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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF LOSARTAN HYDROGEL BEADS

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Abstract:

Losartan is a potent calcium channel blocker used in the treatment of hypertension. Losartan has shorter half life of 2 hours. The objective of study is to formulate and evaluate the alginate hydrogel beads of Losartan as a model drug by ionic geleation method using $cacl_2$ as cross linking agent. the hydrogel beads were formulated using sodium alginate, HPMC and Carbopol as polymers. The drug is deliver at controlled/sustained manner into GIT consequently to the systemic circulation. the prepared hydrogels were evaluated for particle size, flow properties, entrapment efficiency, swelling index, %yield and in-vitro drug release studies.From the five different formulations, we found that F5 has shown best performance and % drug release and when we compare to other formulations.

Keywords: Hydrogel beads, Ionic geleation, HPMC, Losartan.

Introduction

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluids, resembling biological tissues. Because of this property, great interest was devoted to these systems for biomedical applications. Indeed, the physicochemical properties of the hydrogels can be tuned by varying the cross linking degree (physical and/or chemical), thus making these networks suitable devices for a modulated drug delivery[1].

Three dimensional hydrophilic polymer network of hydrogel beads are capable of retaining large amount of water or bio fluids. Hydrogels are thermodynamically compatible with water and exhibits welling in aqueous media. Hydrogels has resemblance with natural living tissues due to their high water retention capacity. Hydrogels have received much attention not only for controlled release but also for the site specific delivery of drugs[2]. pH sensitive hydrogels protects the drugs that are susceptible to enzyme degradation in upper gastrointestinal tract or acidity of stomach and releases the entire drug in the colon. Hydrogel based drug delivery system increases the biological half life of the drugs. Over the past few decades advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery[3].

Since then, hydrogels have found a wide range of biomedical applications including controlled drug delivery systems, replacement blood vessels, wound dressings, soft tissue substitutions, contact lenses and a variety of other related and potential uses[4].

Hydrogels are generally found to be very well tolerated when implanted in vivo and can be easily tailored to suit the many functions of prosthetics in contact with blood or tissues[5]. The success of hydrogels as biomaterials lies in their resemblance to living tissue because of their relatively high water content which minimizes the frictional irritation of surrounding tissue[6].

Losartan is a potent, highly specific angiotensin receptor antagonist with antihypertensive activity[7].losartan have short biological half life i.e. 1.5 hours, it's useful for the preparation of hydrogel beads and produces the sustained release[8].

The relatively high water content of hydrogels makes them also permeable to small molecules like oxygen, nutrients, and metabolites. This high solute permeability makes them ideal materials of choice as devices for the controlled release of many drugs and other active agents[9,10].

MATERIALS:

Losartan procured from Indian drugs, Hyderabad, Sodium alginate, carbopol and Calcium chloride from SD Fine chemicals, Mumbai. Hydroxy propyl methylcellulose purchased from Ontop pharmaceuticals, Bangalore.

METHOD: Ionic geleation method.

FORMULATION OF SODIUM ALGINATE HYDROGEL BEADS[11]:

Hydrogel beads of losartan were prepared by ionotropic gelation technique. In this present work hydrogel beads were prepared by using sodium alginate and combination with coating polymers like HPMC, Carbopol and calcium chloride used as a cross linking agent.

A solution of sodium alginate was prepared in 100ml of deionized water. In 50ml of sodium alginate solution, weighed quantity of losartan (50mg-batch formula) was dispersed uniformly. Bubble free dispersion was dropped through a syringe with needle into 100 ml aqueous calcium chloride solution and stirred at 500 rpm. After stirring for 30 minutes, the gelled beads were separated by filtration, washed with distilled water and finely dried overnight.

