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Development and Characterization of the Floating Beads Containing the BCS Class II Drug Lumafentrine Ternary Complex

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Abstract: Floating Drug delivery systems are designed to prolong the gastric residence time after oral administration. Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. The aim of the present study was to develop a delivery system wherein the retention lumafentrine could be achieved for increasing local action in the gastric region. Various formulations of floating beads of lumafentrine were developed using polymers like Chremophore RH 40, H-p-Beta-Cyclodextrine, sodium deoxycholate, soluplus, PVP K-30, PVP K-60, sodium taurocholate and carbapol. The beads were prepared by emulsion gelation method. The results showed that beads formulated with mixture of drug and polymer (F3) showed the highest drug release compared to other formulations. So the formulation F3 was selected for stability studies according to ICH guidelines for a period of three months.

INTRODUCTION

Oral route is the most preferable route of drug administration due to better patient compliance. However there arises a problem by oral route with the use of certain types of dosage form i.e., fluctuation in plasma drug level. By the use of controlled drug delivery system we can prolong the action of drugs in our body. Gastric emptying is a complex process in our body variable in different individuals. [1] The aim of designing oral controlled drug delivery system is to increase the bioavailability of drugs. A major problem associated with the oral controlled drug delivery system is limited gastric residence time. To improve the retention of an oral dosage form in the stomach various approaches have been developed, eg. Floating systems, swelling and expanding systems, bioadhesive system, altered density systems and other delayed gastric emptying devices. Gastro retentive dosage form prolongs the gastric residence time of drug by remaining in the gastric region for several hours. [2] Floating Beads are one of the gastro retentive dosage forms that float over gastric contents due to their buoyancy and remain in the stomach for prolonged period. Suitable drugs that can be used in gastro retentive system include. [3]

1. Drugs with narrow absorption window in the stomach.
2. Drugs locally acting in the stomach
3. Drugs which are unstable in intestinal and colonic environment

Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine. [4, 5]

In the present study, a multiple unit Floating Drug Delivery System (FDDS) of Lumafentrine was designed keeping in view of the all or nothing response of a single unit system[6]. Sodium alginate (SA) was employed to formulate the alginate beads and to sustain the release of the Lumafentrine due its ability to form a stable and bioadhesive gel with calcium ions. [6]

Hydroxy propyle beta cyclodextrine, sodium deoxycholate and chremophore RH 40 have been incorporated in polymeric matrix to enhance the sustained release properties of the alginate by providing a denser inner matrix. [7]

MATERIALS AND METHODS

Lumafentrine was supplied by the Yellow Chem Pharma Products, Mumbai. A polymer such as Chremophore RH 40, H-p-Beta-Cyclodextrine, Sodium Deoxycholate, Soluplus, PVP K-30, PVP K-60, Sodium taurocholate and Carbapol was supplied by Central Drug House, Ltd., New Delhi, India. All other chemicals used in this study were analytical grade.

Selection of Analytical Wavelengths

100 mg of each pure drug was accurately weighed and transferred to individual 100 ml volumetric flask containing 70 ml methanol and diluted to 100 ml with methanol. Further dilutions carried out to get final concentration of 100 µg/ml of lumafentrine. [8, 9] Appropriate dilutions were prepared for drug from the standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm. Lumafentrine showed absorbance maxima at 215 nm (Figure 1).

Ternary Inclusion Complex

The inclusion complex was prepared by the co-precipitation method. The equimolar quantities of Lumafentrine and respective polymer in presence and/or absence of chremophore RH 40 and sodiumdeoxycholate (1%, w/v) were dissolved in 20 ml of ethanol and 80 ml distilled water, respectively and formulate different type of

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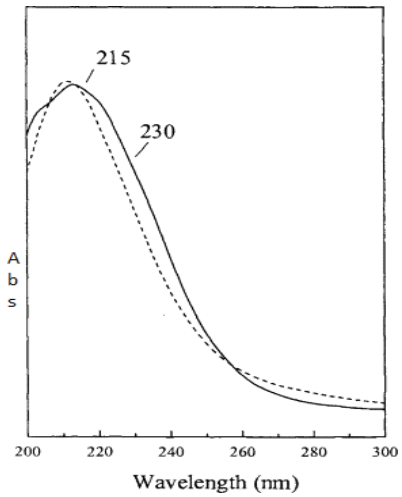

