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A SUSTAINED RELEASE APPROACH TO CAPTOPRIL THROUGH MICROENCAPSULATION USING DIFFERENT TECHNIQUES.

Manivannan R[1*] and Jayalakshmi R[2]

[1] Excel College of Pharmacy, Pallakkapalayam, Namakkal – 637303, Tamilnadu, India.
[2] Research Scholar, Faculty of Pharmacy, Pacific academy of higher Education and Research University, Udaipur, Rajasthan, India.

ABSTRACT

The present study concerns the development of a new dosage form of captopril using the concepts of sustained release and mucoadhesion. Such a system has the advantage of controlling and prolonging the release of the drug by remaining in the stomach for a longer period of time. In the present study microspheres of captopril were prepared using a combination of polymers and different methods. The drug, captopril is selected owing to its water solubility and short half-life. A set of microspheres of captopril were prepared using a mixture of polymers, chitosan and HPMC using the technique of phase separation emulsion technique. Another set of microspheres was prepared with a combination of polymers such as chitosan, sodium alginate and HPMC. The method of preparation was ionic gelation. The prepared microspheres were then evaluated for drug content, particle size analysis, in-vitro drug release, mucoadhesion and stability studies. The SEM studies showed that the prepared microspheres were discrete and spherical in shape. The drug content of the first set of microspheres ranged between 70.3 and 77.4% and that of the second set of microspheres was between 73.6 and 79.6%. The formulations were studied for mucoadhesion and all the formulations showed good mucoadhesion. The drug release pattern for the formulations was slow and prolonged over a period of time.

Key Words: - Captopril, Controlled Release, Ionic Gelation, Microcapsules, Mucoadhesion And Oral Drug Delivery Systems, Sodium Alginate, HPMC and Chitosan.

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Corresponding Author

Dr. R Manivannan
Excel College of Pharmacy, Pallakkapalayam, Namakkal – 637303, Tamilnadu, India.

Email:- manivannanbiotech@gmail.com

INTRODUCTION

Microencapsulation has gained much importance as a process to achieve sustained release of a drug and the technique also helps in achieving drug targeting. Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules, of many useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale (Bansode SS *et al*., 2010).

Mucoadhesion is a topic that has been widely discussed in designing a system that can prolong the residence time of the dosage form at the site of absorption and improve and enhance the bioavailability of drug (Mathiowits E *et al*., 1999). This study concerns the formulation and evaluation of microparticles of captopril employing various mucoadhesive polymers designed for oral controlled release (Garima Chawla *et al*., 2004). Captopril has been widely used as a drug of choice in the treatment of hypertension and congestive heart failure. Captopril (CAP) is an orally active angiotensin converting enzyme inhibitor. After the oral dose, the anti-hypertensive action is only effective for 6–8 h. Therefore, it requires a daily dose of 37–75mg to be taken three times in divided doses. 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. The elimination half-life of captopril is 2hours(www.drugs.com). Based on the above reasons there is a clear need to develop a suitable formulation of captopril that enhances the bioavailability of the drug. The polymers used in the study were chitosan, Sodium alginate and HPMC (Lis Brannon-Peppas,1997).

MATERIALS AND METHODS

Materials

Captopril was obtained as a gift sample from Wock hardt Laboratories Ltd., India. Chitosan was gifted by Cochin Fisheries, India. HPMC was supplied by Kemphasole, India. Sodium alginate was obtained from Lobachemie, India. Calcium chloride was obtained from Ranbaxy, India. All polymers and solvents used were of pharmaceutical or analytical grade.

Preparation of microspheres

Microspheres using chitosan and HPMC (phase separation emulsion)

Weighed quantity of HPMC was dissolved in water. To this solution, was added a weighed quantity of chitosan. The solution was then subjected to constant stirring for about 2 hours until a gel was formed. The process was favored by adding a few drops of acetic acid. An accurately weighed quantity of the drug, captopril was added to the gel and continuously stirred to get a uniform distribution of the drug in the gel. The resultant gel was then added drop wise into a dispersion medium containing liquid paraffin and petroleum ether. The resulting dispersion was stirred using a Remi stirrer at 1000 rpm for 15 minutes. For the cross-linking purpose was added a milliliter of glutaraldehyde saturated with toluene. The solution was again stirred for I hr. The formed microspheres were filtered using a Whatman filter paper. The filtered microspheres were then washed thoroughly with water to remove the traces of solvent and dried at room temperature (Harish Gopinath *et al*., 2013). The procedure was repeated with different drug: polymer ratios 1:1,1:1.5 ,1:2 and 1:2.5.

