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Design and Development of Multiparticulate Floating Drug Delivery System Containing Lisinopril

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Abstract **Original Research Article**

The aim of present work is to design multiple unit floating drug delivery system for prolong release of Lisinopril by using different amount of waxes, and to study effect of pectin on buoyancy of the system. The purpose of the study is to prepare wax-encarporated pectin-based emulsion gel beads using a modified Emulsion-gelation technique. The Model drug was incorporated in pectin wax contain olive oil, Lisinopril, were hot-melted, homogenized and then extruded into calcium chloride solution. The prepared Wax-incorporated Emulsion Gel Beads were evaluated for Micromeritics studies, entrapment efficacy, in-vitro buoyancy rate, dissolution rate, it was concluded that the increase of drug release of Lisinopril could be obtained upto 10 hrs.Various preformulation studies like bulk density, tapped density, Carr's index angle of repose were in the acceptable limits especially for batch F9. Drug and polymer are compatible with each other as they are verified through FTIR spectroscopy. Increasing the amount of wax in the formulation significantly prolonged the drug release but was insufficient for sustaining the release of highly water-soluble drug.

Keywords: Lisinopril, Multiparticulate, gastroretentive, buoyancy.

INTRODUCTION

Gastro retentive systems or dynamically controlled systems are low-density systems that have comparatively more buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying time for a prolonged period of rate & time . 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 [1].

Gastro retentive drug delivery system (GRDDS) is one of the gastro retentive dosage forms which could prolong gastric retention time (GRT) to obtain sufficient drug bioavailability. This system floats in the gastric fluid due to its lower bulk density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This system is also useful for drugs which act locally in the proximal part of gastrointestinal (GI) tract, such as antibiotic administration for Helicobacter pylori eradication in the treatment of peptic ulcer andor drugs which are poorly soluble or unstable in the intestinal fluid [2].

Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even subunits have diameters of less than 2 mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability [3, 4].

It would, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling gastroretentive and bioadhesion characteristics to multiparticulates and developing gastroretentive bioadhesive multiparticulates. These multiparticulates have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site [5-8].

It is stated that, 'the multiparticulates' float on the stomach contents, and then adhere to the mucous linings as the stomach empties. The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach [9-11].

MATERIALS AND METHODS

Material

Lisinopril was obtained as kind gift sample from Yarrowchem Pharma, Mumbai India. Pectin purchased from Research lab fine chem. Industries, Mumbai, White wax & Olive oil was purchased from Thomas baker, Mumbai India. All other materials used of analytical grades.

Methods

Preparation of Conventional CaPG Beads and Emulsion Gel Beads

Conventional CaPG beads were prepared by the ionotropic gelation method 400 mg of pectin were dispersed in water with agitation, and then 100 mg of Lisinopril (80-mesh sieved) were dispersed in pectin solution to make a 100-g solution. The dispersion was then extruded through a plastic needle into 0.34 M calcium chloride which was gentle stirred at room temperature. The gel beads formed were allowed to stand in the solution for 20 min before being separated and washed with distilled water. The beads were dried at 37°C for 12 h.

The emulsion gel beads of calcium pectinate were prepared by emulsion-gelation method 400 mg of pectin were dissolved in water with agitation. 3 ml of olive oil were added to the mixture of pectin and lisinopril (1:1) to make 100-g mixtures and homogenized using a homogenizer, at 3,000 rpm for 5 min. The emulsion gel beads were treated in the same manner as conventional CaPG beads [12-13].

