Leading Article

GASTRIC- MUCOADHESIVE DRUG DELIVERY SYSTEMS OF CAPTOPRIL

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ABSTRACT

A new oral drug delivery system was developed utilizing both the concepts ofcontrolled release and mucoadhesiveness, in order to obtain a unique drug delivery system which could remain in stomach and control the drug release for longer period of time. Gastro-retentive beads of captopril were prepared by orifice ionicgelation method in 1:1 and 9:1 ratio of alginate along with mucoadhesive polymers viz; hydroxyl propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate. The prepared beads were subjected for various evaluation parameters. The percentage drug content was found to be in the range of 59.4 - 91.9 percent forbeads. It was observed that as the alginate proportion was increased, the average size of beads also increased. Photomicrographs revealed that the beads were spherical in shape. Alginate-chitosan (9:1) beads showed excellent microencapsulation efficiency (89.7 percent). Alginate-Carbopol 934P exhibited maximum efficiency of mucoadhesion in 0.1 N HCl (44 percent for 1:1 and 22 percent for 9:1) at the end of 8 hours, whereas least mucoadhesion was observed with alginate-Cellulose acetate phthalate beads. The *in vitro* release studies were carried out in 0.1 N hydrochloric acid and the release were found to be more sustained with Alginate-chitosan beads (9:1) than Alginate-Carbopol 934P (1:1) beads. The alginate-cellulose acetate phthalate beads showed the better sustained release as compared to all other alginate-polymer combinations. Regression analysis showed that the release followed zero order kinetics in 0.1 N HCl (pH 1.2).

Key words: Captopril, controlled release, orifice gelation, beads, mucoadhesion, oral drugdelivery systems, sodium alginate.

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INTRODUCTION

Mucoadhesive is a topic of current interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate

contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drug (Mathiowitz et al., 1999). Microparticulate delivery system includes many pellets, beads, microcapsules, microspheres, lipospheres etc. Generally these micro particulate delivery systems are intended for oral and topical use (Benita S. 1996). This study describes the formulation and evaluation of gastric-mucoadhesive beads of captopril employing various mucoadhesive polymers designed for oral controlled release. Beads are the matrix system containing drug throughout the structure is potential candidates for oral controlled release. The various substances (polymers) used as carriers in microspheres are human serum albumin, bovine, egg albumin, gelatin, waxes, chitosan, sodium alginate, ethyl cellulose etc. Different types of coated particles can be obtained depending on the coating process used. The particles can be embedded within a polymeric or proteinic matrix network in either a solid aggregated state or a molecular dispersion resulting in the formation of microspheres (Abubakr et al., 2003). The ultimate objective of microparticulate delivery system is to control and extend the release of the active ingredient from the coated particles without attempting to modify the normal biofate of the active molecules in the body after administration and absorption.

Captopril is an orally active inhibitor of angiotensin converting enzyme and it is widely used in the treatment of hypertension and congestive cardiac failure. The bioavailability of captopril is approximately 65 % have relatively short half-life of 3 hours and requires frequent administration of dose 25 – 50 mg, 2-3 times daily (Oates 1996). Hence it is necessary to develop sustained release formulation to overcome this draw back. Studies showed that, prolonged inhibition of ACE activity of captopril could be achieved by control release dosage form, using oily matrix formulation filled in gelatin capsules (Mandal et al., 1998). Because of oily vehicles gastric emptying time was delayed and decreased GI motility, thereby retaining the drug for longer period of time at the site of absorption. Captopril is freely water soluble drug and has site specific absorption from GIT and on other hand, the drug is unstable in the alkaline pH of the intestine, where as stable in acidic pH and specifically absorbed from stomach. Based on the above reasons there is a clear need to localize the developed formulation at the target area of the GIT Preparation of mucoadhesive systems of captopril will permit localization of the drug to GI mucosal membrane for a prolonged period of time, due to mucoadhesion. Bioavailability of drug is increased, which leads to significant reduction in the dose and frequency of administration. Controlling the placement of a drug delivery system in a particular region of the GI tract often improves absorption of those drugs. Furthermore, it would be desirable to achieve a longer transit time, especially in the upper part of the GI tract, in order to maximize drug absorption and thus enhance the therapeutic effect (Singh and Robinson, 1988).The purpose of present investigation is to develop calcium-alginate mucoadhesive beads with different mucoadhesive polymers like hydroxy propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate with drug captopril by orifice ionic gelation process.

