DESIGN, DEVLOPMENT AND EVALUATION OF CAPTROPRIL MICROSPHERE BY IONOTROPIC GELATION METHOD

Mr Saurabh Jawahar Sanghavi[1]

[1] *Research Scholar, Pharmaceutical Sciences, Mansarovar Global University, Madhya Pradesh, India*

ABSTRACT

For a considerable amount of time, research has focused on the development of an oral sustained or controlled release dosage form of captopril.difficulties encountered because the medication is readily soluble in water.Due to its effectiveness and widespread use as the drug of choice in the treatment of hypertension and congestive heart failure, numerous sustained and controlled release formulations of captopril have been developed and reported. However, it is difficult to deliver such a drug orally in a sustained or controlled release manner.Captropril microspheres were made by using an ionic cross-linking technique with CaCl2 and a coat of alginate and polymers like HPMC, sodium alginate, and soda carboxymethyl cellulose.

Keyword - *Sodium carboxymethyl cellulose, Captopril, HPMC, Sodium alginate, and CaCl2 etc….*

1. INTRODUCTION

An oral inhibitor of the angiotensin-converting enzyme is captopril (CAP).In the treatment of essential hypertension and congestive heart failure, it has demonstrated excellent clinical efficacy.The development of a controlled delivery system for captopril would be advantageous, particularly in long-term therapy, to maintain relatively constant blood levels for a long period of time.

However, the antihypertensive action is only effective for 6–8 h after a single oral dose. As a result, clinical use requires a daily dose of 37–75mg to be taken three times in divided doses (Nur and Zhang, 2000a). However, it is challenging to develop an oral controlled release formulation for CAP (Nur and Zhang, 2000a).This could be because the drug is unstable in both in vitro and in vivo.In addition, both passive and active absorption of the drug occurs in the GIT. Due to the drug's water-soluble nature, dose dumping and burst phenomena may also occur. On the other hand, when food is present, its bioavailability decreases.

The reference number should be shown in square bracket [1]. However the authors name can be used along with the reference number in the running text. The order of reference in the running text should match with the list of references at the end of the paper.

Floating tablets, bioadhesive systems (Nur and Zhang, 2000b), and sublingual tablets (Chetty et al.) are among the formulations of sustained release captopril that have been attempted.2001), biodegradable (Mandal 1998), and non-biodegradable (Singh and Robinson, 1988) microcapsules.

The creation of sustained release captopril-alginate microspheres with HPMC and Sodium CMC was the goal of this study. The prepared captopril microsphere's particle size, flow properties, morphology, surface properties, and release characteristics were examined in relation to polymer molecular weights and polymer ratios.

2. MATERIAL AND METHODS

2.1 Materials

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

2.2 Preparation of microsphere

The polymeric solution was made by dissolving sodium alginate, HPMC, and Sodium CMC in distilled water. An ionic crosslinking method was used to make the microspheres (Das M.K. et al., 2008).The drug was dissolved in the polymeric solution. A 20-gauge hypodermic needle was used to drop the prepared drug-polymer solution into 50 milliliters of 5% w/v crosslinking agents and stir it for 10 minutes at 200 rpm. Cross-linking agents included calcium chloride. After being stirred in the crosslinking agent solution for an additional one hour, the captropril microspheres were washed three to four times with deionized water.After that, the microsphere was dried for two hours at 80°C.Different parameters were used to evaluate the prepared microspheres.

S.No	Ingredients	Batches			
		F1	F2	F3	F4
1.	Captropril	15mg	15mg	15mg	15mg
2.	Sodium alginate	5gm	5gm	5gm	5gm
3.	$Cacl_2$	2mg	2gm	2mg	2gm
4.	HPMC	10mg	20mg	30mg	40mg

Table 1: Drug/polymer ratio for the formulation

2.3 Assay of captropril

Captopril was prepared as a stock solution in 0.1 N HCl solutions.The resulting solution contains 1000 g/ml.After that, 10 milliliters of this solution are taken, and a stock solution of 100 g/ml is obtained.10 milliliters of this stock solution were pipetted into a 100 milliliter calibrated volumetric flask, diluted with 0.1 N HCl, and subsequent dilutions were performed.Using max at 203 nm, the absorbance was measured with a double beam ultraviolet spectrophotometer.The standard calibration curve was created by plotting the absorbance values against the concentration (g/ml).

