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FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERE OF LOSARTAN POTASSIUM USING NATURAL POLYMER

Yogesh Patel[1], Mr. Pushpendra Kumar Khangar[1]*, Dr. Vivek Jain[2], Dr. Sunil Kumar Jain[2]
[1]Adina Institute of Pharmaceutical Sciences, Sagar, (M.P.)

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Abstract:
Floating microspheres of Losartan potassium was prepared solvent evaporation method with an aim of increasing the gastric residence time and for controlled release. HPMC, EC and Sodium alginate, polymeric mixture were used as polymers. The present work was aimed to control drug delivery and alter the pharmacokinetics and pharmacodynamics of Losartan potassium, to ensure safety, improve efficacy, therapeutic action as well as patient compliance. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 68.65±0.15–80.46±0.42%. The maximum Percentage Yield was found in formulation F4, 80.46±0.42as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 59.25±0.24-74.55±0.64%w/w. The maximum percentage drug entrapment was found in formulation F4 (74.55±0.64% w/w). The maximum Percentage Yield, Drug Entrapment, Percentage Buoyancy and floating lag time was found to be formulation F4 in floating microsphere. The optimized formulation of F4 both batches subjected to further studies. The results of measurement of mean particle size of optimized formulation F4 of floating microsphere was found to be 331.6 nm. Hydrophilic matrix of HPMC and EC alone could not control the release of drug effectively for 12 hours and the release pattern was satisfactory. The use of ec and Sod Alginate along with HPMC proved to show better retarding ability which was clearly seen from the results.

Key words: *Losartan Potassium, HPMC, EC, Sodium alginate, Formulation, Evaluation.*

Corresponding author:
Mr. Pushpendra Kumar Khangar
pushpendra.rai16@gmail.com

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INTRODUCTION:

Medication activity can be enhanced by growing new medication conveyance framework, for example, the microsphere sedate conveyance framework. These frameworks stay in close contact with the ingestion tissue, the mucous layer, discharging the medication at the activity site prompting a bioavailability increment and both nearby and foundational impacts [1]. The oral course of medication organization constitutes the most helpful and favored methods for sedate conveyance to foundational dissemination of body. However oral organization of the greater part of the medications in traditional measurements frames has here and now restrictions because of their failure to limit and confine the framework at gastro-intestinal tract.

Microspheres constitute an essential piece of these particulate medication conveyance frameworks by uprightness of their little size and productive bearer limit. Microspheres are the bearer connected medication conveyance framework in which molecule estimate is ranges from 1-1000 µm extend in distance across having a center of medication and completely external layers of polymer as covering material. Be that as it may, the accomplishment of these microspheres is restricted because of their short habitation time at site of assimilation. It would, in this way be worthwhile to have implies for giving a private contact of the medication conveyance framework with the engrossing layer. Microspheres have focal points like proficient retention and upgraded bioavailability of the medications because of a high surface to volume proportion, a substantially more cozy contact with the bodily fluid layer and particular focusing of medications to the ingestion site[2].

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form [3].

Losartan is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Losartan and its longer acting metabolite, E-3174, lower blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); they compete with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs do not have the adverse effect of dry cough. Losartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic nephropathy. It may also be used as an alternative agent for the treatment of systolic dysfunction, myocardial infarction, coronary artery disease, and heart failure. Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

MATERIAL AND METHOD:

Material:

Losartan potassium was obtained as a gift sample from pharmaceutical compny. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Ethyl cellulose, hydroxyl propyl methyl cellulose was purchased from Loba Chem. Pvt. Ltd, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Methods:

Preparation of Floating microsphere of Losartan potassium:

Floating microspheres loaded with Losartan potassium were prepared using solvent diffusion-evaporation method using HPMC, EC and sodium alginate in different ratio like 1:0.5, 1:0.75, 1:1 w/w. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 hrs at a speed of 500 rpm at 27±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator [4].

Table No. 1: Formulations of the floating microspheres prepared

Sr. No	Formulation Code	Losartan potassium(mg)	HPMC (mg)	EC (mg)	Sod. Alginate
1.	F1	20	50	25	-
2.	F2	20	50	50	-
3.	F3	20	50	75	-
4.	F4	20	75	-	25
5.	F5	20	75	-	50
6.	F6	20	75	-	75
7.	F7	20	100	25	25
8.	F8	20	100	50	50
9.	F9	20	100	75	75

Evaluation of microspheres:

Percentage Yield:

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres [5].

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug Entrapment:

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method [6].

Floating behavior: Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. 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 [7].

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size:

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer 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 [8].

Determination of zeta potential:

The zeta potential of the drug-loaded microspheres 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 [9].

***In-vitro* Release Studies:**

The drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of Floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 277 nm to

determine the concentration of drug present in the dissolution medium [10].

RESULTS AND DISCUSSION:

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

Losartan potassium, an angiotensin II receptor antagonist is used in treatment of hypertension. It is readily absorbed from the GIT following oral administration with poor bioavailability experiencing extensive first pass metabolism and low elimination half-life.

Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 68.65±0.15–80.46±0.42%. The maximum Percentage Yield was found in formulation F4, 80.46±0.42as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 59.25±0.24-74.55±0.64%w/w. The maximum percentage drug entrapment was found in formulation F4 (74.55±0.64% w/w). The maximum Percentage Yield, Drug Entrapment, Percentage Buoyancy and floating lag time was found to be formulation F4 in floating microsphere. The optimized formulation of F4 both batches subjected to further studies. The results of measurement of mean particle size of optimized formulation F4 of floating microsphere was found to be 331.6 nm.

Results of zeta potential of optimized formulation F4 of floating microsphere was found -25.9 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 and 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 microsphere was maximum zero order i.e 0.958 hence indicating drug releases from formulations was found to follow zero order for floating microsphere.

Table No. 2: Results of Evaluation of Different formulations of prepared microspheres

Formulation	Percentage Yield*	Drug entrapment (% w/w) of prepared microsphere	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	69.13±0.42	64.13±0.44	64±4	68±1
F2	74.55±0.22	61.22±0.55	61±6	71±2
F3	68.78±0.46	69.21±0.21	68±5	68±3
F4	80.46±0.42	74.55±0.64	41±6	80±2
F5	72.25±0.11	68.78±0.42	54±6	74±3
F6	68.65±0.15	61.13±0.31	68±8	69±4
F7	74.45±0.48	59.25±0.24	84±3	68±4
F8	70.35±0.55	68.78±0.22	95±2	74±1
F9	72.22±0.11	69.13±0.25	94±4	69±2

***Average of three determination (N=3)**

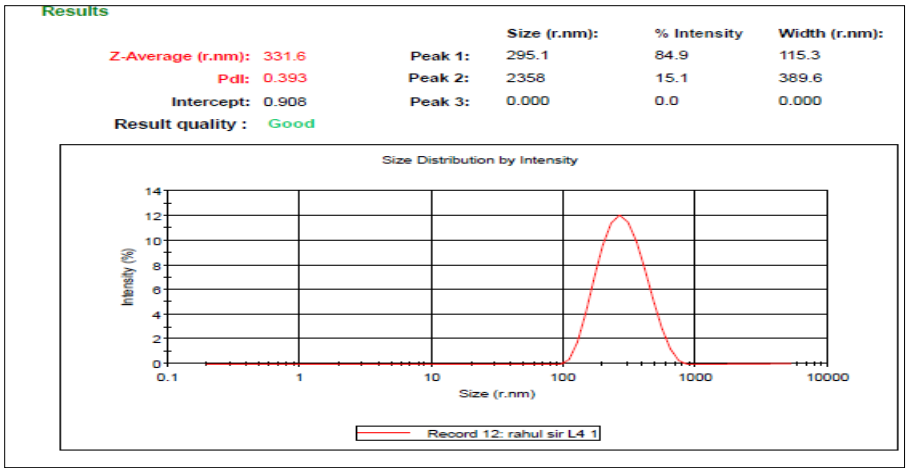

Figure No. 1: Particle size data of optimized microsphere formulation F4

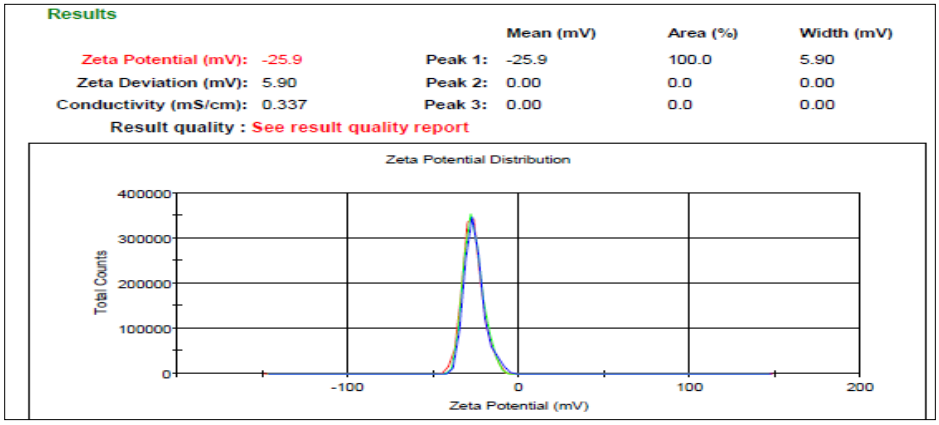

Figure No. 2: Zeta potential data of floating microsphere F4

Table No. 3: Release Kinetics of optimized formulation of microsphere F-4

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	24.46	1.388	75.54	1.878
1	1	0	32.25	1.509	67.75	1.831
2	1.414	0.301	40.56	1.608	59.44	1.774
4	2	0.602	52.32	1.719	47.68	1.678
6	2.449	0.778	70.23	1.847	29.77	1.474
8	2.828	0.903	85.56	1.932	14.44	1.160
10	3.162	1	95.56	1.980	4.44	0.647
12	3.464	1.079	99.45	1.998	0.55	-0.260

Table No. 4: Comparative study of regression coefficient for selection of optimized Formulation F-4

Release Kinetics	Zero order	First order
r^2	0.958	0.866

CONCLUSION:

Losartan potassium can be formulated as a sustained release floating microsphere using HPMC, EC and Sd. Alginate. Hydrophilic matrix of HPMC and EC alone could not control the release of drug effectively for 12 hours and the release pattern was satisfactory. The use of ec and Sod Alginate along with HPMC proved to show better retarding ability which was clearly seen from the results.

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