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DESIGN, FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF LOSARTAN POTASSIUM USING IONOTROPIC GELATION METHOD

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ABSTRACT

The aim this work was to formulate and evaluate multiunit floating microspheres containing Losartan Potassium. The floating microspheres were prepared by Ionotropic Gelation method with the polymer combination of hyroxipropyl methyl cellulose and ethyl cellulose. Losartan potassium is an orally active non-peptide angiotensin-II receptor antagonist and it is readily absorbed from the stomach and upper part of small intestine. The prepared microspheres were evaluated for particle size, encapsulation efficiency, swelling index, buoyancy and drug release. The drug encapsulation efficiency varied from between 53.69 to 75.6 depends upon the drug polymer ratio. The mean particle size of selected batch was 973.5 um. The study on *in vitro* release of all formulation in 0.1 N HCl, the maximum % CDR observed in F5 at the period of 10 hrs. F5 followed zero order and shows controlled release of drug thus reduce frequency of dosing, minimizing of side effects, improve bioavailability and increase the effectiveness of the drug.

Key words: Floating Microspheres, Losartan Potassium, Ionotropic Gelation Method, Gastric Retention.

INTRODUCTION

Gastro retentive drug delivery systems (GRDDS) are the systems which are capable to prolong the retention time of the dosage form in the gastric region and improve the bioavailability of drugs that are mainly absorbed from upper GIT (duodenum and stomach) [1-4]. GRDDS extend the gastric residence time of drugs so that increase bioavailability, reduce drug waste, and improve solubility of drugs [5-7].

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials, that is, biodegradable synthetic polymer and modified natural products such as starches, gums, proteins, fats and waxes. Microparticles can be used for the controlled release of drugs, vaccines, antibiotics and hormones. The microspheres have several advantages over conventional dosage forms *i.e.* it can provide a larger surface area and possess an easier estimation of diffusion and mass transfer behaviour and the encapsulated small molecules can diffuse out of the barrier with precise kinetics modelling and release the drugs to the body fluid in controlled manner [8-15]. Losartan Potassium, chosen for testing, is commercially available only in the form of one compartment tablets (a classic tablets at a dose of 25, 50, 100 mg of active substance) or combined with hydrochlorothiazide [16-17]. Due to the bioavailability of Losartan Potassium at a level of about 33%, half-life in the human body of about 2 h, and very frequent use in a long-term therapy (e.g., in hypertension), there is a need to develop oral formulations of losartan that can guarantee sustained and controlled release of active substances that could simultaneously improve the bioavailability. The administration of Losartan Potassium in the form of a sustained release should be characterized by reaching rapidly the concentration of therapeutic effect. Then, a properly chosen polymer matrix should maintain plasma concentration within the therapeutic range for longer time (about 8-12 h) [18].

Thus, it were decided that in present work is to

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formulate and evaluate the floating microspheres of antihypertensive drug Losartan Potassium which release the drug and maintain uniform drug levels over a sustained period of time.

EXPERIMENTAL

Materials

In this work, the following substances were used: losartan potassium (Aristo Pharmaceuticals, India.), Sodium Alginate (Molychem), Hydroxypropyl Methyl Cellulose (SD Fine-chem, Limited, Mumbai), Ethyl cellulose (SD Fine-chem, Limited, Mumbai), 50 mg tablets of Losartan Potassium (trade standard).

Methods

Technology for Obtaining the Microspheres

The Losartan Potassium floating microspheres were prepared by Ionic Gelation method using different proportion of polymers. A 3% w/v solution of sodium alginate solution was added to weighed amount of ethyl cellulose dissolved in required quantity of ethanol. Weighed quantity of drug and HPMC K4M was triturated then added to the above 3% w/v solution of sodium alginate. Calcium carbonate, a gas forming agent was added to this mixture and the resulting solution was stirred uniformly. Using a 26 G syringe needle the above solution was dropped into 100 ml of gently agitated calcium chloride (1% w/v) solution containing 10% glacial acetic acid to obtain microspheres. The solution containing microsphere was stirred slowly using magnetic bead for about 10 min. The microspheres were further allowed to remain in the same solution for 20 min to improve mechanical strength. The formed microspheres were filtered, washed with distilled water, air-dried at room temperature and stored in desiccators. The composition of each dried mixtures are shown in Table 1.