Preparation of Wax-incorporated Emulsion Gel Beads

Various amounts of different waxes (i.e. white wax and cetyl alcohol) were melted in water bath at 60–85°C, depending on the melting ranges of the waxes used. The molten wax was dispersed in the homogenized emulsion mixture of pectin, oil and Lisinopril which already heated to same temperature, and then mixed until the homogenous mixture was obtained. The hot melted mixture was extruded into 0.34 M calcium chloride (cooled at 5°C). The wax-incorporated emulsion gel beads obtained were treated in the same manner as conventional CaPG beads. The formulations studied are shown in Table

Table-1: Formulation Table

Batches / Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	100	100	100	100	100	100	100	100	100
Pectin	400	400	400	400	400	400	400	400	400
White wax	150	150	150	200	200	200	250	250	250
Cetyl alcohol	100	150	200	100	150	200	100	150	200
Olive oil (ml)	3	3	3	3	3	3	3	3	3
Distilled water	20	20	20	20	20	20	20	20	20
0.340M Cal. chloride (ml)	100	100	100	100	100	100	100	100	100

Evaluation of Lisinopril Beads

Micromeritics studies of floating beads [14]

The microspheres were characterized by their Micromeritics properties, such as particle size, bulk density, tapped density, Carr's compressibility index, hausner ratio and flow property.

Percentage yield of microspheres formed.

The percentage yield of the prepared microsphere determined by weighing after drying. The measured weight of prepared microspheres was divided by the total amount of all the non–volatile components used for the preparation of the microspheres, which gave the total percentage yield of microspheres.

$$\% \textbf{ Yield} = \textbf{Actual wt of product} \div \textbf{Total wt of exipient and drug} \times 100$$

Drug Entrapment Efficiency (DEE)

About 10g of beads were weighed accurately and crushed in glass mortar. Powdered beads were suspended in 100 ml of 0.1N HCL. After 24 hr the solution was filtered and filtrate was analysed for drug content at 230 nm. The results of % lisinopril loading and encapsulation efficiency were calculated using Equation. The drug content was calculated from standard curve.

$$\%\textbf{Drug entrapment} = \textbf{Calculated drug concentration} \div \textbf{Theorotical drug concentration} \times 100$$

In vitro buoyancy study: [16-18]

Appropriate quantity of the floating micro particulate was placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture was stirred with a magnetic stirrer. The layer of buoyant micro particulate 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.

Buoyancy (%) = Wf / Wf + Ws×100

Where,

Wf and Ws are the weights of the floating and settled micro particles.

Dissolution test (in-vitro drug release) of microspheres

The dissolution test was performed using 900 ml 0.1N HCL fluid maintained at 37 ± 0.50C and stirred at 100 rpm for 10 hr. A sample (1 ml) of the aliquots were withdrawn at different time intervals and an equivalent volume of medium prewarmed at 370C was added to maintain sink condition. The withdrawn samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 230 nm. Percentage drug release was calculated using an equation obtained from a standard curve.

Infrared Spectroscopy Interpretation for interaction between drug and polymer in Microsphere

Fourier transforms infrared spectroscopy (FTIR) spectra of the pure drug and the microspheres were produced using by KBr disk method. Powder microsphere and the ingredients used in drug loading were subjected to FTIR with a Shimadzu 8201 PC FTIR. Background spectrum was collected before running each sample. The samples were analyzed between wave numbers 4000 and 400 cm-1 [20-22].

Stability Study for Multiple Unit System

During the stability studies the product is exposed to normal conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. In the present study, stability studies were carried out on optimized formulation. The microspheres were stored at 40 ± 20 C/75 ± 5 % RH for duration of one month. At the interval after thirty days each sample was withdrawn and tested for drug entrapment, and drug release study.

RESULT AND DISCUSSION

Micromeritic Properties

Micromeritic properties for batch F1 to F9 are shown in Table No. 9. The results showed bulk density and Cars index in the range of 12%to 16%, Hausners ratio less than 1.25 which shows good flow properties. The values were found to be in the range of 21°28'±1.4 to 29°69'±1.8, beads shows the angle of repose less than 30º which reveals good flow property. The observed results suggest good flow ability of the beads. Bulk density may affect buoyancy of floating beads. The bulk density of formulations was found to be between 0.165±0.02 to 0.254±0.02g/cm$^{3.}$ This indicates good packing capacity. The tapped density of beads was found to be in range of 0.197±0.032 to 0.308±0.018g/cm^3, which shows good packability of beads. The mean particle sizes of all formulations were ranged from 2.04±0.37mm to 2.32±0.60 mm as shown in Table No 10. Higher particle size was obtained when the proportion of waxes was increased in polymer and drug mixture of pectin: lisinopril. As the amount of calcium chloride was increased, more crosslinking structure was observed that lead to a decrease in particle size.

