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Formulation and evaluation of captropril microspheres by ionic gelation technique

S. Sahu[1]*, A. Chourasia[2], A. Toppo[3] and A. Asati[2]

1, Department of Pharmaceutical Chemistry, Vedica College of Pharmacy, Bhopal, (M.P.) - India
2, Department of Pharmaceutics, Vedica College of Pharmacy, Bhopal, (M.P.) - India
3, Department of Pharmacognosy, Vedica College of Pharmacy, Bhopal, (M.P.) - India

Abstract

The development of oral sustained or controlled release dosage form of captopril has been an interested topic of research for a long period of time. Difficulties encountered on the fact that the drug is freely water soluble. Such drug is difficult to be delivered orally in a sustained or controlled release manner and, Due to its effectiveness and intensive use as a drug of choice in the treatment of hypertension and congestive heart failure, numerous sustained and controlled release formulations of captopril have been made and reported.Captropril microsphere were prepared with a coat consisting of alginate and polymer such as HPMC,Sodium alginate,Sodiun Carboxy methyl cellulose, by Ionic cross linking technic using $CaCl_2$.

Key-Words: Captopril, HPMC, Sodium alginate, Sodiun Carboxy methyl cellulose, $CaCl_2$

Introduction

Captopril (CAP) is an orally active angiotensen converting enzyme inhibitor. It has proven to have excellent clinical effectiveness in the treatment of essential hypertension and congestive heart failure. However,after single oral dose, the anti-hypertensive action is only effective for 6–8 h. Hence, clinical use requires a daily dose of 37–75mg to be taken three times in divided doses (Nur and Zhang 2000a), development of a controlled delivery system for captopril would be advantageous especially in long-term therapy to maintain relatively constant blood levels for a long period of time. However, the development of oral controlled release formulation for CAP is somewhat difficult (Nur and Zhang 2000a). This could be due to the fact that the drug suffering in vitro and in vivo instability. Besides that the drug is absorbed passively and actively from the GIT. In addition, the drug being water soluble could suffer from dose dumping and burst phenomenon. On the other hand, its bioavailability decreases in the presence of food.

*** Corresponding Author**
E-mail: sandeepsahu17@gmail.com
Mob.: +91-9752701401

Several attempts have been made to formulate sustained release captopril formulations, for example floating tablets and,bioadhesive systems (Nur and Zhang 2000b), sub-lingual tablets (Chetty et al. 2001), biodegradable(Mandal 1998) and non-biodegradable microcapsules (Singh and Robinson 1988).The objective of this study was to formulate sustained release captopril-alginate microspheres using HPMC and Sodium CMC. The effects of polymer molecular weights and polymer ratios on the particle size, flow properties, morphology, surface properties and the release characteristics of the prepared captopril microsphere were examined.

Material and methods

Materials

Captopril powder (CAP), Sodium alginate, Sodium carboxy methyl cellulose, hydroxy propyl methyl cellulose.

Preparation of microsphere

The Microspheres were prepared using an ionic crosslinking technique (Das M.K.et al, 2008).The polymeric solution was prepared by dissolving sodium alginate, HPMC, Sodium CMC, in Distilled water. The drug was dissolved in the polymeric solution .The prepared drug-polymer solution was added drop wise by a 20 gauge hypodermic needle in to 50 ml of 5%w/v of crosslinking agents, being stirred at 200rpm for 10 min . Calcium chloride were used as a cross linking agents. The formed captropril microspheres were

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further allowed to stir in the solution of crosslinking agents for an additional 1 hour .the prepared microsphere was washed with 2-3 times with deionized water. The microsphere was thereafter dried 80^o for 2 hr. prepared microsphere were evaluated by different parameters.

Table 1: Drug/polymer ratio for the formulation

S.No	Ingredients	Quantity (1:1 ratio)
1.	Captropril	2 gm
2.	Sod. alginate	1gm
3.	Sod CMC	500mg
4.	HPMC	500mg

Assay of captropril

Stock solution Captopril was prepared in 0.1 N HCl solutions. The solution resulted is ≈1000 µg/ml. Then 10 ml of this solution is taken and obtain solution of 100 µg/ml served as stock. From this stock solution 10ml was pipette out in 100ml calibrated volumetric flask and dilution was made with 0.1 N HCl and from this serial dilutions were done.