Scanning Electron Microscopy (SEM)

SEM has been used to determine surface topography, texture and to examine the morphology of sectioned surface. The dried samples were sprinkled on a adhesive carbon tape. Thin coating of a gold-palladium was applied to the mounted sample using sputter coater (Quorum SC7620). The sample were removed from the sputter and mounted on a sample holder of Zeiss Japan EVO 18 SEM and scanned by an electron beam scanning microscope. The detector produced three dimensional images of the sample. Morphology of the microspheres was determined by using scanning electron microscope.

Determination of Drug Entrapment Efficiency

The Drug Entrapment Efficiency (DEE) of floating microspheres was performed by taking the equivalent amount of microspheres in which 10 mg. drug was present. Then the microspheres were crushed and suspended in 10 ml of stimulated gastric fluid 0.1 N HCl (pH 1.2) and kept for 24 h at room temperature. After 24 h it was stirred for 5 minutes and filtered. Then the resulting solution was analysed by UV- Visible Spectrophotometer at 250 nm against pH 1.2 buffer solutions as blank. The drug loading in microspheres was estimated using following formula:

$$\text{Drug Loading} = \left(\frac{\text{Total wt. of the drug loaded in the microspheres}}{\text{Total wt. of the microspheres}}\right) \times 100$$

$$\text{Entrapment Efficiency} = \left(\frac{\text{Actual drug content}}{\text{Theoretical drug content}}\right) \times 100$$

In vitro Release Studies

In vitro drug release from alginate microspheres was performed at 37°C in dissolution apparatus at 100 rpm. Drug release from the microspheres was studied in SGF at regular intervals, aliquots were withdrawn and the fresh medium was added to maintain the sink condition. Drug content of the microspheres were determined by UV visible spectroscopy at 250 nm.

Test for Buoyancy

The microspheres (300 mg) were transferred to a USP dissolution apparatus type II containing 900 ml of simulated gastric fluid (pH 1.2) maintained at 37°C. The medium was stirred at 100 rpm for 12 hr. The floating and non-floating microspheres were separated, dried at 45°C until a constant weight is obtained. Then the percentage of buoyancy is calculated by using following equation:

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

Where, Qf is the weight of floating microspheres and
Qs is the weight of settled microspheres.

Swelling Index

A known weight of microsphere without drug was placed in 500 ml of different solutions: distilled water and enzyme free simulated gastric fluid (pH 1.2) and allowed to swell for sufficient time at 37±0.5°C using the USP type 1 dissolution apparatus at 50 rpm. The microspheres are removed, blotted with filter paper and their change in weight was measured during swelling until equilibrium was attained. Finally the weight of swollen microsphere was recorded after 4 h and swelling ratio (SR) was calculated by the following formula:

SR = (We – Wo) x 100

Where, W_E = weight of the swalloen microsphere at equilibrium state

Wo = initial weight of dry microsphere.

Kinetic Treatment of Dissolution Data

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In order to describe the kinetics of the release process of drug in the different formulations, models were fitted to the dissolution data of optimized formulations using linear regression analysis. In order to study the exact mechanism of drug release from microspheres, drug release data was analyzed according to Zero Order Kinetics; First Order Kinetics, Higuchi square root equation, Hixon-Crowell equation. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Results and Discussion

The Losartan potassium floating microspheres were prepared by ionic gelation method using different proportion of polymers. Floating microspheres were prepared by 3% w/v solution of sodium alginate solution. Calcium carbonate was used as a gas forming agent. Calcium chloride (1% w/v) solution was used as a cross linking agent to obtain microspheres. The Polymers HPMC used as a gelling agent and EC as rate retardant. Floating microspheres were prepared by gradually increasing EC concentration in combination with a fixed concentration of HPMC.

The surface morphology, texture and cross section of the drug loaded microsphere (optimized) were studied by SEM studies. SEM images of all formulations were shown in **Figure 1-3**. The images revealed that the Losartan potassium loaded floating microspheres prepared by ionotropic gelation method were spherical in appearance, discrete and uniform in size. Their cross section shows that there is a large pore inside the microsphere due to CO_2 gas entrapment. This makes it lighter in weight and helps in buoyancy in GI fluid. The porous nature of the microspheres was evident by SEM examination.