CALIBRATION CURVE[12]:

a).Construction of calibration curve at pH1.2 buffer:

An accurately weighed 100mg Losartan was dissolved in 0.1N HCL (pH1.2 HCL) as per I.P and make up the volume up to 100ml (stock solution I, 1000µ g/ml). From this 10ml of stock solution were pipette out and make up the volume up to 100ml (stock solution II, /100µg/ml). Then the aliquots were prepared, whose concentration ranging from 2-20µg/ml and absorbance was measured at 234nm respectively against the reagent blank.

b).Construction of calibration curve at p^H7.4 phosphate buffer:

An accurately weighed 100 mg of losartan was dissolved in phosphate buffer pH7.4and volume made upto 100ml (Stock solution-1,1000mcg/ml).From this 10 ml solution were pipette out and volume is made upto 100 ml(Stock solution-2,100 mcg/ml).then aliquots are prepared, whose concentration ranging from 2to 20 mcg/ml and the absorbance was measured at 234 nm by using UV spectrophotometry[13].

Beer'sLambert's range: 2 to20 mcg/ml.

EVALUATION PARAMETERS:

Granulometric studies:

Particle size distribution pattern was determined by sieve analysis on mechanical sieve shaker, using different meshes (12, 16, 20 and 30)[14].

Flow properties of Beads:

Angle of repose[15]:

The flow properties of prepared hydrogel beads were investigated by measuring the Angle of Repose by using fixed funnel method. Depend upon these values we can assume the flow properties of the hydrogel beads.

Angle of repose $(\theta) = \tan^{-1}(h/t)$

Drug entrapment efficiency:

The 100 mg equivalent weight hydrogel accurately weighed suspended in 100 ml of pH 7.4 phosphate buffer solution for 24 hours. Then, it was stirred for 15mins and filtered. After suitable dilution, losartan content in the filtrate was analyzed spectrophotometrically at 234 nm using U.V.Spectrophotometer[16]. The encapsulation efficiency was calculated according to the following equation:

$$\text{Percentage encapsulation efficiency} = \frac{\text{Drug content}}{\text{Theoretical drug content}} \times 100$$

Estimation of Drug content:

100 mg of Hydrogel beads were weighed and triturated in mortar using pestle placed in 100 ml volumetric flask and volume was made up to the mark with phosphate buffer (pH 7.4). The resulting mixture was agitated on mechanical shaker for 24 hrs, then solution was filtered and the drug content was estimated at 234 nm spectrophotometrically after suitable dilution[17].

Swellingratio:

Swelling of hydrogels was carried out in triplicate by gravimetric method. Known weight of hydrogels were taken and immersed in pH7.4 phosphate buffer solution at 37^0c.Then the hydrogels were removed at particular interval, wiped with tissue paper to remove excess of solvent and weighed immediately. The difference in weight has given the amount of P^H 7.4 phosphate buffer solution uptake by hydrogel after definite time interval(60 min)[18].

The weights determined were used for plotting the swelling profile.

The percent water uptake (Q) at different time intervals was calculated using the following equation.

$Q=[(W_2 - W_1)/W_1]\times 100$.
Where, W_1 is mass of the dry beads and
W_2 is the mass of swollen beads.

% Yield:
% Yield was calculated using equation given below
% Yield = practical yield / Theoreticalyieldx100

% Practical Yield:
The percentage yield of each formulation was calculated from practical yield using
the following formula

% practical yield =

$$\frac{\text{Weight of hydrogels obtained}}{\text{Weight of drug and polymer initially fed}} \times 100$$

***In-vitro* drug release studies of losartan[19]:**
In-vitro drug release studies of Losartan was performed using USP dissolution test apparatus (paddle method).The USP dissolution apparatus was thermostated at temperature of 37±1oc and stirred at 50 rpm. Each 100mg equivalent hydrogels of every formulation were taken and placed on 900ml of pH 1.2 HCL buffer for 2 hours and in pH 7.4 phosphate buffer for 6 hours. The aliquots of 1ml were withdrawn at time interval of every one hour and filtered and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analysed spectro photometrically at 234nm and finally cumulative amount of drug release at various time intervals was calculated.