Table-2: Micromeritics studies of floating beads

Para-meters / Batches	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index	Hausner ratio	Angle of repose (θ)	Particle size (mm)
F1	0.246±0.02	0.308±0.018	20.12±0.15	1.25±0.12	28°65'±0.8	2.23±0.35
F2	0.165±0.02	0.197±0.032	16.24±0.12	1.19±0.006	26°50'±2.5	2.2±0.43
F3	0.186±0.02	0.219±0.041	15.06±0.26	1.17±0.005	29°69'±1.8	2.24±0.35
F4	0.236±0.03	0.265±0.027	10.94±0.18	1.12±0.006	27°23'±1.5	2.22±0.19
F5	0.222±0.01	0.255±0.019	12.94±0.20	1.14±0.007	28°65'±0.8	2.04±0.37
F6	0.254±0.02	0.306±0.029	16.99±0.23	1.20±0.004	26°50'±2.1	2.15±0.222
F7	0.250±0.03	0.283±0.04	11.66±0.21	1.13±0.002	26°69'±2.3	2.32±0.60
F8	0.217±0.01	0.261±0.030	16.85±O.24	1.20±0.004	21°28'±1.4	2.26±0.23
F9	0.225±0.02	0.257±0.023	12.45±0.19	1.14±0.007	27°23'±1.2	2.26±0.20

Determination of Percentage yield

It was found that the average percentage yield was greater than 80% for all formulations. The drug loading was found to be in range of 84.21±0.5% to 97.22±0.2%. Formulation F1 showed highest loading of 97.22±0.2%. Whereas formulation F9 showed lowest drug loading of 84.21±0.5%. Overall the drug loading

was decreased with increase in the concentration of waxes.

Drug entrapment efficiency

Ionic gelation technique is convenient method for the preparation of floating beads with good drug loading and encapsulation efficiency. In this method drug is dispersed equally in the polymer matrix so drug can be loaded easily in the polymer. The drug entrapment efficiency of the prepared beads was found to be increased progressively with an increase in concentration of waxes and polymers. This might be due to increased matrix density.

In vitro buoyancy study

The formulation F1 gives best floating ability of 92.38% in 0.1 N HCL for 10 hrs. This may be due to its low bulk density. The floating ability of the formulations ranges from 65.52% to 93.20%, which shows the excellent floating ability of the beads. In this as the concentration of wax increases, the viscocity of mixture increases and thus leads to good floating ability.

Table-3: Percentage yield, In vitro buoyancy study, Drug entrapment efficiency

Batch	Drug entrapment efficiency (%)	Yield (%)	(%) buoyancy
F1	86.45%	97.22±0.2	92.38%
F2	93.20%	94.11±0.7	84.34%
F3	88.67%	92.94±0.2	90.67%
F4	76.25%	95±0.4	79.33%
F5	65.52%	86.87±0.5	69.32%
F6	83.34%	91.73±0.3	78.34%
F7	75.38%	96.47±0.3	86.12%
F8	76.50%	88.88±0.4	83.78%
F9	89.42%	84.21±0.5	77.23%

In vitro drug release study

It was observed that the beads ascended to the upper part of the dissolution vessels and remains floated until the completion of release studies. The drug release study was carried for 10 hrs. This showed as the concentration of waxes increases the release rate of the drug decreases which were attributed to increase density of the polymer matrix at highest concentration causing decreased diffusional path length, and increases drug release from the polymer matrix. Moreover dissolution study data revealed that release from the beads was largely dependent on the polymer swelling and drug diffusion. The percentage drug release from batches F1 to F9 varied from 61.01 % to 96.31 %. The in-vitro drug release of the formulation F1 to F9 displayed in Table where comparative release of drug is shown.