2.4 Partical size analysis

Using optical microscopy, the microsphere's partical size was determined;Using a calibrated optical microscope, approximately 100 microspheres were counted for partical size (Trivedi et al., 2008).

2.5 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:

$\tan \alpha = \frac{H}{R}$

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

Bulk density = W / V_o 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± 0.5oC 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 λmax 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

According to Najib and Suleiman (1985), the obtained dissolution data were fitted to zero order and first order, respectively.1966), Higuchi (Higuchi, 1963), and Korsmeyer-Peppas models to figure out how the prepared microspheres release CAP.

Stability studies

The stability tests were the only way to determine whether or not a formulation was successful.The goal of stability testing was to produce a product that remained stable throughout its shelf life, ensuring its safety and effectiveness.At temperatures like Room temp., a stability study was conducted in this study.RT), 30°C at 60% relative humidity (RH), and 40°C at 75% RH for two weeks. The samples were tested for drug content on a regular basis.

3. RESULTS

Captopril sustained release microspheres were developed and evaluated using the ionic cross linking method in this study.Table 1 displays microsphere formulations. when the ratio of polymer to drug was too low (1:1)

3.1 Micromeritic properities of the microspheres

The microspheres' angle of repose ranged from 38 to 12 degrees, indicating excellent flow ability in terms of angle of repose (40 degrees).The tapping method was used to determine the tapped density, which ranged from

0.312 to 0.365 gm/cm3. The tapped density of the microspheres ranged from 0.357 to 0.400 gm/cm3. The microspheres had a Carr's index of 12.60 percent and a Hausner ratio of 1.14

3.2 Percentage drug entrapment

The ratio of drug polymer to polymer type and stirring speed had no effect on the formulations' high percentage of drug entrapment in microspheres.

Formulation code	CMC (%)	HPMC (%)	Mean particle size (µm)	Amount of polymer (mg)	Amount of CMC (mg)	Amount of HPMC (mg)
F1	71.5±1.5	82.64±0.93	641.24±2.432	1219.2	300	4.3
F2	73.45±1.25	86.789±0.986	675.64±2.565	1219.2	400	6.4
F3	76.534±3.67	83.468±1.32	689.71±1.281	1219.2	600	9.6
F4	78.667±2.45	82.862±1.75	730.55±1.582	1219.2	1200	19.2

Table 2: Formulation, drug entrapments and mean particle size of microspheres

Formulation (Drug:Polymer)	Zero-Order		First-Order		Higuchi Model		Korsenmeyer Peppas Model	
CMC	r^2	Ko	r^2	K1	r^2	Kh	r^2	n
1.1	0.7406	6.9769	0.9707	0.104	0.9842	26.287	0.9907	0.2506
1.2	0.7908	5.5131	0.9687	0.068	0.9523	23.334	0.9926	0.2798
1.3	0.8461	4.4599	0.955	0.037	0.9782	18.44	0.9902	0.2334
HPMC	r^2	Ko	r^2	K1	r^2	Kh	r^2	n
1.1	0.767	9.5228	0.9579	0.213	0.9525	33.335	0.9811	0.4225
1.2	0.7951	6.8991	0.9873	0.131	0.9879	27.889	0.9919	0.4447
1.3	0.8671	4.8203	0.9636	0.043	0.9763	19.903	0.9973	0.3037

Table 3: Correlation coefficient (r2), Constant (K) and Diffusion exponent (n) after fitting of dissolution data into various release kinetic models

