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Research Article

Formulation and invitro evaluation of captopril floating microspheres

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ABSTRACT

Captopril is an ACE inhibitor used for the management of essential or renovascular hypertension. The present work is formulation of captopril floating microspheres by using xanthan gum, guar gum and karaya gum. All the formulations were subjected for preformulation evaluation. Results of preformulation studies, FTIR, SEM, particle size and size distribution, % yield, drug content, buoyancy time, entrapment efficiency, in vitro dissolution and release kinetics. The FTIR Spectra revealed that, there was no interaction between polymers and Captopril. On the basis of release data of Captopril formulation F6 showed a good controlled release profile with maximum entrapment efficiency because of optimum drug polymer concentration i.e., 1:1:1 ratio (guar gum+ xanthum gum) with sodium alginate than other drug: polymer ratios. The invitro dissolution data for best formulation F6 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyerpeppas equation. Optimized formulation F6 shows zero order drug release with Super case II transport mechanism.

Keywords: Captopril; ACE Inhibitor; Renovascular Hypertension

INTRODUCTION

The new method is called novel medication delivery systems. Recent developments in the knowledge of drug pharmacokinetic and pharmacodynamic behaviour provide a more logical approach to the creation of an ideal drug delivery system. These carriers, known as new drug delivery systems (NDDS), keep the drug concentration in the therapeutic range for a longer period of time. Novel drug delivery systems have a number of advantages over traditional drug delivery.

1. Optimum therapeutic- drug concentration in the blood or in tissue may be maintained over a prolonged period of time.
2. Pre- determined release rates of extended period of time may be achieved.
3. Duration for short half- life drug may be increased
4. By targeting the site of action, side effects may be eliminated.
5. Frequent dosing and wastage of the drug may be reduced or excluded.
6. Better patient compliance may be ensured.[1]

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Oral Controlled Release Drug Delivery System:
Because the oral route contributes to a bigger active surface area than any other drug delivery mechanism for the delivery of diverse medications, oral drug administration is the most advantageous and acceptable strategy. The oral controlled release delivery system's drug release pattern regulates the level of plasma drug concentration within the therapeutic level at a set rate and duration, leading to continuous therapeutic activity. The importance of these dosage forms is due to the toxicity and ineffectiveness of medications when administered orally using the traditional method un the form of tablets and capsules. Contrarily, the traditional oral drug delivery method has a number of disadvantages, including a larger propensity for plasma drug concentration variations, an increase in dosing frequency, and a shorter period for medication efficacy at the specific site of action, reduced drug availability there as well as restricted oral bioavailability of some medications due to interactions with food, as well as numerous side effects brought on by high dosages of medication. Controlled release oral drug delivery is a strategy that provides continuous drug administration via the mouth at predetermined and repeatable kinetics for a predictable period throughout the digestive tract transit system. It also uses an approach that concentrates the drug on a particular region of the digestive tract for either local or systemic activity. [3].

Advantages of Oral Controlled Release Drug Delivery Systems:
Oral controlled release drug delivery system offer many advantages, such as:

- Approximately constant drug level at the specific site of action
- Protection of peak-trough fluctuations
- Reduction in dose of drug
- Decreased dosage frequency
- Reduced side effects
- Improved patient compliances
- Taste masking
- Enteric prevention[4,5].