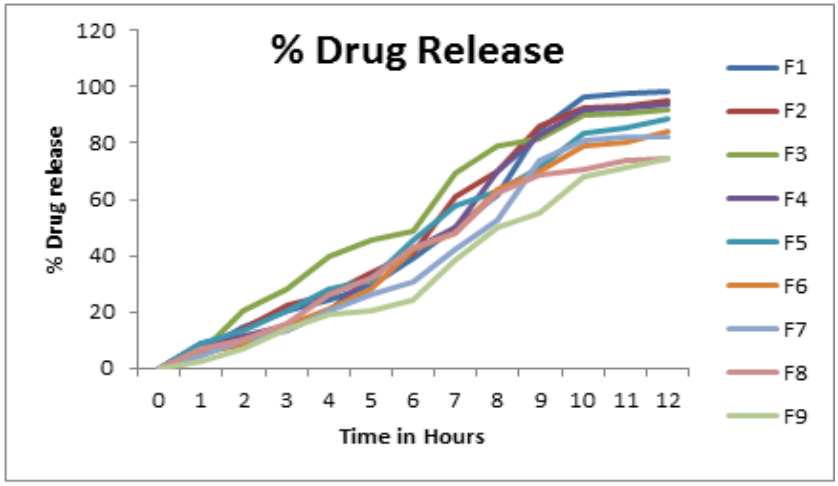

Fig-1: In vitro drug release study

IR Study

The infrared absorption spectrum of pure lisinopril and the sustained release microsphere of optimized polymer were recorded on FT-IR spectrophotometer (Model-8400S, Shimadzu, Japan) and the spectrum analysis was done for functional groups. The FT-IR spectra of drug with polymer were compared with the standard FT-IR spectrum of the pure drug.1658, 1611 (the vibrations characteristic to carboxyl group), 1578 cm−1(NH bending group vibration) and 1546 cm−1for pure lisinopril compound are shifted to 1637 and 1592 cm−1for all IC products. These frequency shifts can be explained probably by breaking the hydrogen bonds in the case of NH groups

and respectively by the formation of hydrogen bonds in the case of car-boxyl groups. Consequently, FTIR studies established clearly the functional groups implied in the inclusion process. In the 4000–2500 cm−1spectral region, see Fig. 4, the most important contributions are due to the O–H stretching vibrations of primary (3504 cm−1[9]), secondary OH groups of the groups and soft water molecules present inside CD cavity, also. The different shape of this mass if (corresponding to ICs').