MATERIALS AND METHODS

Captopril a gift sample obtained from Lupin Laboratories, Ahmedabad, Sodium alginate obtained from LobaChemie, Mumbai, Hydroxy propyl methyl cellulose, Carbopol 934P, Cellulose acetate Phthalate from Glenmark Pharmaceuticals, Chitosan from Central Institute of Fisheries Technology, Kochi, and all Chemicals used are of analytical grade.

Preparation of Drug Encapsulated Beads

Beads containing captopril was prepared, by employing sodium alginate in combination with hydroxy propyl methyl cellulose, carbopol 934P, Chitosan and cellulose acetate phthalate. An orifice ionic gelation process was used to prepare large sized alginate beads (Chowdary and Srinivasa, 2003). Core coating material (sodium alginate) and polymers were dissolved in distilled water (32 ml) to form a homogeneous polymer solution; core material (captopril) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion.The resulting dispersion was then added in a thin stream to a 300 ml of Arachis oil contained in a 500 ml beaker with stirring at 400 RPM using a mechanical stirrer. The stirring was continued for 5 min to emulsify the added dispersion as fine droplets. Calcium chloride (10 % w/v) solution (40 ml) was then added slowly while stirring for ionic gelation (or curing) reaction. Stirring was continued for 15 min to complete the curing reaction and to produce spherical beads. Mixture was then centrifuged and the product thus separated was washed repeatedly with water and dried at 45 ^{0}C for 12 hours[7]. The prepared beads were stored in desiccators for further studies (Table-1).

Table 1.Formulations of various captopril entrapped mucoadhesive beads

Formulation code	Ratio	Quantity of	Quantity of mucoadhesive polymers				
		Drug	**Alginate**	**HPMC**	**Carbopol**	**Chitosan**	**CAP**
B1H	1:1	2gm	1 gm	1 gm			
B2C	1:1	2 gm	1 gm		1 gm		
B3C	1:1	2 gm	1 gm			1 gm	
B4C	1:1	2 gm	1 gm				1 gm
B5H	9:1	3 gm	2.7 gm	300mg			
B6C	9:1	3 gm	2.7 gm		300mg		
B7C	9:1	3 gm	2.7 gm			300mg	
B8C	9:1	3 gm	2.7 gm				300mg

Characterization of Beads

The developed mucoadhesive beads were studied for compatibility studies by FTIR and subjected for various characterizations like Size and Shape analysis, Drug content, Microencapsulation efficiency, *In vitro* wash off test for mucoadhesion, Stability study.

FTIR Studies

IR spectroscopic studies were carried out for prepared beads, by using Shimadzu FT IR 8700 model to determine the integrity of the drug in the formulation.

Size and shape analysis

Microscopic analysis was performed to determine the average size of microcapsules. The microcapsules prepared were dispersed in liquid paraffin and a drop of above dispersion was put on a glass slide and observed under a microscope. The diameter of 100 microcapsules was determined using calibrated eyepiece micrometer and stage micrometer. The average diameter was calculated using the following formula (Singh and Robinson, 1988)

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

Where,

n = number of microcapsules.

d = diameter of the microcapsules, C.F = calibration factors

Drug content estimation

Drug content estimation was done by stirring 20 mg microcapsules in 3 ml of sodium citrate solution (1 % w/v) until complete dissolution occurs. 1 ml of methanol was added to sodium citrate solution to gel the solubilized calcium alginate and further solubilise captopril. This solution was then filtered to obtain drug solution. The filtrate is suitably diluted with 0.1N hydrochloric acid and absorbance was taken at 212 nm (El-Kamel et al., 2003).

