicals limited, Mumbai, Maharashtra, India. All other chemicals and reagents used were of analytical grade.

Methods

Experimental Methods

Preparation of floating microspheres

Simvastatin floating microsphere was prepared by the reported method i.e. non aqueous solvent evaporation method with slight modification. Different batches of floating microspheres of simvastatin were prepared using two different polymers (Table1& Table 2). The drug and different polymers were mixed in acetone at various ratios and the slurry was obtained which slowly introduced into 30 ml of liquid paraffin while being stirred at 1200 rpm using a mechanical stirrer equipped with a three blade propeller. The solution was stirred for 2 hours and the solvent was allowed to evaporate completely and the microspheres were collected by filtration. The microspheres obtained were washed repeatedly with petroleum ether until free from oil. The collected microspheres were dried for 1 hour at room temperature and subsequently stored in desiccators over fused calcium chloride [6].

Table 1 Composition of different batches of microspheres using chitosan

S.No.	Ingredient	Batch Code			
		FF1	FF2	FF3	FF4
1	Simvastatin (mg)	100	100	100	100
2	Chitosan (mg)	100	200	300	400
3	Acetone (ml)	20	20	25	25

Table 2 Composition of different batches of microspheres using sodium alginate

S.No.	Ingredient	Batch Code			
		FF5	FF6	FF7	FF8
1	Simvastatin (mg)	100	100	100	100
2	Sodium Alginate (mg)	100	200	300	400
3	Acetone (ml)	20	20	25	25

Characterization of Formulations

Rheological Properties

The prepared microspheres were characterized for their rheological properties such as angle of repose, carr's Index, bulk density, tapped density and hausner's ratio to assess the flow property of the prepared microspheres [7].

Angle of repose

Angle of repose was determined by using funnel method. Accurately weighed amount of microspheres were taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the pile. The microspheres were allowed to flow through the funnel freely on to the surface. The diameter of powder cone was measured and the angle of repose was calculated using the following formula:

$\text{Tan } \theta = h/r$

Where, h is the height of the pile; θ is the angle of repose; and r is the radius of the heap [8].

Bulk Density

The apparent bulk density (ρ_b) was determined by accurately weighing 10 g of the microspheres and transferring it to a 100 mL graduated cylinder. The volume occupied by the microspheres was determined and the bulk density was calculated using the formula.

$\rho_b = M/V_b$

Where, ρ_b is the bulk density; M is the mass of the microspheres and V_b is the volume occupied by the microspheres [9].

Tapped Density

The measuring cylinder containing a known mass (M) of the microspheres was tapped for a fixed time and the volume occupied by the blend after tapping was measured. The tapped density ρ_t was calculated using the formula [10].

$\rho_t = M/V_t$

Hausner's Ratio

Hausner's ratio was calculated from the bulk and tapped density using the formula [11]

Hausner's Ratio = Tapped density/ Bulk density

Percent compressibility (Carr's Index)

The consolidation index (Carr's compressibility index) was determined by comparing the bulk density and the tapped density of the powder. Carr's compressibility index is calculated using the formula:

Carr's Index = Tapped density-Bulk density / Tapped density ×100

In Carr's Index, the value below 15% indicates good flow properties whereas a value above 25% indicates poor flow characteristics [12].

Determination of Yield

The dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formulae given below [13].

% Yield = Mass of the dried microspheres obtained/ Total weight of drug and polymer × 100

Determination of particle size of microspheres

Particle size of the microspheres was determined by using a Malvern particle size analyzer [14].

