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Formulation and Evaluation of Mucoadhesive Microsphere Drug Delivery System of Losartan Potassium

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Abstract

Drug absorption in the gastrointestinal tract is a highly variable process. Chitosan Mucoadhesive microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance.

Chitosan Mucoadhesive microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development.

Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems. *In-vitro* data obtained for Chitosan mucoadhesive microspheres of Losartan potassium showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results it can be concluded that the drug release from the floating microspheres controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

Key-words: Chitosan Microsphere, Losartan Potassium, Formulation

Introduction

Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1-1000 µm range in diameter having a core of drug and entirely outer layers of polymer as coating material. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres and developing "mucoadhesive microspheres". Mucoadhesive microspheres 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 [1-2].

Losartan is a nonpeptide angiotensin II receptor antagonist with high affinity and selectivity for the AT $_1$receptor.

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Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor AT_1receptor blockade results in an increase in plasma renin activity (PRA) followed by increases in plasma angiotensin II concentration. The potential clinical consequences of these increases are not clear. Angiotensin II agonist effects have not been demonstrated.

The purpose of this research was to formulate and systematically evaluate in vitro performances of chitosan mucoadhesive microspheres of Losartan potassium.

Material and Methods

Preformulation study

Preformulation study was carried out as per standard procedure.

Characterization of drug

Organoleptic evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor etc.

Solubility (at room temp :) Solubility is determined in different solvents example – water methanol, 0.1 N HCL, Ethyl Alcohol, and Chloroform [3].

Identification Test

FTIR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound.

The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region.

Loss on drying:

Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

Determination of pH (1% w/v solution in water)

pH was determined by digital pH meter. In this method 1gm of the powder was taken and dissolved in 100ml of distilled water with sonication and filtered, pH of the filtrate was checked with standard glass electrode.

Melting point:

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Flow property

The flow property was determined as per standard procedure.

Moisture content

It was determined by standard procedure.

Determination of $\lambda_{max.}$

The absorption maxima of Losartan potassium were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure for the determination of $\lambda_{max.}$

Accurately weighed 10 mg of Losartan potassium separately and dissolved in 10 ml of 0.1N HCL in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 10 μg/ml make adequate of sample with concentration range of 5-25 μg/ml Losartan potassium calculate the spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer. (Labindia UV 3000 +)

Formulation Development[4]

Preparation of Chitosan Mucoadhesive Microsphere of Losartan potassium

Chitosan Mucoadhesive microsphere containing Losartan potassium was prepared using emulsion solvent diffusion technique. Chitosan solutions with concentrations of 1.2 and 1.5% (w/v) were prepared by dissolution of chitosan flakes in 0.35 M acetic acid and were filtered through 0.45 μm membrane filter (Millipore) for removing any nondissolved residue particles. Chitosan microspheres were prepared via freeze-drying method which was described as follows. Firstly, the concentrations of chitosan (1.2%) and sodium tripolyphosphate (0.6% and 1%) were selected based on the particle size and distribution of microspheres, and the experiments were designed as groups.

Table 1: Formulations of the Chitosan Mucoadhesive Microspheres Prepared

Sr. No	mulation Code	Losartan potassium (gm)	Chitosan (%)	TPP (%)
1	F_1	0.1	1.2	0.8
2	F_2	0.1	1.2	0.7
3	F_3	0.1	1.2	0.6
4	F_4	0.1	1.2	0.5
5	F_5	0.1	1.2	0.4
6	F_6	0.1	1.2	0.3
7	F_7	0.1	1.2	0.2
8	F_8	0.1	1.2	0.1

Evaluation Parameter

Particle size analysis:

Particle size analysis plays an important role in determining the release characteristics and mucoadhesive property. The sizes of Mucoadhesive microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.