Microencapsulation Efficiency

Microencapsulation efficiency was calculated using the reported formula (Chowdary and Srinivasa, 2003).

$$\text{Microencapsulation efficiency} = \frac{\text{Estimation \% drug content}}{\text{Theoretical \% drug content}} \times 100$$

***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). This was evaluated by an *in vitro* adhesion testing method, known as wash

off method. The mucoadhesive property of beads was compared with that of a non-adhesive material, ethylene vinyl acetate beads. A piece of sheep stomach mucosa (2×2 cm) was mounted onto glass slide (3×1 inch) with cyanoacrylate glue and one more glass slide was connected with a support. The beads (50 no) were counted and spread over the wet rinsed tissue specimen and immediately thereafter the support was hung on the arm of a USP tablet disintegrating test machine as shown in photographs in Figure 1a and 1b. By operating the disintegration machine the tissue specimen was given a slow regular up and down moment. 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 8 hours (Hari et al., 1996).

Stability Studies

Stability studies were carried out for captopril loaded beads at various temperatures as per ICH guidelines. The samples were weighed in two sets and wrapped in a butter paper and placed in Petri dishes. These containers were stored at ambient humid condition at room temperature (27 ± 2^o C) and at elevated temperature (45 ± 2^o C) for a period of 8 weeks. Then beads were analyzed for physical changes such as color, texture and drug content. The drug content was estimated for an interval of 2 weeks as per the procedure reported earlier. The drug solutions were further scanned to observe any possible spectral changes and no changes have been reported

In Vitro Drug Release Studies

Dissolution studies were performed for beads containing quantity equivalent to 100 mg of drug filled in capsules by using USP 23 TDT-06T (Electrolab- paddle method) at 50 RPM. The media used were 900 ml of 0.1N hydrochloric acid (pH 1.2), maintained at 37 ± 0.5^0C, 5 ml of samples were withdrawn at different time intervals and replace with 5 ml of dissolution medium (Kim and Lee, 1992 and Indian Pharmacopoeia 1996). The samples were filtered and assayed spectro-photometrically at 212 nm after appropriate dilutions. Dissolution testing was also performed for 100 mg pure drug.

RESULTS AND DISCUSSIONS

Formulation of captopril control release gastric mucoadhesive beads was done by using alginate as core coating polymer, as alginate is easily gelled by the addition of Ca^{+2}. An aqueous in-soluble calcium-alginate gel is formed by cation exchange between Na+ and Ca+2 (Kim et al, 1992). The gelation and cross linking are due to the stacking of the glucoronic acid-G blocks of alginate chains with the formation of egg-box junction. An orifice-ionic gelation process was used to prepare captopril encapsulated beads, employing sodium alginate in combination with four mucoadhesive polymers like hydroxy propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate in 1:1 and 9:1 ratios. Beads were found to be discrete, large, spherical, free flowing, monolithic matrix and had smooth surfaces, an exception of alginate-hydroxy propyl methyl cellulose beads.

Table 2.Characterization of drug encapsulated beads

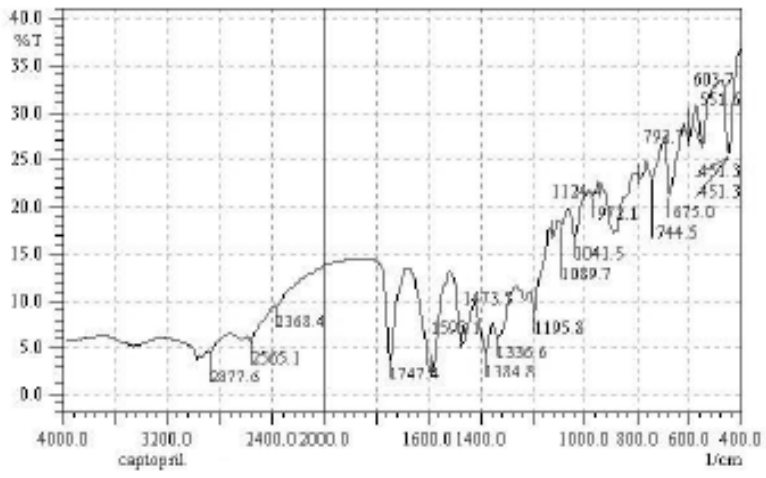
Formulations	Percentage Yield *	Average Diameter * (µm)	Drug content * (mg)	Microencapsulation efficiency	Characterization
B1H	59.43 ±8.05	600 ±05.3	1.32±0.049	65.90	Slightly
B2C	63.03 ±3.43	710 ±04.6	1.29 ±0.055	64.72	irregular
B3C	77.13±08.0	600 ±06.8	1.67 ±0.023	83.44	
B4C	85.43 ±8.10	600 ±07.2	1.15 ±0.062	57.50	
B5H	78.85±06.5	1400 ±08.5	2.17 ±0.033	72.30	Spherical
B6C	91.90 ±08.2	1400 ±06.9	2.30 ±0.052	76.72	Free flowing
B7C	79.94 ±09.9	1400 ±07.6	2.69 ±0.048	89.70	
B8C	89.73 ±08.9	1400 ±06.8	1.92 ±0.039	64.08	