3.3 In Vitro drug release

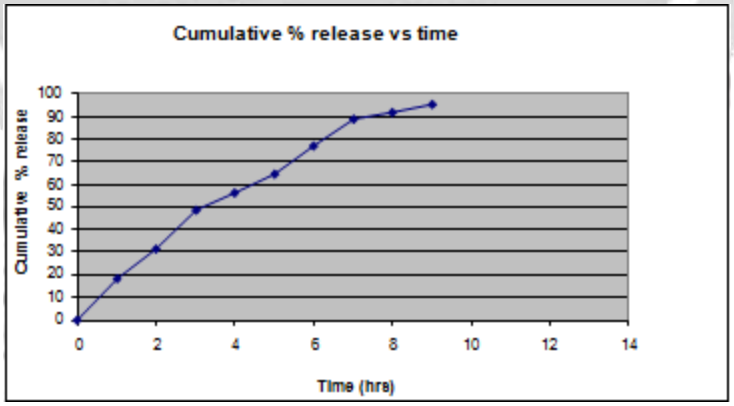

Fig-1 Cumulative % release Vs time

A 12-hour in vitro dissolution study was conducted with phosphate buffer pH 6.8 and 0.1N HCl (pH 1.2).It was discovered that the formulations had a slow release rate.The formula had the highest rate of drug release.Using HPMC, sodium alginate, and sodaun carboxymethyl cellulose as a polymer, the ionic cross-linking method was used to successfully create the sustained release microspheres. According to the findings of this study, the drug-to-polymer ratio and stirring speed were crucial for producing the spherical particles that were desired. The

formulations were found to have a high yield. Depending on the quantity and type of polymers used, captropril released slowly from the microspheres.

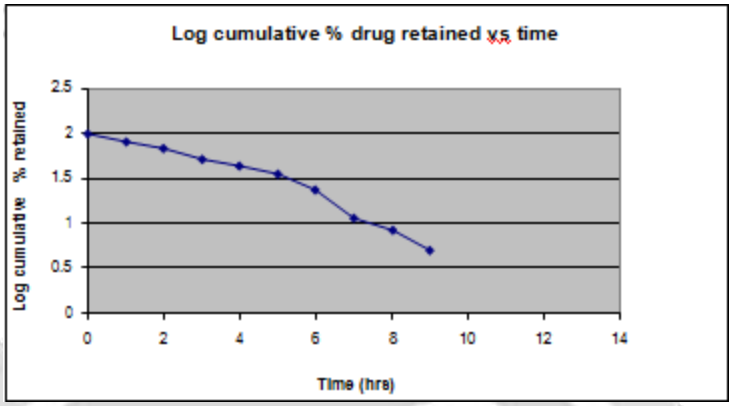

Fig-2 First order rate kinetics

4. CONCLUSIONS

In this study, the morphology, buoyancy, and release of a novel floating system of oil-entrapped alginate microspheres were investigated. The system was designed and prepared using an emulsion-gelation technique.With more oil phase, the average diameter of microspheres increased.Depending on the oil's relative density, the oil-entrapped alginate microspheres displayed excellent, immediate, and sustained buoyancy in the acidic gastric fluid (pH 1.2) environment.Due to its sustained drug release and complete set of physicochemical properties, formu lation F3 was chosen as the most optimal from the results.

The Korsemeyer-Peppas model predicted higher values from the in vitro release data, indicating that the release was non-Fickian diffusion (anomalous transport) with an n value between 0.5 and 1.Oil-entrapped alginate microspheres are an excellent option for an intragastric floating drug delivery system due to their enhanced buoyancy.By slowing down gastric emptying, this property will be useful for drug delivery systems with gastro-retention.A controlled release dosage form's long-lasting intragastric buoyancy may also make it possible to deliver drugs that are locally active to the stomach's gastric mucosa and maintain a site-specific therapeutic effect. As a result, the oil entrapment technique represents a novel approach to the creation of a multiparticulate system for the sustained delivery of drugs.

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