***In vitro* Drug Release Studies**

Drug release from microspheres decreased with increase in EC concentration due to its less permeability. It increases the polymer matrix density leading to decrease in drug release from the microspheres.

Figure 1: SEM Photograph of Floating Microsphere Containing Losartan Potassium

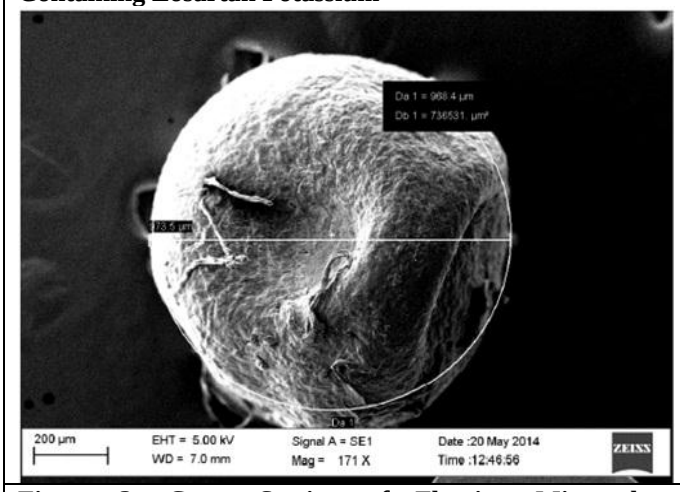

Figure 2: Surface Morphology of Floating Microsphere Containing Losartan Potassium

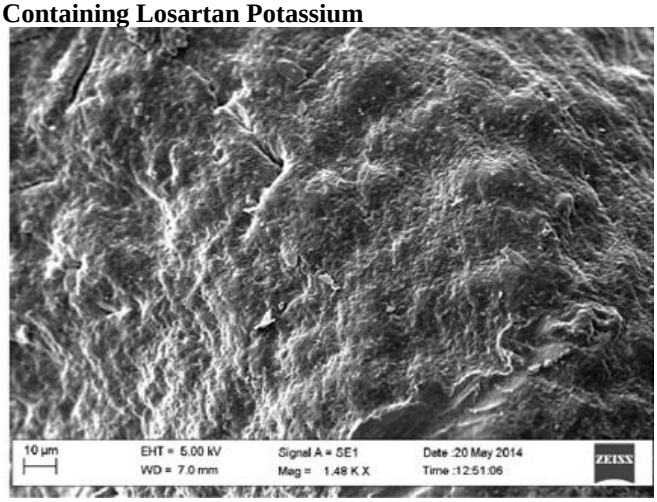

Figure 3: Cross Section of Floating Microsphere Containing Losartan Potassium

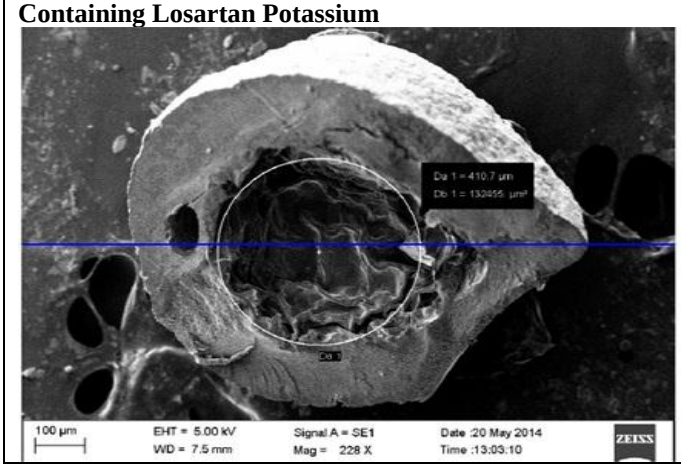

Figure 4: *In vitro* Release Profile of All Formulations

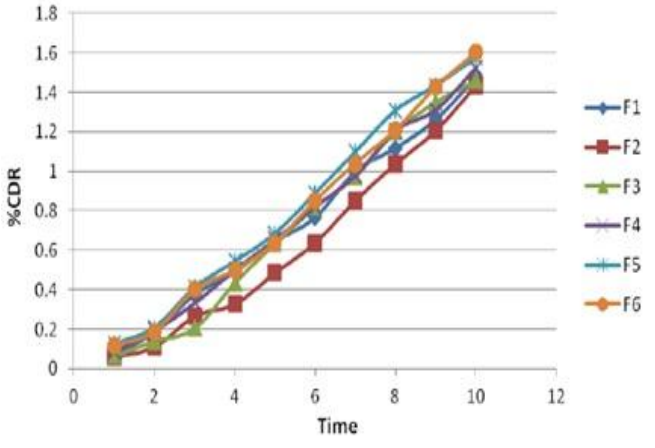

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Table 1. Batch Specification of Floating Microspheres