RESULTS AND DISCUSSION:
In the present study the formulations are prepared by using different proportions of polymers like HPMC, Carbopol and Sodium alginate.The prepared polymers are evaluated for granulometric studies, flow properties,swelling ratio, entrapment efficiency and Drug content.

Flow properties:
The hydrogel beads are evaluated for angle repose and the results were tabulated.

Drug entrapment efficiency:
Drug entrapment efficiency for all formulations are calculated.Drug entrapment efficiency obtained maximum for F4 and F5 formulation(93%,84.3%).

Drug content:
The less drug content for all formulationF1-F5 found to be 19.24%.drug content obtained was maximum for F4 and F5.

Swelling ratio:
Swelling of hydrogels was carried out in triplicate by gravimetric method. Among all formulations F1 formulation showed maximum swelling index and results are tabulated in **Table no:6**

%YIELD:
%Yield was obtained for F1, F3 and F5 formulations (97.32,96.32,98.25%) respectively. Formulation F5 having the high percentage yield i.e.98.25%.

***INVITRO* DRUG RELEASE STUDIES:**
An *in-vitro* drug release study of losartan was performed using USP dissolution test apparatus (paddle method). The USP dissolution apparatus was thermostated at temperature of 37±1oC and stirred at rate of 50rpm. Each 100mg equivalent hydrogels of every formulation was taken and immersed in 900ml of pH 1.2 HCL buffer for 2 hours and then in pH 7.4 phosphate buffer for 6 hours. The maximum drug release was obtained for F5formulation.

CONCLUSION:
Losartan hydrogel beads were prepared by utilizing the ionic gelation method using the polymers like HPMC and Carbopol with different ratios.
From the 5 different formulations:
F1 having the excellent flow property,
F5 shows the high drug content compared to the other formulations,
F4 shows the high entrapment efficiency,
F5 shows the high %yield compared other formulations,
F5 shows the high % Drug release i.e. 89.2% compared other formulations,
From the five different formulations, we found that F5 has shown best performance from all other formulations, because F5 shows high % drug release and when we compare to other formulations.

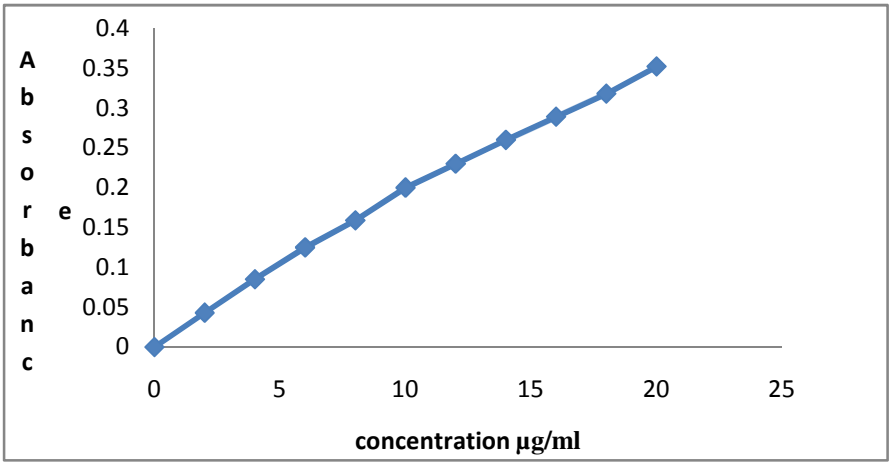
Table no:1 Formulation table.