*Each value is an average mean of 3 replications

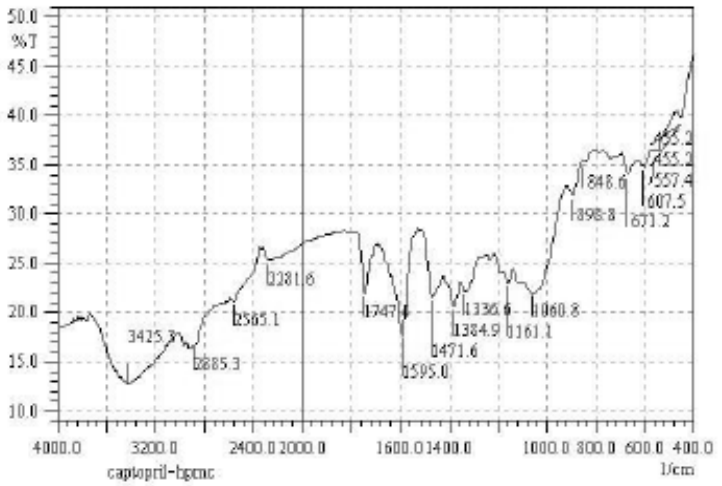
IR spectroscopic studies were carried out for prepared beads, by using Shimadzu FT IR 8700 model. In order to check the integrity of the drug in the formulation, IR spectra of the pure drug captopril and that of captopril encapsulated formulations were taken and compared (Figure 2a to 2e).

Which showed prominent peak at 1747.4 Cm-1 because of C = O stretching and vibration due to the presence of carboxylic group. Peak at 1384.8 Cm-1 because of C-N stretching due to the presence of tertiary amine group, Peak at 2565 Cm-1because of S-H vibration due to the presence of thiol group.After comparing all the IR spectra, that there was no significant interaction between the captopril and various polymers.

Figure 2. FTIR spectra of pure drug & captopril (a), captopril encapsulated alginate-HPMC beads (b), captopril encapsulated alginate-carbopol 934p beads (c), captopril encapsulated alginate-chitosan beads (d) and captopril encapsulated alginate- CAP beads (e)


%T
captopril
1/cm

(a)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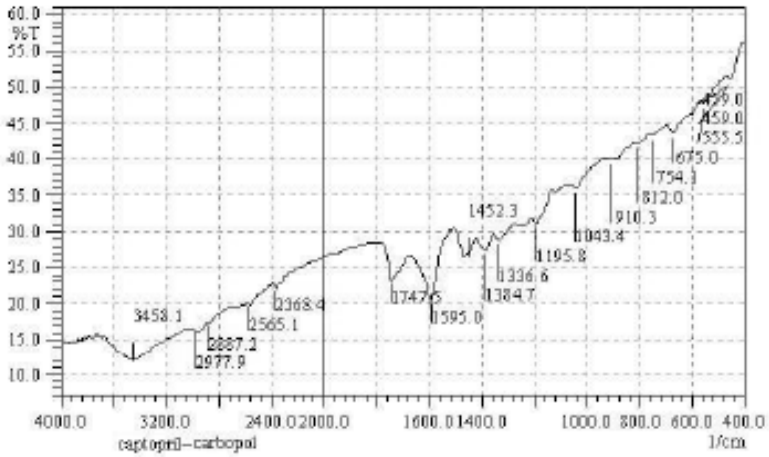
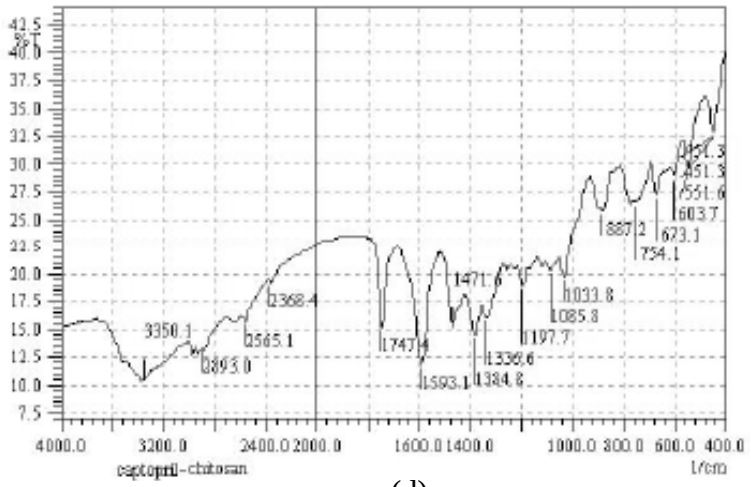
(b)