S. No.	Formulation Code	Drug (mg)	Ethyl Cellulose (mg)	Calcium Chloride (% w/v)
1	F1	50	15	1
2	F2	50	20	1
3	F3	50	25	1
4	F4	50	30	1
5	F5	50	35	1
6	F6	50	40	1

Table 2. *In vitro* Release Profile of All Formulations.

Time	F1	F2	F3	F4	F5	F6
1	0.0712±2.04	0.0604±1.76	0.0658±1.98	0.0874±1.87	0.1270±2.57	0.1162±2.48
2	0.1868±2.24	0.1112±1.85	0.1400±1.73	0.1941±2.76	0.2087±2.81	0.1871±2.68
3	0.3768±2.98	0.2666±2.47	0.2056±1.84	0.3338±1.53	0.4115±2.75	0.4005±1.35
4	0.4905±1.85	0.3274±2.63	0.4353±2.49	0.5012±1.79	0.5434±1.72	0.4981±1.94
5	0.6444±1.29	0.4859±3.21	0.6339±2.67	0.6552±2.82	0.6850±3.19	0.6377±1.83
6	0.7668±3.05	0.6379±1.58	0.8192±3.51	0.8208±1.76	0.8885±2.63	0.8518±2.89
7	0.9996±2.35	0.8520±2.79	0.9749±2.62	0.9801±2.84	1.0986±1.84	1.0400±1.76
8	1.1185±1.76	1.0385±1.82	1.2016±1.69	1.2087±3.67	1.3080±1.76	1.2095±1.68
9	1.2614±1.58	1.2062±1.42	1.3504±1.73	1.3125±2.99	1.4340±1.98	1.4267±3.53
10	1.4752±1.92	1.4342±1.74	1.4604±1.76	1.5248±2.68	1.5750±1.83	1.6019±2.94

CONCLUSION

In the present study, an attempt was made to develop floating microspheres of Losartan potassium with polymers HPMC and EC by Ionotropic gelation method. Preformulation studies of like melting point, solubility study, UV spectroscopy of Losartan potassium were complied with IP standard. The FT-IR spectra of physical mixture of LP and polymers showed that there was no significant shifting of peak, so that there was no interaction between LP and polymers. Various formulation (F1, F2, F3, F4, F5, F6) were developed by using polymer combination of HPMC and EC. Developed formulations were evaluated for the parameters such as particle size, scanning electron microscopy, drug entrapment efficiency, swelling index, buoyancy test and *in vitro* release study.

The Scanning electron microscopy revealed that the Losartan potassium loaded floating microspheres were spherical in appearance and uniform in size. Their cross section shows that there was a large pore inside the microsphere due to CO_2 gas entrapment. This makes it lighter in weight and helps in buoyancy in GI fluid.Particle size determination showed that all the microspheres were in micrometer size.

Drug entrapment efficiency increased with increase in polymer concentration. The DEE increased with increase in Ethyl cellulose concentration. This could be because of the less permeability of EC than HPMC. EC is insoluble and unswellable whereas HPMC swells and erodes with time, so that buoyancy is increases with increase in concentration of EC. Formulation F5 showed higher drug entrapment efficiency and higher than all other formulations. Among the different batches, Formulation F5 was selected as the optimized formulation, after considering their better drug encapsulation efficiency, buoyancy study and *in vitro* drug release. In vitro drug release study showed the prolong release of drug from the microspheres. Release kinetic study indicates that the release data were best fitted with zero order kinetics.

From the experimental result it can be concluded that floating microspheres of Losartan potassium with the polymers EC and HPMC can be successfully developed by ionotropic gelation method which prolong the retention time in stomach and increase the bioavailability of drug.

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