Figure 1: Standard Spectra of the drug lumafentrine

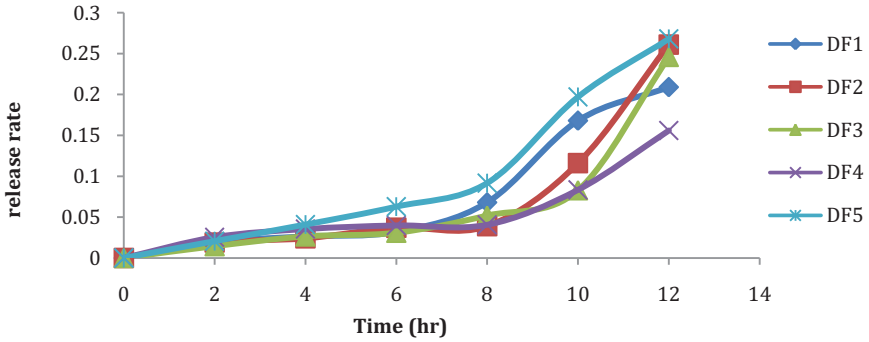

Figure 2: Solubility parameter of the different formulation (DF1 to DF5)

Table 1: Different Type of the Formulation Batch of the Lumafentrine Ternary Inclusion Complex

Ingredients	DF1	DF2	DF3	DF4	DF5
Lumafentrine	20 mg	20 mg	20 mg	20 mg	20 mg
H-P-β-cyclodextrine	100 mg	100 mg	100 mg	100 mg	100 mg
Chremophore RH 40	100 mg	100 mg	100 mg	-	-
Sodium deoxycholate	-	-	-	100 mg	100 mg
Soluplus	10 mg	15 mg	20 mg	10 mg	20 mg
PVP K-30	20	-	-	20 mg	-
PVP K-60	-	20 mg	-	-	20 mg
Sodium Taurocholate	-	-	20 mg	-	-
Carbapol	20 mg	-	-	20 mg	20 mg

formulation shown in the Table 1. After mixing, both the solutions were transferred to conical flask and allowed to stir for 2 h at a room temperature (25°C) using magnetic stirrer (2MLH, Remi Laboratory Instruments, Mumbai, India). The resultant solutions were filtered, dried at room temperature. Light hand crush via the mortar and pestle formulation was bulky and pass to the sieve number 100. All the formulations DF1-DF5 stored in desiccators until further analysis. [10, 11]

Solubility Study of the Formulations

All the prepared formulation was weight and filled in the capsule about 50 mg for the analysis of the solubility parameter. Each capsule was placed in the 250 ml of the distilled water in a 500 ml beaker and placed at the orbital shaker (Lab HOSP – Shaker) at room temperature (25±2°C) for the 2 hr. and further take the sample 10 ml, take the absorbance at the UV – spectroscopy (Shimadzu 1700, Japan) after dilution at the range of 215 nm. [12, 13]

On the basis of the solubility data (Figure 2) of the different formulation, formulation DF5 show the better solubility as compared to the other formulations. So we select the formulation F5 for the development of the floating beads. Because of the, Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. [14]

Formulation of Floating Beads

The Floating Beads was prepared using the ionotropic gelatine method. Sodium alginate is added to 10 ml of

Table 2: Different Type of the Formulations Table

Ingredients	F1	F2	F3	F4	F5
Formulated Drug (DF5) mg	100	100	100	100	100
Sodium alginate (mg)	0.2	0.4	0.6	0.8	1.0
Sodium bicarbonate (mg)	0.5	0.5	0.5	0.5	0.5
Water (ml)	100	100	100	100	100
Calcium chloride (gm)	2	2	2	2	2
Acetic acid (ml)	10	10	10	10	10