%T
captopril-carbopol
1/cm

(c)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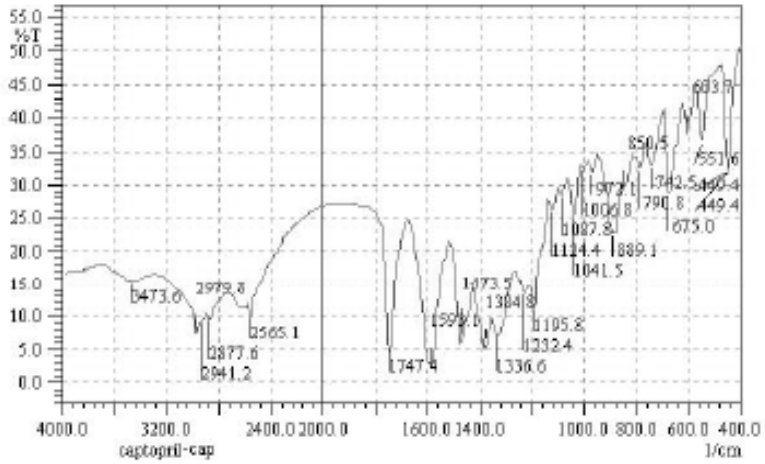
captopril-chitosan
1/cm

(d)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captopril-cap
1/cm

(e)

Sodium alginate 1 gm and 2.7 gm were employed in the preparation of 1:1 and 9:1 beads respectively. The amount of captopril taken was kept constant at ratio 1:1 based on the total polymer concentration in all the formulations. It was observed during preparation of beads that 9:1 polymer solution had higher viscosity and excellent spherical droplets were formed. Whereas 1:1polymer solution was comparatively less viscous and retaining spherical form was difficultduring the process of drying. The beads were sieved using a set of standard sieves with different apertures. The granulometric class of particles were smaller than 100 µm were determined by a microscopic method. All beads were found to be uniform in size i:e 1400 µm and 600 µm for beads of 9:1 and 1:1 ratio respectively, except alginate-carbopol 934P beads, which were larger in size and mean size was found to be 710 µm. Shape of beads (Figure 3) was found to be discrete, large, spherical, free flowing, monolithic matrix and had smooth surfaces. A significant increase in the percentage yield was observed (Table 2) with increase of alginate concentration. In case of all 1:1 formulations, alginate-chitosan beads demonstrated highest yield i.e 77.13 % and in case of all 9:1 formulations, Alginate- Carbopol 934P beads demonstrated highest yield i.e 91.90 %Drug loading was observed good (Table 2) from all the alginate-chitosan beads. This is attributed to the very good inter-polymeric complex formation of alginate and chitosan. The complex formed between both polymers is produced by electrostatic attraction between amine group of chitosan and the carboxylic group of alginate.