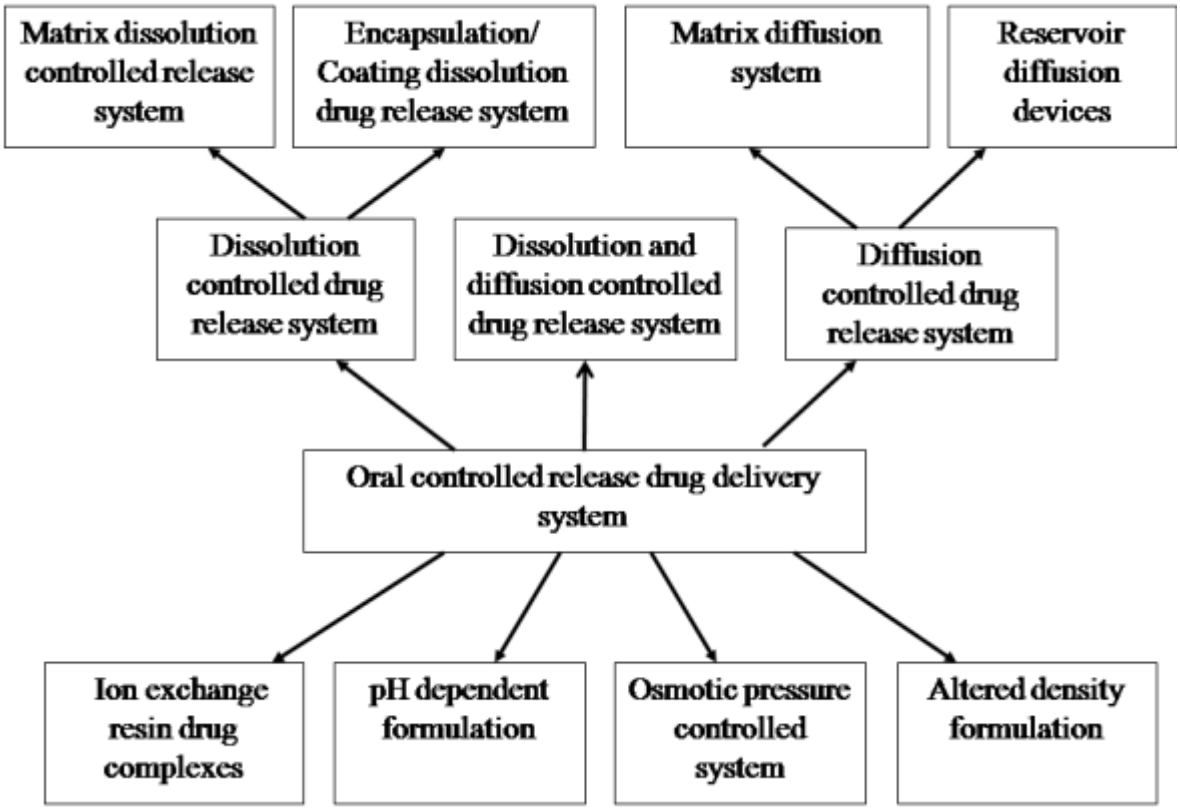


Figure: Approaches of oral controlled release drug delivery system

Gastro retentive delivery systems: A sustained and prolonged input of the medicine to the upper section of the gastrointestinal (GI) tract is made possible by gastro retentive delivery systems, which are intended to be held in the stomach for an extended period of time and release their active ingredients.

Stomach physiology: Understanding the anatomy of the stomach and the related gastric emptying process is crucial to the effectiveness of GRDDS. After the diaphragm, in the upper left portion of the abdominal cavity, is where the stomach is located.[6] The fundus, body, and antrum, or pylorus, are the

three anatomical components that make up the human stomach[7]. After food has been removed from the stomach, only 25–30 cc are left in the stomach. The stomach's antrum serves as the primary location for mixing, and the area formed by the fundus and body is where undigested food is kept. The antrum, which is located at the base of the stomach, serves as a gastric emptying pump by expelling the contents.[8]

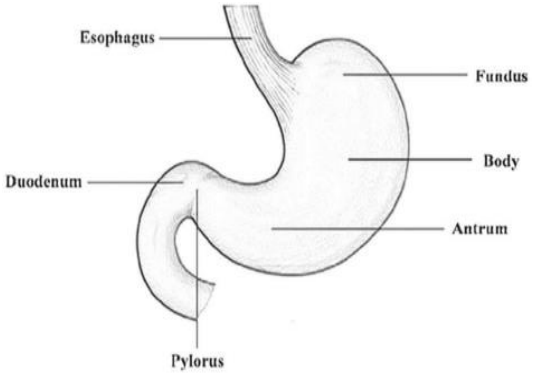


Figure: Human's Stomach

Captopril An ACE inhibitor, captopril is [2S]-1-([2S]-2-methyl-3-sulfanylpropanoyl) pyrrolidine-2-carboxylic acid. It interferes with the rennin-angiotensin system, which prevents angiotensin I from becoming angiotensin II. The medication is seen as a therapy option for congestive heart failure and hypertension. 10 After an oral dose, captopril has an elimination half-life of 2-3 hours and a bioavailability of around 60-75%. It is selectively absorbed from the stomach and is stable at an acidic pH (1.2). The medication becomes unstable and experiences a pseudo-first order degradation reaction as the pH rises.[11,12] The medication is likely to experience stability issues. [13] due to the degradation process in aqueous liquids. Because it is freely soluble in water, the medication experiences dose dumping when it is manufactured as a sustained release form.or well formulated. It is crucial to concentrate the new captopril formulation in the gastrointestinal tract's target region. [14]The current study aims to produce a floating dosage form to remain buoyant in the stomach, increasing gastric residence length, stability, patient compliance, and enhancing the drug's bioavailability through prolonged release in order to solve the aforementioned limitations.