***In vitro* wash-off test**

The mucoadhesive properties of the microspheres were evaluated by *in vitro* wash-off test. A 4cm x 4cm piece of goat intestinal mucosa was tied onto the paddle bottom of a USP dissolution test apparatus - II using a thread. A specified number of microspheres, i.e. 100 microspheres were spread onto the wet, rinsed tissue specimen. The dissolution test apparatus was operated such that the tissue specimen was rotated at a speed of 25 rpm in buffer (pH 1.2). At the end of 1 hour, and at hourly intervals up to 10 hours, the number of microspheres still adhering onto the tissue was counted.

Drug Entrapment [5-6]

The various formulations of the Chitosan Mucoadhesive microspheres were subjected for drug content. 50 mg of Chitosan Mucoadhesive microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No.

44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and add 2 ml of Rhodamine B and Extracted with Chloroform and the absorbance was measured at 558 nm against blank.

Percentage Yield [7]

The prepared microspheres with a size range of 609-874 µm 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.

Microspheres by Scanning Electron Microscopy:

From the formulated batches of Mucoadhesive microspheres, formulations (F_4) which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope JEOL, JSM-670F Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

***In-vitro* Release Studies** [8]

The drug release rate from Chitosan Mucoadhesive microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of

Chitosan Mucoadhesive 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 100 rpm. 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 were treated with methyl orange and analyzed spectrophotometrically at 416 nm to determine the concentration of drug present in the dissolution medium.

Drug Release Kinetic Data Analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppa's equation (Plotted as Log cumulative percentage of drug released vs Log time).

To study the release kinetics of Losartan potassium from the Chitosan Mucoadhesive microspheres the release data was fitted to three equations.

Results and Discussion

Table 1: Organoleptic property of Losartan potassium

Color	:	Light yellow
Odor	:	Odorless
Taste	:	Bitter

Table 2: Solubility studies of Losartan potassium in different solvent

S. No.	Solvent used	Solubility
1.	Water	Very Soluble
2.	0.1 N HCL	Very Soluble
3.	Ethanol	Freely Soluble
4.	Methanol	Freely Soluble
5.	0.1N NaOH	Slightly Soluble
6.	Chloroform	Slightly Soluble

Table 3: IP Index

Descriptive term	Parts of solvent required for Parts of soluble
Very soluble	Less than 1
Freely soluble	From 1to 10
Soluble	From 10 to 30
Sparingly soluble	From 30to 100
slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 or more

The melting point of the drug sample range of the drug is 183.5 - 184.5 °C. Partition Coefficient measurement of drug sample is 1.21±0.001. The percentage of loss on drying of Losartan potassium was found to be 0.78% w/w respectively. The pH of Losartan potassium was determined by Digital pH meter and found to be 6.

Table 4: Bulk Density of Losartan potassium

S. No.	Density	Losartan potassium
1	Untapped Density	0.69g/cc
2	Tapped Density (after 50 tapping)	0.86g/cc

The compressibility index of Losartan potassium was found to be 11.1%.The Hausner ratio of Losartan potassium was found to be 0.88.The Angle of repose of Losartan potassium is 40.57 degree.The Moisture content of Losartan potassium is 0.81%

The λ_{max} found for Losartan potassium is 277.0 nm as shown in Figure.

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Table 5: Calibration curve of Losartan potassium

Replicate	5	10	15	20	25
1	0.191	0.275	0.389	0.530	0.652
2	0.191	0.276	0.388	0.531	0.651
3	0.192	0.275	0.389	0.532	0.652
Mean	0.191	0.275	0.389	0.530	0.652