Microencapsulation efficiency was found to be (Table 2) increases when the alginate concentration is increased. This is due to the alginate droplets forms gel spheres instantaneously and entrap the drug in a three dimensional lattice of ionically cross-linked alginate. Increasing the amount of polymer in aqueous solution increases the number of lattice and therefore drug loading. In all formulation of chitosan - alginate beads showed excellent microencapsulation efficiency and was observed with 9:1 alginate chitosan beads with 89.70 % efficiency.

Mucoadhesive property was studied on beads and all the formulated beads demonstrated good mucoadhesive property compare to non-mucoadhesive polymer (ethylene vinyl acetate). The following stages may have occurred during mucoadhesion. Initially, an intimate contact i: e (wetting) between the mucus gel and the swelling of mucoadhesive polymer.

Which makes the polymer strands to relax; this is followed by the penetration of the mucoadhesive polymer into the mucus gel network and finally the formation of secondary chemical bonds between the mucus and the mucoadhesive polymer. It was observed that as the concentration of mucoadhesive polymer decreased from 1 gm to 300 mg, mucoadhesion of beads also decreased (Table 3).

Mucoadhesion of alginate-carbopol 934p was found to be significantly high, this may be due to significant mucus gel strengthening, which results in formation of stable mucoadhesive joint. Hence the large force required to detach the mucoadhesive dosage form from the mucosal surface. Mucoadhesion of alginate-cellulose acetate phthalate beads was found to be poor when compared to

alginate- carbopol 934p, this is due to their low swelling capacity.