Table 3: Attribute of the Formulated Floating Beads

Formulation Code	Mean diameter ± SD (mm)	Drug content (mg)	% EE	% Swelling
F1	1.521±0.034	1.426±0.046	60.41	0.45
F2	1.465±0.074	1.921±0.091	72.96	0.62
F3	2.091±0.064	2.468±0.065	75.14	0.81
F4	2.198±0.049	2.073±0.074	63.85	0.76
F5	1.549±0.046	1.652±0.015	75.07	0.49

distilled water in a beaker and stirred well to obtain a clear solution in a magnetic stirrer. To the above solution 100 mg of lumafentrine (previous formulation DF5) is dissolved. To the above solution sodium bicarbonate is added and sonicated for 30 min to remove air bubbles. It is kept aside for 30 min. The resultant dispersion is dropped via 23-gauge needle into 100 ml 2% w/v Calcium chloride solution containing 10% acetic acid. [15] Then washed with distilled water and dried at room temperature. Formulation details are given in Table 2.

Evaluation of the Physiochemical Parameter of the floating Beads of the drug Lumafentrine

1. Determination of Bead Diameter

The diameter of a sample of gel beads (25 beads) of each formulation was determined using a dial thickness meter.

2. Drug Content

An accurately weighed sample of beads (100 mg) was crushed in a mortar and added to 100 ml of 0.1N hydrochloric acid buffer (pH 1.2) and kept overnight under stirring to elute complete drug from the polymer matrix. It was filtered and analyzed at of 215 nm (UV spectrophotometer, 1601, Shimadzu, Japan) against blank bead mixture, which was treated similarly. The drug content of each formulation was recorded as mg/100mg of gel beads.

3. Drug Entrapment Efficiency

The percentage drug entrapment efficiency (% EE) of each bead formulation was calculated using the following equation:

EE % = Actual drug content / theoretical drug content *100

4. Determination of Swelling Index

The swelling behavior of the Lumafentrine beads was studied in 0.1 N HCl (pH 1.2) buffer. Approximately 100mg of beads were taken in a dissolution basket and weighed (W1); the baskets along with the beads were immersed in 0.1N HCl buffer. The weight (W2) of the basket along with the beads was determined for 8 h: every 30 minutes for the first 2 h, and then every h after that. The swelling index (SI) of each formulation was calculated using the following equation:

$$\% SI = (W_2 - W_1) / W_1 * 100$$

5. Buoyancy Studies

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the time for which the formulation constantly floated on the surface of the medium (floating duration) were measured simultaneously as a part of dissolution studies by visual observation.

6. *In-Vitro* Drug Release Studies

In vitro release characteristics of Lumafentrine floating gel beads (n = 3) were evaluated employing USP XIV dissolution testing apparatus 2 (paddle method) using 500ml of 0.1 N HCl buffer as dissolution medium maintained at 37±0.5°C. The contents were stirred at 50 rpm. A 5ml aliquot of the solution was withdrawn at predetermined time intervals for 8 h and fresh 5ml dissolution media was replaced to maintain sink condition. The sample aliquots were analyzed at a wavelength of 215 nm.

7. Scanning Electron Microscopy (SEM)

Morphological examination of the surface and external structure of the dried beads of formulation F1, F2, F3, F4 and F5 (Both drug loaded and blank beads) was performed using a scanning electron microscope (SEM) (model JEOL, JSM-840A). The samples were gold coated prior to the scanning.

RESULTS AND DISCUSSIONS

Drug Content, Drug Entrapment Efficiency and Swelling Index

The percent drug content, entrapment efficiency and swelling index for various lumafentrine floating bead formulations is shown in Table 3.

Table 4: Buoyancy Study of the Formulated Floating Beads

Formulation Code	Amount of Oil (5 w/v)	Floating Time (hr.)
F1	10	8.0
F2	15	7.2
F3	20	7.5
F4	25	6.2
F5	25	6.3

Table 5: *In-Vitro* Dissolution Profile of the Formulated Floating Beads

Time (hr.)	% Cumulative Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	45.16	46.34	48.64	44.25	45.62
1.0	58.56	59.43	55.46	48.62	49.42
1.5	63.49	63.44	64.82	55.25	52.14
2.0	70.31	71.81	73.46	59.34	56.95
4.0	71.46	71.92	76.09	62.43	61.98
6.0	73.57	74.15	81.56	65.12	63.44
8.0	75.18	74.82	83.44	68.46	64.94
10.0	76.44	75.46	85.61	71.08	68.16
12.0	78.61	77.92	87.43	71.58	72.09