Formulation code	Drug	Sodium alginate(%w/v)	HPMC (%w/v)	Carbopol (%w/v)	$Cacl_2$ (%w/v)
F1	50mg	1%	2%	-	2%
F2	50mg	1%	-	2%	2%
F3	50mg	1%	0.5%	1.5%	2%
F4	50mg	1%	1.5%	0.5%	2%
F5	50mg	1%	1%	1%	2%

Table no:2 Calibration data of Losartan in pH1.2 buffer solution

S.no	Concentration(mcg/ml)	Absorbance at 234nm
1	0	0
2	2	0.043
3	4	0.085
4	6	0.125
5	8	0.169
6	10	0.2
7	12	0.23
8	14	0.26
9	16	0.289
10	18	0.318
11	20	0.352

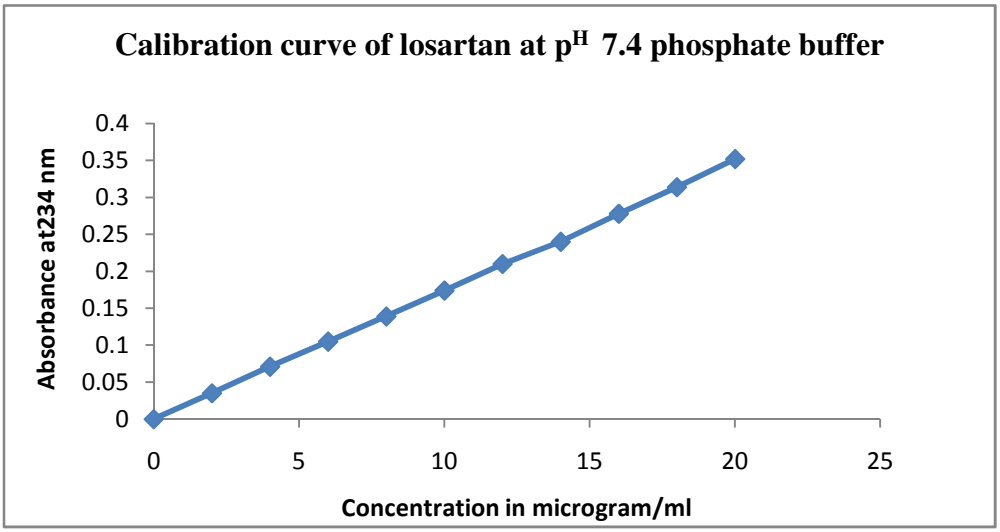
Table no: 2calibration data



Graph:1calibration curve of Losartan at pH 1.2 buffer

Table no: 3 Calibration data

S.NO	CONCENTRATION mcg/ml	ABSORBANCE AT 234 nm
1	0	0
2	2	0.035
3	4	0.071
4	6	0.105
5	8	0.139
6	10	0.174
7	12	0210
8	14	0.24
9	16	0.278
10	18	0.314
11	20	0.352



Graph:2 calibration curve of Losartan at pH 7.4 buffer

Table no:4 Percentage weight remained on various sieve size

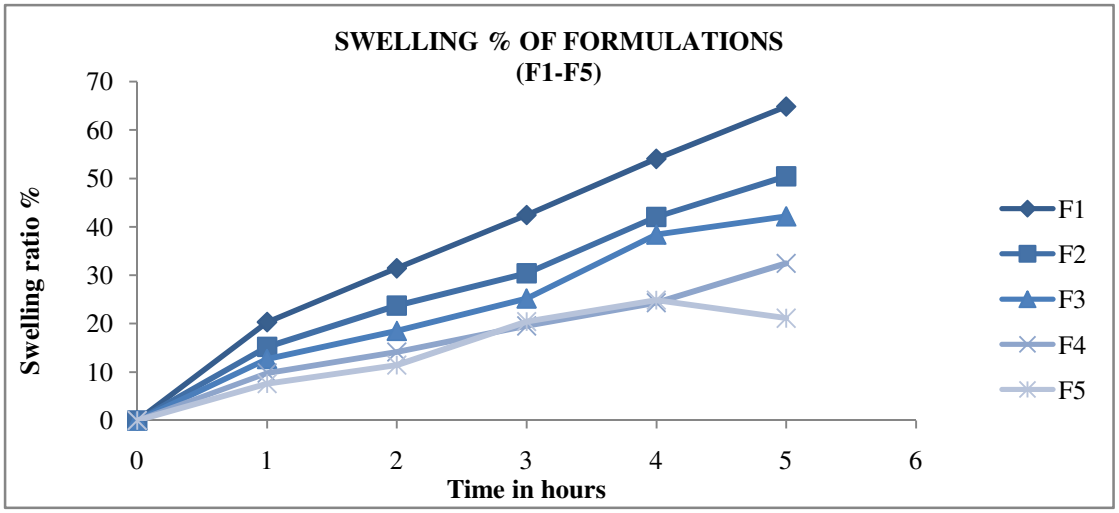
BATCH NO	#12(1.68mm)	#16(1.19)	#20(0.84)	#30(0.59)
F1	14.5	6.2	9.6	4.6
F2	13.6	8.5	7.5	3.5
F3	17.8	8.9	5.8	2.3
F4	23.6	9.4	5.1	1.8
F5	27.8	9.8	4.8	0.85