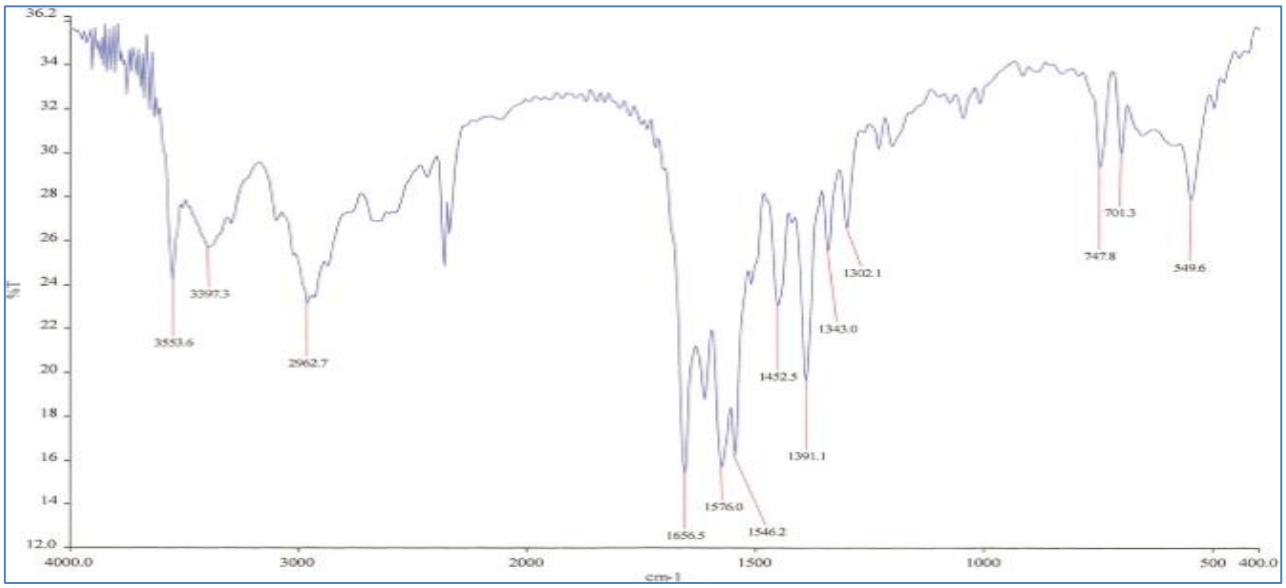

Fig-2: FTIR of Lisinopril

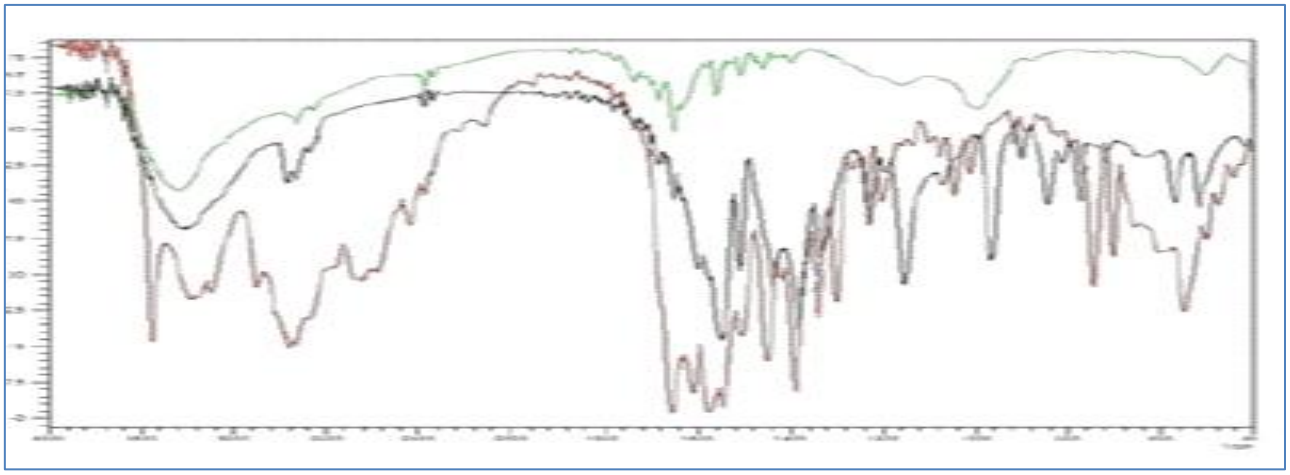

Fig-3: FTIR of Lisinopril physical mixture

CONCLUSION

Intragastric floating drug delivery system was prepared by incorporating low density materials, e.g. oils and/or waxes. Incorporation of wax into the beads influenced the drug release. It can be concluded that the drug Lisinopril multiparticulate floating beads for the treatment of hypertension were prepared and the release kinetics of the optimized batch could show the assured sustain release of drug. By using waxes it was concluded that the increase of drug release of Lisinopril could be obtained upto 10 hrs.Various preformulation studies like bulk density, tapped density, Carr's index angle of repose were in the acceptable limits especially for batch F9. Drug and polymer are compatible with each other as they are verified through FTIR spectroscopy. Increasing the amount of wax in the formulation significantly prolonged the drug release but was insufficient for sustaining the release of highly water-soluble drug.

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