Determination of drug entrapment in the microspheres

The various formulations of the floating microspheres were subjected to drug content analysis. 50 mg of the microspheres were accurately weighed and crushed. The powdered microspheres were dissolved in 10 ml ethanol, in a 100 ml volumetric flask and the volume was made up to the mark with 0.1M HCl. The solution was filtered through whatman filter paper No. 44. After filtration 10 ml of this solution was pipette out and diluted up to 100 ml with 0.1M HCl. 2 ml of this solution was then diluted up to 10 ml with 0.1M HCl and the absorbance was measured at 238 nm against 0.1M HCl as blank. The percentage drug entrapment was calculated as follows [15].

$$\% \text{ Drug Entrapment} = \frac{\text{Calculated Drug Concentration}}{\text{Theoretical Drug Concentration}} * 100$$

Measurement of Floating Capacity

An *in vitro* floating study was carried out using 0.1M HCl as the dispersion medium. Microspheres were spread over the surface of 400 ml of the dispersing medium at 37±0.5°C. A paddle rotating at 100 rpm was used to agitate the dispersion medium. Each fraction of the microspheres floating on the surface and those settled down were collected at a predetermined time. The collected samples were weighed after complete drying [16].

% of floating microspheres = Weight of floating microspheres / Initial weight of the microspheres× 100

Determination of swelling properties

The dynamic swelling property of microspheres in the dissolution medium was determined by placing a known weight of microspheres in the dissolution solution for 3 hours and collecting the swollen particles by centrifugation. The particles were blotted on filter paper to remove the absorbed water and then weighing immediately on electronic balance. The percentage swelling of microspheres was calculated using the following formula.

$S_w = (W_t - W_o) / W_o \times 100$

Where S_w is the swelling index; W_t is the wet weight; and W_o is the dry weight of microspheres [17].

In vitro release study

USP type II dissolution apparatus (paddle type) was performed at 50 rpm in 900 ml 0.1M HCl. 5 ml of the sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding equal volume of fresh dissolution medium. The absorption of the withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve. The temperature was maintained at 37°C throughout the study [18].

RESULTS AND DISCUSSION

The apparent bulk density of the formulations was measured with help of measuring cylinder. The bulk density value ranged from 0.350 to 0.571 g/cm^3. The tapped density was determined using tapping method. The tapped density value of various formulations of the microspheres was found to be in the range from 0.390 to 0.666 g/cm^3. The density value of the microspheres was less than the density of gastric fluid (1.004 g/cm^3) thereby the microspheres possessed the ability to be buoyant in the stomach. Angle of repose of microspheres was determined by fixed funnel method. The angle of repose was found to be in the range of 21.32 to 29.72. All the formulations exhibited excellent flow properties as represented by the angle of repose (<40°) (Table 3)

Table 3 Bulk, tapped density and angle of repose of the microspheres

Batch Code	Bulk Density	Tapped Density	Angle of repose (°)
FF1	0.444	0.487	24.33
FF2	0.408	0.465	21.32
FF3	0.416	0.487	27.54
FF4	0.350	0.390	24.32
FF5	0.571	0.666	27.86
FF6	0.500	0.571	29.72
FF7	0.444	0.487	21.60
FF8	0.400	0.425	23.02

It is one of the methods for determining the flow properties of powders. It is also called as the Carr's Index of compressibility. It is determined using the bulk and tapped density data. The formulations prepared in the present work were found to have the Carr's Index between 5.58 to 14.57 % (Table 4). The percentage compressibility value less than 20 for all the formulations suggested excellent flow properties. The Hausner's ratio of various formulations was found to be ranging from 1.062 to 1.170 %.

Table 4 Carr's Index and Hausner's ratio of various formulations

Batch Code	Carr's Index	Hausner's ratio
FF1	8.82	1.096
FF2	12.25	1.139
FF3	14.57	1.170
FF4	10.25	1.114
FF5	14.26	1.166
FF6	12.43	1.142
FF7	8.82	1.096
FF8	5.58	1.062

The various formulations of the prepared microspheres were evaluated for the percentage process yield. The percentage yield varied from 65-81%. The particle size of various formulations was determined by particle size analyzer and reported as number, intensity and volume. If the size of microspheres is less than 500 μm, the release rate of drug will be high and the floating ability will reduce whereas in the microspheres ranging from 500-1000 μm, the floating ability will be more and the drug release rate will be in a sustained manner. The mean particle size of the hollow microspheres was found to be in the range 650-1034μm (Table 5)