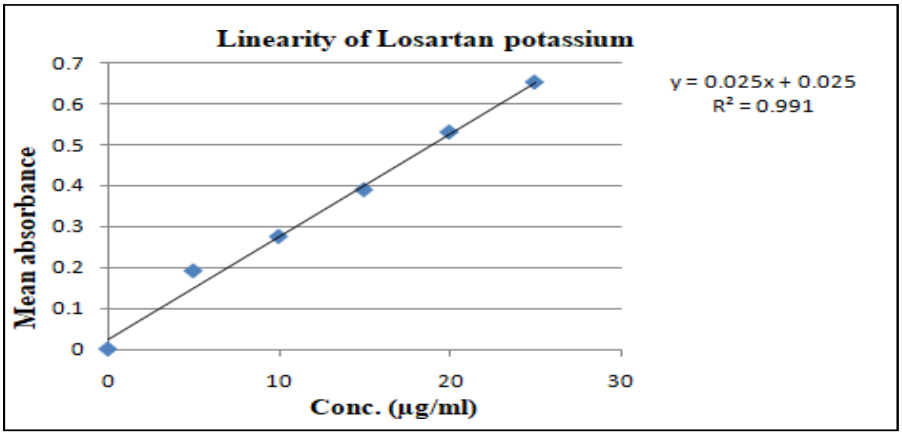

Figure 1: Calibration Curve of Losartan potassium

Table 6: Stastical Data For Linearty

S.No.	Parameter	Remark
1	Linearty Range	5-25 µg/ml
2	Regression Equation	0.014x+0.001
3	Correlation Cofficient	0.999

Mean particle size of Different Batches of Losartan potassium microsphere

Table 7: Mean particle size

S. No	Formulation code	Mean particle size (□m)
1.	F_1	170±4
2.	F_2	176±21
3.	F_3	178±23

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4.	F_4	184±25
5.	F_5	201± 24
6.	F_6	244±40
7.	F_7	210±23

Table 8: Drug Entrapment for Different Formulation

Formulation	*In vitro* wash-off test (%)	Drug entrapment (% w/w)
F_1	**72**	**76.19**
F_2	68	70.59
F_3	65	66.23
F_4	65	64.76
F_5	62	61.01
F_6	60	57.38
F_7	58	48.47

Table 9: Percentage Yield for Different Formulation

Formulation	Percent Yield (%)
F_1	82.87
F_2	78.53
F_3	76.47
F_4	71.56
F_5	69.31
F_6	66.03
F_7	56.84

Table 10: Release study of Formulation F-1

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.023	0.016	1.643	16.429	0.821	16.429
1	0.036	0.026	2.571	25.714	1.286	26.536
1.5	0.040	0.029	2.857	28.571	1.429	30.679
2	0.075	0.054	5.357	53.571	2.679	57.107
3	0.091	0.065	6.500	65.000	3.250	71.214
4	0.101	0.072	7.214	72.143	3.607	81.607
6	0.115	0.082	8.214	82.143	4.107	95.214
8	0.116	0.083	8.286	82.857	4.143	100.036

Table 11: Release study of Formulation F-2

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.021	0.015	1.500	15.000	0.750	15.000
1	0.025	0.018	1.786	17.857	0.893	18.607
1.5	0.036	0.026	2.571	25.714	1.286	27.357
2	0.042	0.030	3.000	30.000	1.500	32.929
3	0.078	0.056	5.571	55.714	2.786	60.143
4	0.098	0.070	7.000	70.000	3.500	77.214
6	0.105	0.075	7.500	75.000	3.750	85.714
8	0.106	0.076	7.571	75.714	3.786	90.179

Table 12: Release study of Formulation F-3

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.019	0.014	1.357	13.571	0.679	13.571
1	0.024	0.017	1.714	17.143	0.857	17.821
1.5	0.032	0.023	2.286	22.857	1.143	24.393
2	0.04	0.029	2.857	28.571	1.429	31.250
3	0.058	0.041	4.143	41.429	2.071	45.536
4	0.065	0.046	4.643	46.429	2.321	52.607
6	0.098	0.070	7.000	70.000	3.500	78.500
8	0.104	0.074	7.429	74.286	3.714	86.286

Table 13: Release study of Formulation F-4

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.02	0.014	1.429	14.286	0.714	14.286
1	0.025	0.018	1.786	17.857	0.893	18.571
1.5	0.036	0.026	2.571	25.714	1.286	27.321
2	0.042	0.030	3.000	30.000	1.500	32.893
3	0.051	0.036	3.643	36.429	1.821	40.821
4	0.065	0.046	4.643	46.429	2.321	52.643
6	0.089	0.064	6.357	63.571	3.179	72.107
8	0.105	0.075	7.500	75.000	3.750	86.714