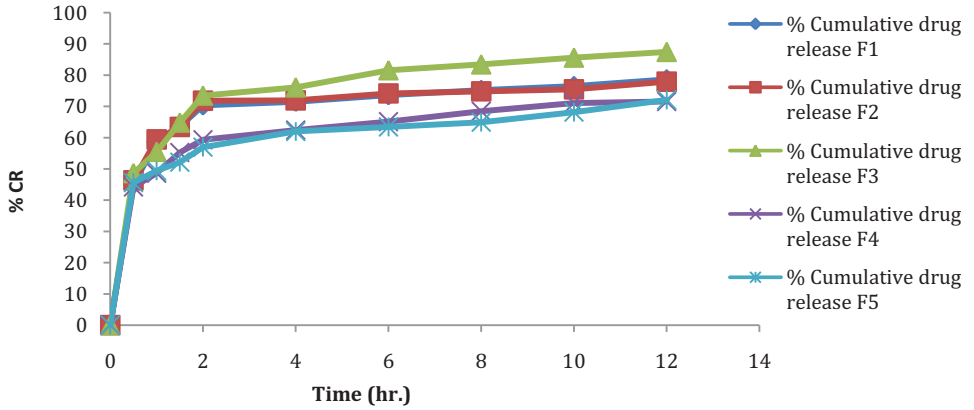

Figure 3: *In-vitro* dissolution plot of the formulated floating beads

The percent drug entrapment efficiency for various lumafentrine floating bead formulations was found to vary between 60.41 % and 75.14 %. Formulation F3 showed the highest drug entrapment and formulation F1 showed the lowest entrapment of drug. The low drug entrapment efficiency of the F1 formulation may be attributed to the highly porous nature of the alginate matrix, due to which the drug may diffuse back into the cross linking solution from the bead matrix during cross linking period. The drug entrapment also increases with addition of the copolymers into the bead formulation.

The beads were also not swollen or eroded during the dissolution studies in 0.1 N HCl. Thus, from these results, it could be assumed that the drug release was not under the control of the swelling behavior but rather was controlled by the dissolution of the famotidine in the dissolution medium and diffusion of the famotidine through polymer matrix.

Buoyancy Studies

The floating ability of prepared beads was evaluated along with dissolution studies. The beads without oil sank immediately in 0.1 N HCl (pH 1.2), while beads containing sufficient amount of rice bran oil (25%) demonstrated instantaneous and excellent floating properties (Table 4).

*In-Vi*tro Drug Release Studies

In vitro drug release study of Lumafentrine floating beads was carried in 0.1N HCl (pH 1.2), for a period of 12 h. In the 0.1N HCl, the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) followed by a sustained, gradually increasing drug release phase after 1 h extending up to 8 h (Table 5). Formulations contained F1, F2 and F3 released 68.42%, 63.12% and 78.05 % of drug respectively at the end of 12hrs. Whereas formulations contained F4 and F5 released 65.04 % and 61.01% of drug respectively at the end of 12hrs and the release profile is shown in Figure 3. The results show that incorporation of rate controlling polymers such as cyclodextrine, PVP K 60 and sodium alginate bead formulations can sustain the drug release from Lumafentrine beads. Incorporation of these copolymers into the cyclodextrine matrix increases the viscosity of the polymers matrix and correspondingly decreases the drug

release. Results also show that as the concentration of the copolymers increases in the formulation, the drug release is further decreased and more sustaining of drug release is observed because as the concentration of copolymers is increased the viscosity of the polymer matrix is further enhanced.

CONCLUSION

Various formulations of floating beads of lumafentrine were developed using polymers like h-p-beta-cyclodextrine, PVP and other polymer. The beads were prepared by emulsion gelation method. Beads formulated with mixture of lumafentrine and other polymer (F3) showed the highest drug release compared to other formulations. The selected formulation showed no more changes in drug content, floatability or *in-vitro* drug release profile after storage at 75 ± 5%, RH at 40±2°C during stability study for two months. Thus, the objective of the present work of formulating a dosage form of lumafentrine by using a low density oil and different proportions and combinations of release rate controlling polymers has been achieved with success.

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