Figure 1. Apparatus showing in vitro wash off test

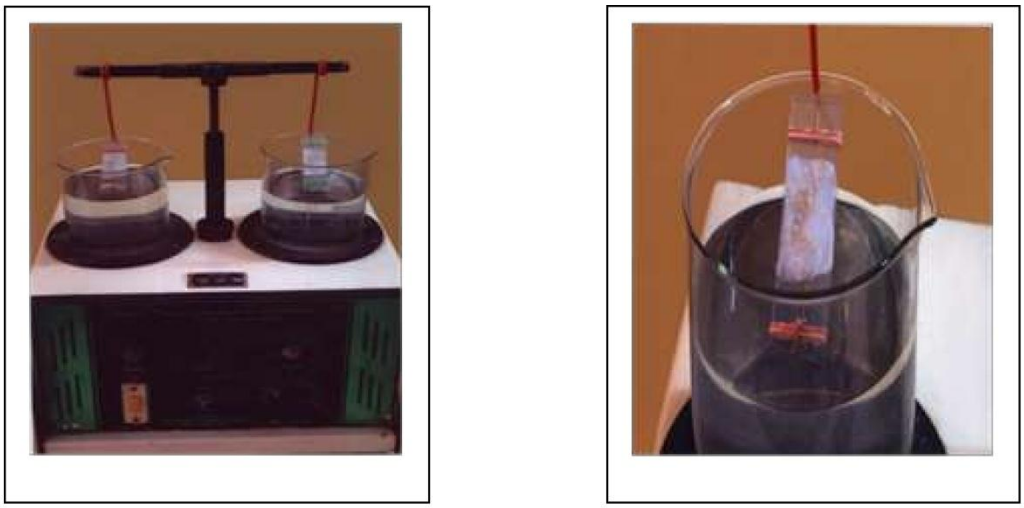


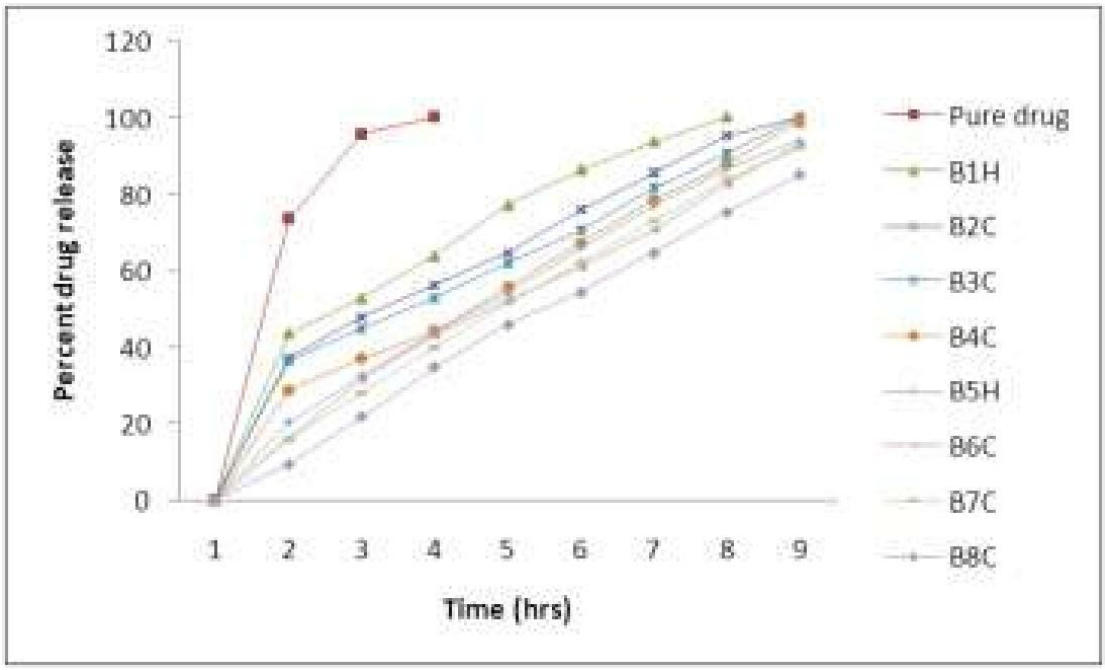
Table 3.Results of*in vitro*wash off test in 0.1N hydrochloric acid.

	Percentage beads adhering to stomach mucosa in hours*				
Beads 1:1	**1**	**2**	**4**	**6**	**8**
HB1	94 ± 1.0	82 ± 1.5	74 ± 2.0	68 ± 1.2	44 ± 1.0
CB2	96 ± 2.0	92 ± 1.4	86 ± 1.7	84 ± 0.7	62 ± 1.5
CB3	78 ± 1.5	62 ± 1.4	56 ± 1.8	44 ± 0.5	12 ± 0.3
CB4	56 ± 1.0	46 ± 0.5	41 ± 0.8	32 ± 0.5	16 ± 2.2
EVA1	46 ± 2.8	28 ± 0.8	16 ± 2.4	--	--
Beads 9:1					
HB5	84 ± 1.2	76 ± 2.0	62 ± 1.7	46 ± 1.9	22 ± 2.3
CB6	92 ± 2.1	86 ± 2.2	78 ± 1.5	56 ± 2.2	54 ± 1.9
CB7	78 ± 1.8	42 ± 1.8	42 ± 2.1	36 ± 1.5	12 ± 2.0
CB8	64 ± 1.5	64 ± 1.4	50 ± 1.8	32 ± 0.8	08 ± 1.2
EVA2	44 ± 3.6	14 ± 1.9	--	--	--

Stability studies for the captopril encapsulated beads and microcapsules did not show any significant change in color, texture and drug content at the end of eight weeks. The above results indicate all the formulations were stable. This was further confirmed by UV Scanning

An *in vitro* dissolution study was carried out in USP dissolution apparatus by basket method. Since the stomach mucosal pH is between 1 and 3, an acidic medium pH 1.2 was used for the dissolution studies. The release of the drug from the dosage form follows diffusion or erosion mechanisms through the matrix. Thus as long as there is sufficient drug solubility, these mechanisms control the drug release.The pure drug release was found to be 73.8 percent in first hour of dissolution test and complete drug release of total content of capsule was within 2 hours.The *in vitro* release studies of drug encapsulated beads in acidic medium are shown in figure 8. The alginate-hydroxy propyl methyl cellulose beads demonstrated a drug release of 100 percent in 7 hours and 93.7 percent in 8 hours for 1:1 and 9:1 beads respectively. The release of captopril from alginate-carbopol 934p beads was 100 percent in 8 hours and 92.8 percent in 8 hours for 1:1 and 9:1 beads respectively. The release of captopril from alginate-chitosan beads was 99.96 percent and 92 percent in 8 hours for 1:1 and 9:1 beads respectively. The release of captopril from alginate-cellulose acetate phthalate beads was 98.8 percent and 85.1 percent in 8 hours for 1:1 and 9:1 beads respectively. The release pattern of captopril from beads of all the formulations is given in Figure 3. A perusal of Figure 4 indicated a slow release of captopril from both 1:1 and 9:1 alginate-cellulose acetate phthalate beads at the end of 8 hours. It was observed that only 37.1 and 21.8 percent of drug released from 1:1 and 9:1 alginate-cellulose acetate phthalate beads at the end of 2 hours as compared to pure drug, 100 percent of drug was released at the end of 2 hours. While comparing 1:1 and 9:1 beads, 9:1 beads showed delayed release property. The results clearly indicate that the rate of drug release decreased with the increase of coating thickness, because the drug cannot diffuse through the pore of alginate gel matrix, which has not swollen. The order of increasing release rate observed with beads was alginate-cellulose acetate phthalate beads < alginate-chitosan beads < alginate-carbopol 934p beads < alginate-hydroxy propyl methyl cellulose beads in 0.1 N hydrochloric acid.