Table 5 Particle size of various formulations

Batch Code	Particle Size (μm)
FF1	650
FF2	782
FF3	856
FF4	1034
FF5	710
FF6	854
FF7	752
FF8	852

The drug entrapment of various formulations of simvastatin was carried out as per the procedure and performed in triplicate. The drug entrapment efficiencies of different formulations were in the range of 63.50 to 86.00% (Table 6). Drug entrapment slightly decreases with increase in chitosan and increases with an increase in alginate concentration. This may be due to the permeation characteristics of chitosan and alginate.

Table 6 Drug entrapment efficiency of various formulations

Batch Code	Drug entrapment (%)
FF1	73.36
FF2	72.50
FF3	64.26
FF4	63.50
FF5	76.00
FF6	77.20
FF7	86.00
FF8	81.00

Hollow microspheres were dispersed in 0.1M HCl containing Tween 20 (0.02% w/v). The floating ability of different formulations was found to differ according to the ratio of the polymer used. Both sodium alginate and chitosan exhibited good floating capacities (Table 7).

Table 7 Floating capacity of prepared formulations

Batch Code	% Floating Capacity	Floating duration
FF1	83	12
FF2	81	14
FF3	76	8
FF4	72	16
FF5	74	15
FF6	77	19
FF7	78	10
FF8	75	18

The dynamic swelling property of the microcapsules in the dissolution medium was determined and was found to be in the range of 14.5 to 19.9 % (Table 8).

Table 8 Swelling index of various formulations

Batch Code	Initial weight (mg)	Final weight (mg)	% Swelling of microspheres
FF1	100	114.5	14.5
FF2	100	115.3	15.3
FF3	100	115.8	15.8
FF4	100	114.7	14.7
FF5	100	119.9	19.9
FF6	100	118.3	18.3
FF7	100	119.6	19.6
FF8	100	115.5	15.5

The in vitro drug release study of the microspheres was evaluated in 0.1M HCl. The % release, % cumulative release and % log cumulative release was calculated (Table 9, 10 & Fig 1).

Table 9 *In vitro* release data of FF1

S No	Time (h)	Sq root of time	log time	Abs (238 nm)	conc (µg/ml)	Conc (mg/ml) in 900 ml	% release	% cumulative release	log % cumulative release
1	0	0	0	0	0	0	0	0	0
2	1	1	0	0.127	2.594	23.347	23.347	23.349	1.368
3	2	1.414	0.301	0.234	4.78	43.016	43.016	43.021	1.634
4	3	1.732	0.477	0.298	6.087	54.782	54.782	54.788	1.739

5	4	2	0.602	0.31	6.332	56.988	56.988	56.994	1.756
6	5	2.236	0.699	0.324	6.618	59.561	59.561	59.568	1.775
7	6	2.449	0.778	0.336	6.863	61.767	61.767	61.774	1.791
8	7	2.646	0.845	0.351	7.169	64.525	64.525	64.532	1.81
9	8	2.828	0.903	0.356	7.272	65.444	65.444	65.451	1.816
10	9	3	0.954	0.359	7.333	65.995	65.995	66.003	1.82
11	10	3.162	1.00	0.361	7.374	66.363	66.363	66.37	1.822