The absorbance was taken on double beam U.V. spectrophotometer using λmax at 203nm.The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Partical size analysis

The partical size of microsphere was determine using optical microscopy method; approximately 100 microsphere were counted for partical size using a calibrated optical microscope (Trivedi et al, 2008)

Micromeritic proprieties

Angle of repose:

Angle of repose of different formulations was measured according to the fixed funnel standing cone method and was given by:

$$\text{Tan}\,\alpha = \frac{H}{R}$$

Where,α is the repose angle, r is the radius and h is the height.

Bulk density and tapped density

The Density was measured by tapping method. The bulk density, and tapped density were calculated using the following formulas

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the powder,V_O = initial volume, V_F = final volume

Compressibility index (Carr's index)

Carr's index calculated as per given formula

$$C.I\ (\%) = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. Hausner Ratio=Tapped density / Bulk Density

In-vitro release studies

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of 0.1N HCl (pH 1.2), phosphate buffer pH 6.8 for 12 hours. The temperature of the dissolution medium was kept at 37± 0.5^{o}C and the basket was set at 50 rpm. 1 ml of sample solution was withdrawn at specified interval of time. The absorbance of the withdrawn samples was measured at λ_{max} 203 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of captopril prepared in distilled water at λ max 203 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Kinetic treatment of release data

The obtained dissolution data were fitted to zero order (Najib and Suleiman 1985), first order (Desai et al. 1966), Higuchi (Higuchi 1963), Korsmeyer-Peppas models to determine the mechanism of CAP release from the prepared microspheres.

Stability studies

The success of an effective formulation was evaluated only through the stability studies. The purpose of stability testing was to obtain a stable product which assures its safety and efficacy up to the end of shelf life. In this study, stability study was done for at conditions like Room temp. (RT), 30ºC & 60 % RH, 40ºC & 75% RH.The samples were assayed for drug content at regular intervals for two weeks.

Results and Discussion

The present study was taken to formulate and evaluate sustained release microspheres of captopril by Ionic cross linking technique. Formulations of microsphere are shown in table 1. When drug and polymer ratio was too low (1:1)

Micromeritic properities of the microspheres

Angle of repose of microspheres was in the range of 38º12′. Shown excellent flow ability as represented in term of angle of repose (<40°). *Bulk density* values ranged from 0.312 to 0.365 gm/cm^3 *Tapped density* was determined by the tapping method. The tapped density values of the microspheres ranged from 0.357to0.400 gm/cm^3 *Carr's index* values of microspheres was found to be 12.60 % *Hausner ratio* of microspheres was found to be 1.14.

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Percentage drug entrapment

The Percentage drug entrapment of microspheres was high for the formulations and was not affected by the type of polymer and drug polymer ratio and stirring speed.

***In Vitro* drug release**

In Vitro dissolution study was carried out using 0.1N HCl (pH 1.2), phosphate buffer pH 6.8 for 12 hours. The Release rate for the formulations was found to be slow. Formulation showed best drug release rate. Results are given in the fig.1 and fig.2

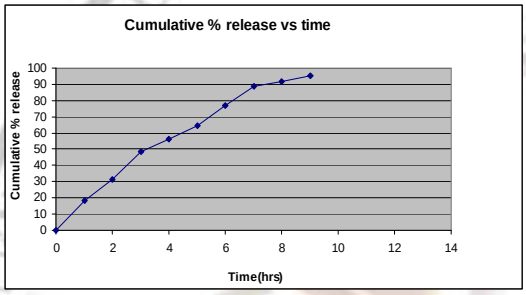

Fig. 1: Cumulative % release Vs time

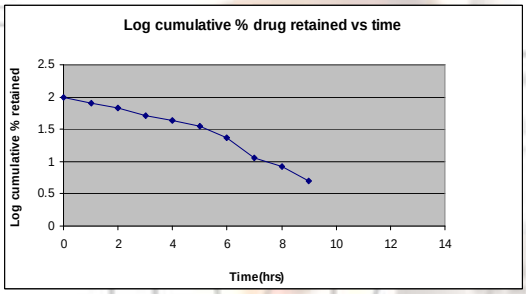

Fig. 2: First order rate kinetics

The sustained release microspheres were successfully developed by Ionic cross linking technique using HPMC, Sodium alginate, Sodiun Carboxy methyl cellulose as a polymer. From this study it is concluded that the drug polymer ratio and stirring speed were important for obtained desired spherical particles. The yield was found to be high in the formulations.

The release rate of captropril from the microspheres was slow depending upon the amount and type of polymers used.

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