Table no: 5 Flow properties, % Entrapment Efficiency, Drug Content & Yield for various formulations

S.NO	FORMULATION CODE	ANGLE OF REPOSE	% Entrapment efficiency	Drug content	%yield
1	F1	27	75.6	22.3	97.32
2	F2	30	81	19.4	95.21
3	F3	29	82.7	22.5	96.32
4	F4	32	93	23.7	94.34
5	F5	28	84.4	27.3	98.25

Table no:6

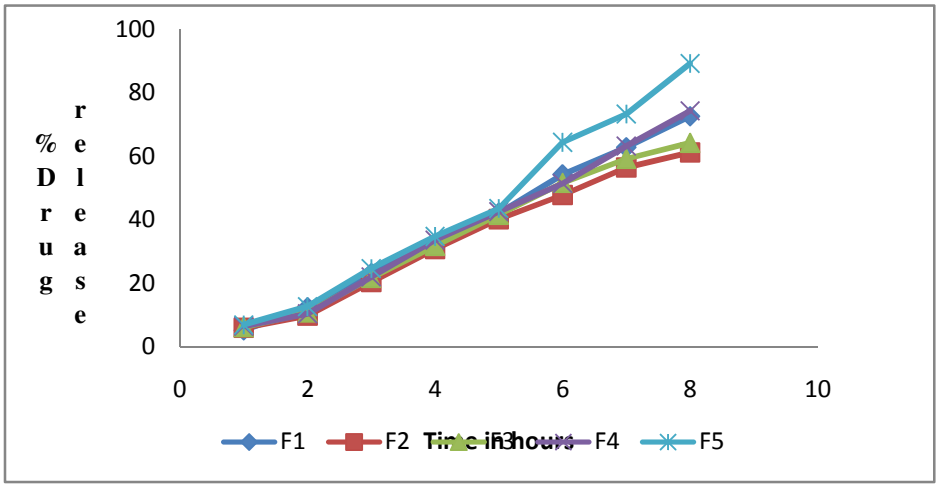
TIME IN HOURS	F1	F2	F3	F4	F5
1	20.3±0.015	15.20±0.25	12.70±0.015	9.8±0.015	7.60±0.25
2	31.42±0.015	23.72±0.25	18.50±0.02	14.12±0.25	11.40±0.25
3	42.40±0.16	30.40±0.015	25.20±0.16	19.52±0.035	20.42±0.16
4	54.00±0.02	42.02±0.02	38.40±0.015	24.23±0.25	24.82±0.25
5	64.8±0.16	50.40±0.015	42.70±0.02	32.42±0.25	29.10±0.25



Graph3:Swelling index

Table no: 7 percentage drug release:

Time in hours	F1	F2	F3	F4	F5
1	5.2	6	6.2	6.5	7
2	12.4	9.8	10.8	10.4	12.7
3	23.2	20.4	21.7	22	24.7
4	32.6	30.8	31.8	33.6	34.8
5	42.2	40.2	41.6	42.6	43.6
6	54.3	47.8	51.6	51.4	64.4
7	62.8	56.5	59.2	63.2	73.3
8	72.6	61.2	64.2	74.3	89.2



Graph no: 4 percentage drug release:

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