Table 14: Release study of Formulation F-5

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.025	0.018	1.786	17.857	0.893	17.857
1	0.038	0.027	2.714	27.143	1.357	28.036
1.5	0.045	0.032	3.214	32.143	1.607	34.393
2	0.056	0.040	4.000	40.000	2.000	43.857
3	0.078	0.056	5.571	55.714	2.786	61.571
4	0.088	0.063	6.286	62.857	3.143	71.500
6	0.093	0.066	6.643	66.429	3.321	78.214
8	0.112	0.080	8.000	80.000	4.000	95.107

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Table 15: Release study of Formulation F-6

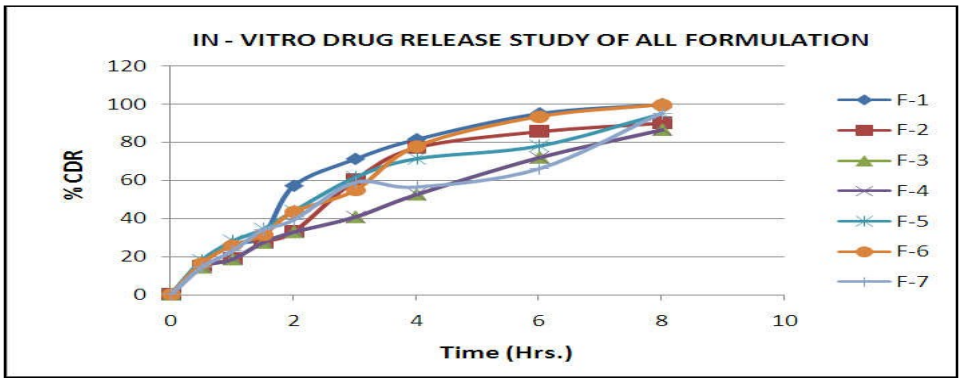
Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.023	0.016	1.643	16.429	0.821	16.429
1	0.035	0.025	2.500	25.000	1.250	25.821
1.5	0.041	0.029	2.929	29.286	1.464	31.357
2	0.056	0.040	4.000	40.000	2.000	43.536
3	0.069	0.049	4.929	49.286	2.464	54.821
4	0.098	0.070	7.000	70.000	3.500	78.000
6	0.115	0.082	8.214	82.143	4.107	93.643
8	0.118	0.084	8.429	84.286	4.214	99.893

Table 16: Release study of Formulation F-7

Time (hrs.)	Abs.	Amt. in (mg)	DR	%DR	Drug in 5 ml	% CDR
0.5	0.02	0.014	1.429	14.286	0.714	14.286
1	0.031	0.022	2.214	22.143	1.107	22.857
1.5	0.045	0.032	3.214	32.143	1.607	33.964
2	0.05	0.036	3.571	35.714	1.786	39.143
3	0.075	0.054	5.357	53.571	2.679	58.786
4	0.068	0.049	4.857	48.571	2.429	56.464
6	0.078	0.056	5.571	55.714	2.786	66.036
8	0.115	0.082	8.214	82.143	4.107	95.250

Table 17: Comparative Release Study data of formulation F1-F7

Time	% of Drug Release						
(hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0.5	16.429	15.000	14.286	14.286	17.857	16.429	14.286
1.0	26.536	18.607	18.571	18.571	28.036	25.821	22.857
1.5	30.679	27.357	27.321	27.321	34.393	31.357	33.964
2.0	57.107	32.929	32.893	32.893	43.857	43.536	39.143
3.0	71.214	60.143	40.821	40.821	61.571	54.821	58.786
4.0	81.607	77.214	52.643	52.643	71.500	78.000	56.464
6.0	95.214	85.714	72.107	72.107	78.214	93.643	66.036
8.0	100.036	90.179	86.714	86.714	95.107	99.893	95.250



Conclusion

In-vitro data obtained for Chitosan mucoadhesive microspheres of Losartan potassium showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results it can be concluded that the drug release from the floating microspheres controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

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