Microspheres using chitosan, sodium alginate and HPMC

An accurately weighed quantity of chitosan was added to water and stirred continuously to form a gel. The process was facilitated by adding a small amount of acetic acid. A weighed amount of sodium alginate was added into the gel and continuously stirred to get a uniform gel. This is followed by adding a measured amount of HPMC and the mixture was stirred vigorously. Into the gel, was added a measured amount of the drug, captopril with continuous and vigorous stirring to get a uniform distribution. The prepared drug-polymer solution was extruded by a 20-gauge hypodermic needle into 50 ml of 5%w/v of cross linking agents, which was then stirred at 200rpm for 10min. Calcium chloride was used as a cross linking agents. The formed microspheres were filtered using a Whatman filter paper. The collected microparticles were washed with water to remove any traces of solvents and dried at 70 °C. (Sahu S *et al*., 2012). The procedure was repeated with different drug: polymer ratios 1:1,1:1.5 ,1:2 and 1:2.5.

Based on the above procedures, different formulations were developed and is given in Table 1.

Standard Graph of Captopril

10mg of drug was dissolved in 10ml of 0.1N Hydrochloric acid. From this stock solution, different dilutions were prepared in the range of 5,10,15,20 and 25µg/ml. 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. Correlation coefficient=0.9999.

Microencapsulation Efficiency

An accurately weighed 20 mg of the microcapsules was stirred in a suitable extracting solution, Sodium Citrate (1% w/v) using a magnetic stirrer for about 30 minutes until complete dissolution occurs. One milliliter of methanol was added to sodium citrate solution to further solubilize captopril. This solution was then filtered through a 5 µm membrane filter to obtain drug solution. The filtrate was suitably diluted with 0.1N HCl and absorbance of the solution was taken at 203 nm. The standard graph is used to determine the amount of the drug in the prepared microparticles. Microencapsulation efficiency is the ratio of estimated percentage of drug content to the theoretical percentage of drug content into 100(Venkata Naga Jyothi *et al*.,2010).

Particle size analysis

The diameter of 200 microcapsules was determined using calibrated eyepiece micrometer and stage micrometer. The average diameter was calculated using the following formula

$$\text{Average diameter} = \frac{\Sigma n d}{n} \times C.F$$

Where, n = number of microcapsules, d = diameter of the microcapsules and C.F = calibration factors

Micromeritic properties

Angle of repose was calculated using the formula,

$$\text{Tan } \Theta = h / r$$

Where, Θ = repose angle
r = radius and
h = height.

Bulk density and tapped density were calculated using the following formulas
Bulk density = W / Vo
Tapped density = W / VF
Where, W = weight of the powder, VO = initial volume, VF = final volume

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's Ratio=Tapped density / Bulk Density
Porosity is the fraction or percent of void space in the microcapsules and can greatly affect its properties (Devesh Kapoor *et al*., 2012).

***In- vitro* release studies**

The *in-vitro* dissolution study was carried out using USP XXIV basket-type dissolution apparatus using 900ml of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C as the dissolution medium at a rotation speed of 100 rpm. 5 ml of sample was withdrawn at each 1-hour interval and analyzed spectrophotometrically at 203 nm using a UV visible spectrophotometer and the concentration of the drug in the sample was determined from the standard graph. The dissolution study was continued for 8 hours. The *in vitro* profile was obtained by plotting the percentage release versus time in hours (Sivakumar HG *et al*., 2004).

***In- vitro* test for mucoadhesion**

The test is done to evaluate the time the beads take to detach from a piece of sheep stomach mucosa.). The test is known as an *in vitro* adhesion testing method or wash off method. The beads (200 no) were counted and spread over the wet rinsed tissue specimen of sheep stomach mucosa and immediately thereafter the support was hung on the arm of a USP tablet disintegrating test machine. 0.1N hydrochloric acid (pH 1.2) was used as the medium. By operating the disintegration machine, the tissue specimen was given a slow regular up and down movement. The slides move up and down in the test fluid at 37 ± 0.50 C. The number of beads adhering to the tissue was counted at 2-hour intervals up to 10 hours (Sandra Kokisch *et al*., 2003).

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. ICH guidelines were followed in conducting the stability study of the prepared Captopril microspheres. In this study, stability study was done for at conditions like Room temp. (RT), oven temperature and temperature in refrigerator. The test was carried out for 60 days. The drug solution was further scanned to observe any possible spectral changes.

RESULT AND DISCUSSION

Microspheres of captopril was prepared using a mixture of polymers such as chitosan and HPMC by phase separation emulsion method. Another set of microspheres of captopril was prepared with a mixture of polymers, chitosan, sodium alginate and HPMC using the technique of ionic gelation. The formulations are shown in Table 1.