MATERIALS & METHODS

Captopril API was procured from LEE Pharma Pvt Ltd, xanthan gum, guar gum, karaya gum, Hydrochloric acid, Calcium chloride were procured from Lobachemie Pvt. Ltd.

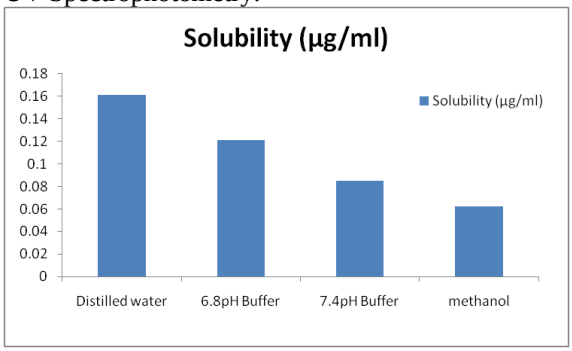
Table: Composition of Captopril floating microspheres

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Captopril	50	50	50	50	50	**50**	50	50
Sodium Alginate	25	25	25	25	25	**25**	25	25
Xanthan gum	50	--	-	25	--	**50**	--	50
Guar gum	--	50	--	25	25	**50**	50	--
Karaya gum	--	--	50	--	25	**--**	50	50
Drug:polymer	1:1	1:1	1:1	1:0.5:0.5	1:0.5:0.5	**1:1:1**	1:1:1	1:1:1
NaHCO3	5	5	5	5	5	5	5	5
Calcium chloride(gm)	1	1	1	1	1	**1**	1	1

EVALUATION STUDIES

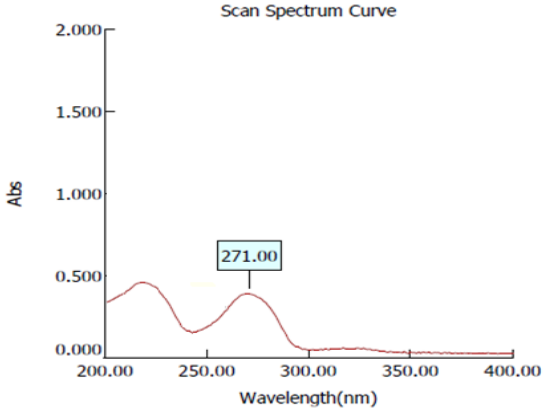
Preformulation studies: Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

Solubility: Solubility of Captopril was determined in water, 0.1 N HCl, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Captopril in different beakers containing different solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 271nm by using UV Spectrophotometry.



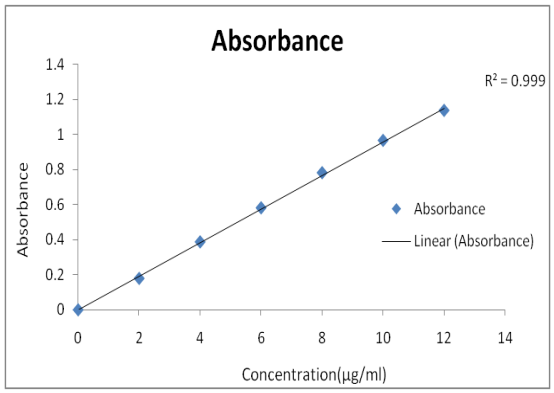
From the solubility studies it was observed that the Captopril have higher solubility in 6.8 pH buffer than the other buffers.

Determination of λ max:
10mg of Captopril was dissolved in 2ml of methanol then make upto10 ml with 6.8 pH phosphate buffer so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10 ml using 6.8 pH phosphate buffer to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10 ml using 6.8 pH phosphate buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.