Figure 3. Captopril release from 9:1 beads in 0.1 N hydrochloricacid



The precise determination of the mechanism of drug release from the matrix is complex, especially when there is more than one polymer as matrix. The performance of the hydrophilic swelled matrices as a prolonged drug release system is dependent on the hydration properties of the polymers, gel forming properties and relaxation of polymer chains when the fluid gets into the matrix. The release data of captopril was processed to understand the linear relationship i:e., kinetic principles. The parameters and equations, given in Table 4 indicated that the release kinetics of captopril from the alginate beads followed zero order (R^2 value was above 0.99 for all formulations on an average).

Table 4.Comparison of order of*in vitro*release of captopril frombeads in 0.1 N HCl

SL. No	Formulation	*In vitro* drug release in 0.1 N HCl Regression equation	
		Zero order	First order
1.	**HB1**	y = 8.6698 t + 38.1836 R2 = 0.9602	log y = 0.0530 t + 1.6319 R2 = 0.9245
2.	**CB2**	y = 9.2131 t + 28.9286 R2 = 0.9959	log y = 0.0607 t + 1.5525 R2 = 0.9711
3.	**CB3**	y = 9.1526 t + 26.1957 R2 = 0.9984	log y = 0.0621 t + 1.5263 R2 = 0.9879
4.	**CB4**	y = 10.2238 t + 16.3179 R2 = 0.9963	log y = 0.0768 t + 1.4148 R2 = 0.9834
5.	**HB5**	y = 10.6786 t + 11.2464 R2 = 0.9962	log y = 0.09059 t + 1.3188 R2 = 0.93345
6.	**CB6**	y = 10.5202 t + 8.9214 R2 = 0.9953	log y = 0.0965 t + 1.2633 R2 = 0.9044
7.	**CB7**	y = 10.9976 t + 6.3357 R2 = 0.9977	log y = 0.1025 t + 1.2268 R2 = 0.9204
8.	**CB8**	y = 10.6774 t + 0.9393 R2 = 0.9967	log y = 0.1224 t + 1.0583 R2 = 0.8764

CONCLUSION

An Orifice ionic gelation process was employed for the preparation of various alginate beads in 1:1 and 9:1 alginate-polymer ratio. The techniques were simple, reproducible and produced beads of regular shape and size. The FTIR studies indicated that there was no interaction between the drug and polymer. Among all the formulations, alginate-carbopol 934p beads (9:1) showed the highest percentage of yield. The prepared beads were spherical in shape, discrete and free flowing. The size of beads was found to be in range of 600 µm to 1400 µm.

In vitro release studies were carried out in 0.1 Nhydrochloric acid (pH 1.2), which indicated that there was a slow and controlled release of drug for all the formulations. Alginate-cellulose acetate phthalate beads and microcapsules demonstrated sustained release compared to all other alginate polymer combinations. The order of drug release was found to be zero order for all the formulations. Drug release data was better fit toHiguchi's diffusion model and the release of drug from all theformulations is diffusion rate limited. The objectives of the present work was achieved i; e, formulation, evaluation and usefulness of sodium alginate mucoadhesive beads of captopril with different mucoadhesive polymers. Certainly these findings can be applied for sustained delivery of drugs with mucoadhesion. Further these findings help the industry to scale up the commercial production.

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