Microencapsulation Efficiency

The formulations of captopril with Chitosan and HPMC showed a percentage incorporation efficiency ranging from 70.3 to 77.4%. Among the four formulations prepared, H4 shows the maximum drug content,77.4%. The formulations of captopril with chitosan, sodium alginate and HPMC showed a percentage incorporation efficiency ranging from 73.6 to 79.6%. Out of the four formulations, CSH4 showed the maximum drug content,79.6%.

Particle size distribution

All the formulations of captopril were subjected to particle size distribution study by microscopic method. The formulation, H1 had an arithmetic mean particle size of 261.9 µm whereas that of H2 was 269.33 µm. H3 had an arithmetic mean of 275.737 µm. H4 showed an arithmetic mean particle size of 278.437 µm. The arithmetic mean particle size of the formulation, CSH1 was calculated and found to be 265.95 µm. CSH2 was found to have an arithmetic mean particle size of 270.33 µm. CSH3 was found to have an arithmetic mean particle size of 276.07µm. The arithmetic mean particle size of CSH4 was 280.12 µm.

Micromeritic Properties

The formulations of captopril with chitosan and HPMC showed good micromeritic properties. Bulk density of the formulations was in the range of 1.227 to 1.072. True density lied between 1.435 and 1.199. Porosity was ranging between 14.60 and 6.14. Angle of repose was in the range of 23.7 and 29.87. Hausner's ratio varied between 1.17 and 1.065. The formulations of captopril with chitosan, sodium alginate and HPMC showed good micromeritic properties. The bulk density of the formulations ranged from 1.21 to 1.05. Porosity ranged from 14.98 to 7.01. The formulations had good angle of repose varying from 23.98 to 29.13. The Hausner's ratio was between 1.18 and 1.08(Leon Lachman *et al*., 1990).

***In Vitro* drug release**

In Vitro dissolution study was carried out using 0.1NHCl (pH 1.2) for 8 hours. The rate of release of the drug was slow and extended over a period of time. The results are given in the figures.

***In-vitro* test for mucoadhesion**

The time taken for detachment of beads from

sheep stomach mucosa was measured in 0.1N hydrochloric acid (pH 1.2). Formulations H1 and H2, H3 and H4 exhibited a poor mucoadhesion. H4 showed a better strength with 3 beads adhered to the mucosa after 8 hours and 1 after 12 hours. The formulations CSH1, CSH2, CSH3 and CSH4 had excellent mucoadhesive property. For the formulations CSH4, 9 beads were adhered to the mucosa after 8 hours and 5 beads after 10 hours.

Stability studies

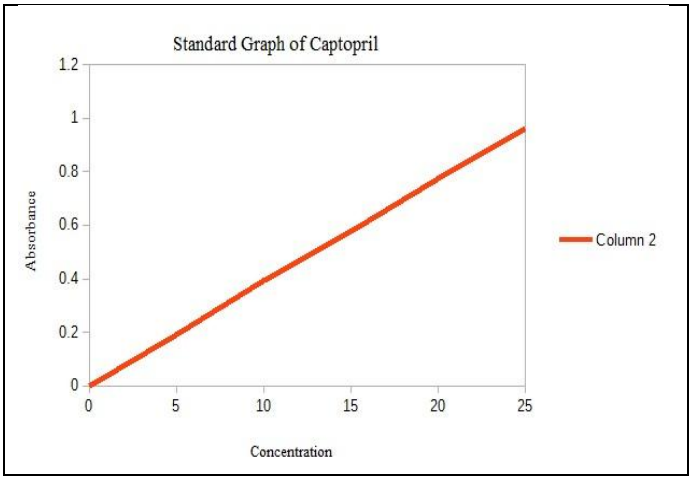
From the evaluations, formulation CSH4 was chosen as a better one and stability study was carried out for this formulation. The formulation was found to be stable when stored at the temperatures as specified by ICH