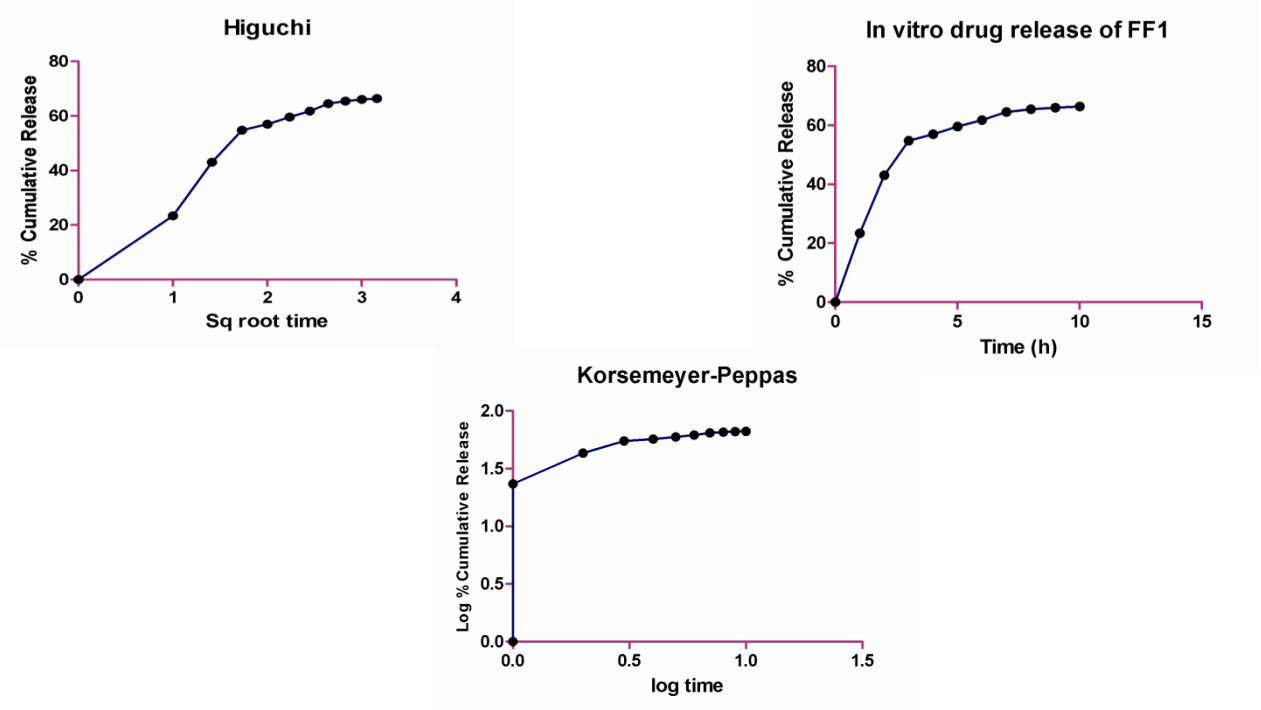

Figure 1 Release profile of FF1

Table 10 Results of correlation coefficients of release data

Batch Code	Zero Order		Higuchi Equation		Peppa's	
	Regression	Slope	Regression	Slope	Regression	Slope
FF1	0.8422	0.1313	0.9545	0.043	0.7223	0.4836
FF2	0.9823	0.1528	0.9807	0.0439	0.8958	0.5929
FF3	0.7905	0.1348	0.9308	0.046	0.6724	0.4562
FF4	0.9035	0.2319	0.9626	0.0711	0.8781	0.6374
FF5	0.8933	0.1557	0.9672	0.049	0.806	0.5558
FF6	0.8874	0.2381	0.9547	0.074	0.8758	0.6344
FF7	0.9963	0.1513	0.9455	0.041	0.9471	0.6239
FF8	0.9809	0.0435	0.9909	0.044	0.9505	0.6401

CONCLUSIONS

In the present study, gastroretentive microspheres loaded with simvastatin were prepared using non-aqueous solvent evaporation methods using chitosan and sodium alginate as the natural polymers. The results obtained showed that this methodology was able to produce reproducible microspheres and for sustained release of drug from the formulations. The microspheres were able to exhibit floating ability in simulated gastric medium. Consequently, it can be concluded that the microspheres produced from chitosan and sodium alginate using non-aqueous solvent evaporation method is an excellent delivery system that has good release behavior for actively releasing drug in the stomach due to its gastro-retentive (floating) ability and therefore, this system would provide a safe and effective strategy for treatment of ulcers of the stomach or other diseases of the gut.

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