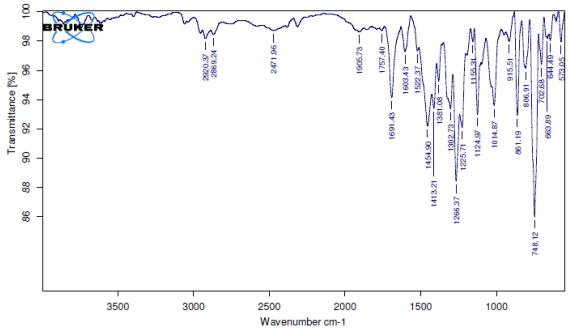
Uv spectrum of captopril

Calibration curveof Captopril in 7.4 pH phosphate buffer: 10mgofCaptoprilwasaccurately weighedandtransferredinto10mlvolumetric flask. It was dissolved and diluted to volume with 7.4 pH phosphate buffer to give stock solution containing1000µg/ml. The standard stock solution was then serially diluted with 6.8 pH phosphate buffer r toget2to12 µg/ml of Captopril. The absorbance of the solution were measured against 6.8 pH phosphate buffer as blank at 271nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

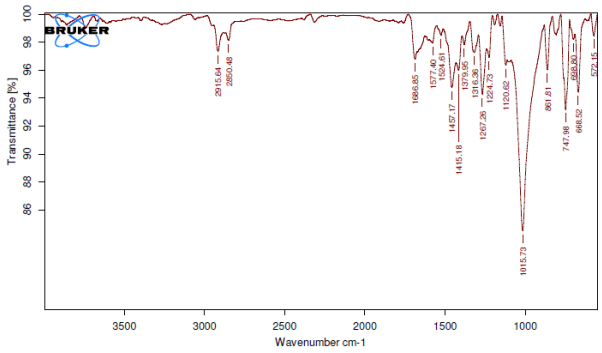


Result: For the developed UV method for estimation of Captopril, the calibration curve data is presented in Table. The linearity range was found to be 2-12µg/ml. Goodness of fit of regression equation was supported by highly significant value of 'r' (0.999).

Drug polymerinteraction (FTIR)study: In the present study FT-IR data of drug and excipient was compared with standard spectrum of pure drug. The characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there is no significant evidence for interaction between the drug and the excipients. The figure shows the IR spectrum of pure Captopril, and captopril + excipients.



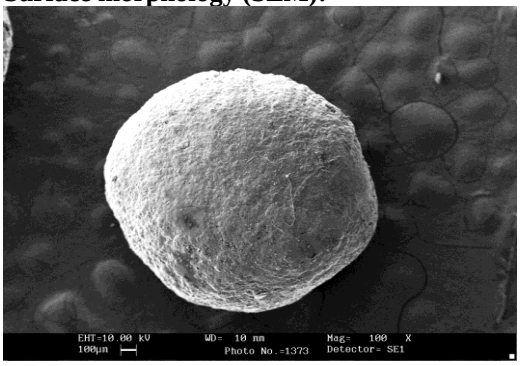
Pure drug



Pure drug+Exciepients

Result: From the Drug & Excipient compatability study it was observed the drug and excipients were compatible.

Surface morphology (SEM):



SEM photographs of floating microspheres using sodium alginate and guar gum

From the results of SEM analysis it was observed that the surface area of Microspheres was spherical and found to be rigid in nature, due to the higher polymer concentration, and the viscosity of the guar gum.

Buoyancy characteristics:

Table.: Buoyancy characteristics of Captopril Floating Microspheres

Sl. No.	Formulation code	Floating duration (hrs)
1	F1	7
2	F2	9
3	F3	10
4	F4	10
5	F5	11
6	F6	12
7	F7	9
8	F8	10

Dissolution parameters :

***In-vitro* dissolution studies:**

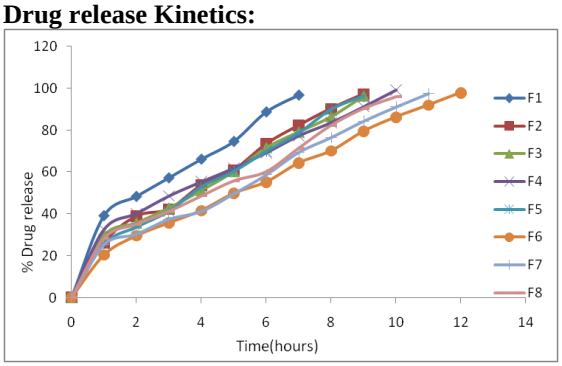
Procedure for In-vitro dissolution study:

The release rate of Captopril Microspheres was determined by employing USP apparatus II (Paddle method). The dissolution test was performed using 900 ml 0.1N HCL, in 37 ±0.5°C at 50 rpm. Captopril microspheres equivalent to 75 mg of Captopril was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 210 nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