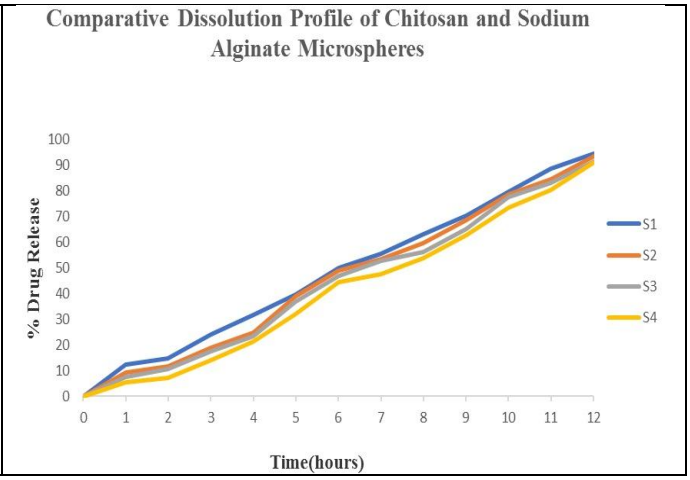
Table 1. Polymer, Formulation code and Drug: polymer Ratios

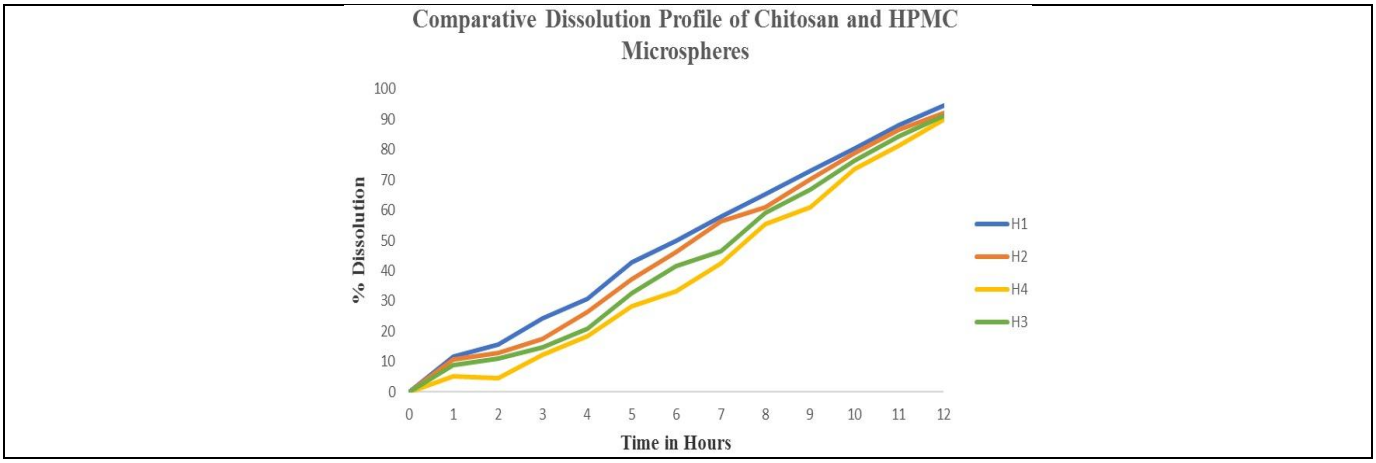
Polymer	Formulation Code	Drug: Polymer
Chitosan+ HPMC	H1	1:1
	H2	1:1.5
	H3	1:2
	H4	1:2.5
Chitosan+ Sodium alginate+ HPMC	CSH1	1:1
	CSH2	1:1.5
	CSH3	1:2
	CSH4	1:2.5

Table 2. Drug Content and Micromeritic Properties of The Formulations

Formulation	Drug content (%)	Arithmetic mean particle size	Bulk density	True density	Porosity	Angle of repose	Hausner's ratio
H1	70.3	261.90	1.22	1.43	14.60	23.7	1.17
H2	72.7	269.33	1.20	1.37	9.48	25.87	1.05
H3	75.9	275.737	1.18	1.25	7.81	27.62	1.08
H4	77.4	278.437	1.07	1.19	6.14	29.87	1.06
CSH1	73.6	265.95	1.21	1.42	14.98	23.98	1.18
CSH2	76.8	270.337	1.19	1.35	9.82	22.87	1.10
CSH3	77.5	276.07	1.17	1.12	6.72	26.8	1.07
CSH4	79.6	280.12	1.05	1.08	7.01	29.13	1.08







CONCLUSION

The microspheres of captopril were prepared with different combination of polymers such chitosan and HPMC and chitosan, sodium alginate and HPMC. Formulation CSH4 was found to be an ideal formulation. The microparticles were found to have a good spherical shape and were non-aggregated and exhibited good flow properties. The drug content of the formulations was in good range. The drug release from the formulation was very slow and steady and extended over a period. This helps to reduce the dosing frequency and thereby helps to increase patient compliance. It is obvious and hence concluded from the above work that the study has engineered a drug delivery profile where the drug delivery can be sustained and extended over a period which helps to increase patient compliance and reduce untoward side effects.

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