***Table. In vitro* release data of Floating Microspheres of Captopril**

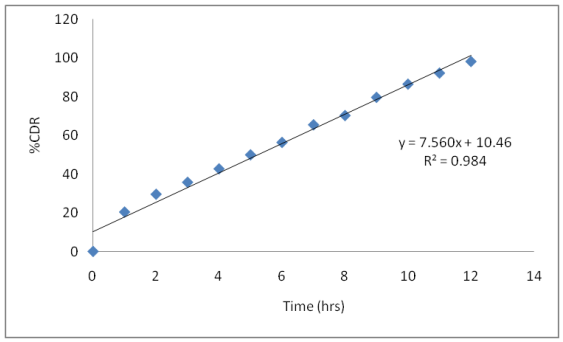
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	**0**	0	0
1	39.16	26.12	29.63	32.52	25.52	**20.34**	25.25	28.26
2	48.36	38.86	35.64	40.16	33.63	**29.52**	30.32	35.11
3	57.24	42.25	42.79	48.52	41.25	**35.68**	37.42	41.25
4	66.16	53.67	51.15	55.37	52.85	**41.63**	41.18	48.61
5	74.63	60.94	60.25	61.85	60.25	**49.85**	49.62	55.85
6	88.75	73.42	71.63	69.25	69.85	**55.25**	58.67	60.27
7	96.78	82.26	79.14	77.36	78.61	**64.35**	69.42	71.53
8		90.34	86.43	83.67	89.85	**70.14**	76.54	82.49
9		97.25	96.34	91.28	96.24	**79.52**	84.35	90.54
10				99.28		**86.34**	91.14	96.14
11						**92.05**	97.54	
12						**98.02**		

Drug release Kinetics:

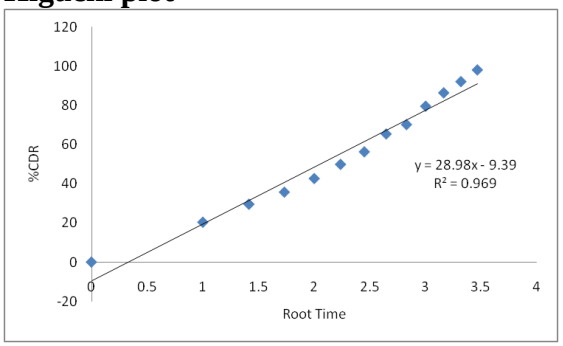


%Cummulative drug release of F1-F8

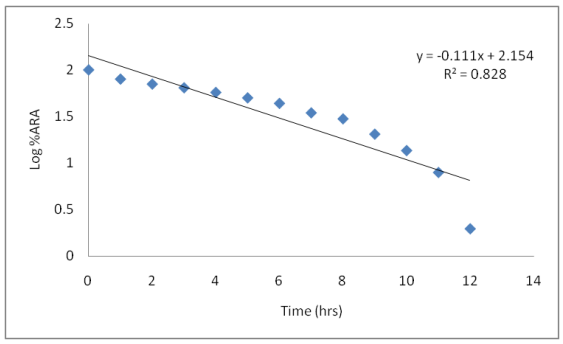
Zero order



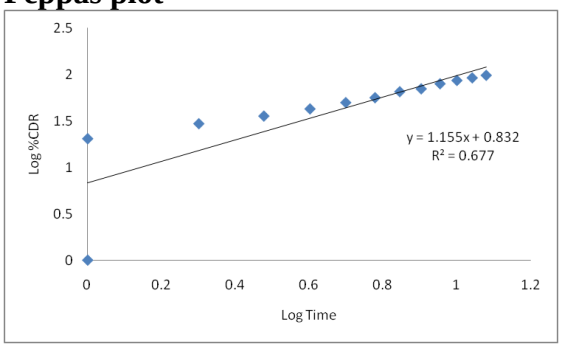
Higuchi plot



First order



Peppas plot



Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	n
F6	0.984	0.828	0.969	0.677	1.155

From the drug release kinetics it was observed the optimized formulation F6 follows first order drug release with non-fickian diffusion mechanism.

CONCLUSION

The *in vitro* performance of captopril Floating micropsheres showed prolonged and controlled release with with guar gum than the Xanthan gum and karaya gum. The invitro dissolution data for best formulation F6 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F6 shows R^2 value 0.984. As its value nearer to the 'captopril' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is captopril. captopril55 for the optimized formulation (F6) i.e., n value was >0.89 this indicates Super case transport. Based upon the preliminary data and in vitro dissolution studies of captopril floating microspheres it was concluded that the formulation of floating micropsheres was successfully formulated by using sodium alginate along with guar gum in captopril:3 ratio.

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