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FORMULATION AND EVALUATION OF CONTROLLED-RELEASE OF BENAZEPRIL MICROSPHERES

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ABSTRACT

Microspheres of Benazepril HCl were prepared using Chitosan and Xanthan gum by solvent evaporation technique. Compatibility study was carried out by using FTIR and results showed that there was no significant interaction between drug and excipients. Microspheres thus obtained were found to be pale yellow in color and showed free flowing character. The Scanning electron microscopy results indicate that microspheres are of smooth and spherical in shape. Particle size was performed by using optical microscope and particle sizes are found in the range 152.8±8.35 to 276.2±5.47µm and particle size depends up on the concentration of Xanthan gum i.e. formulation containing higher concentration of Xanthan are larger size when compared to Chitosan containing batches. Entrapment efficiency results showed that formulation F10 containing 1:9 ratio of Chitosan: Xanthan gum showed highest percentage of entrapment (95.90%) and showed 59.74% of drug loading. Dissolution studies showed decreases as concentration of Xanthan gum increases the dissolution profile of Benazepril HCl from prepared formulation. Formulation F2 containing 9:1 ratio of Chitosan: Xanthan gum showed 94.86% of drug release at the end of 12 hours. Short term stability study showed that prepared Benazepril microsphere formulation was physicochemically stable throughout stability period. Hence it was conclude that, microspheres offer a practical and suitable approach to prepare controlled release dosage form of Benazepril HCl with natural gums like Chitosan and Xanthan gum.

KEYWORDS: Benazepril HCl; Chitosan; Xanthan gum; microspheres; Solvent evaporation.

INTRODUCTION

In the past three decades, the treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various conventional dosage forms like tablets, capsules, ointments, liquids, and injectable, as drug carriers. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take the conventional type of drug delivery systems several times a day. This results in a significant fluctuation of drug levels in the body.[1]

Oral route is considered to be most convenient route for the administration of drugs to patients. The drug normally dissolves in the gastro-intestinal (GI) fluids and is absorbed from these regions of the gastro-intestinal tract (GIT), and both process depends upon the physicochemical properties of the drug.[2]

Controlled drug delivery system is one which delivers the drug at a predetermined rate, locally or systemically, for a long period of time. Products of this type have been formulated for oral, injectable and topical use and include inserts for placement in body cavities a well. Continuous oral drug delivery at predictable and reproducible kinetics for predetermined period throughout the course of GIT. Recently, a new generation of pharmaceutical products, called controlled release drug delivery systems.[3]

Microspheres are solid, approximately spherical particles ranging in size up to 1000µm. They are prepared by a process by means of applying relatively thin coating to small particle of solid or liquid droplets and dispersions. Microspheres are made from polymeric, waxy or other protective materials they are biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The solvents used to dissolve the polymeric materials are chosen according to

the polymer and drug solubility, process safety and economic considerations. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size they have colloidal properties. The interfacial properties of microspheres [4]

- The use of microspheres are potential in pharmaceutical industry
- The conversion of oils and other liquids to solids for ease of handling
- To mask the taste and odour
- To delay the volatilization
- Separation of incompatible materials.
- Increases the flow properties of powders
- Safely handling of toxic materials
- Increases the solubility of water insoluble substances by addition of dispersion of that material in aqueous media
- Production of sustained, controlled release and targeted medications.
- Reduce the dose dumping potential compared to large implantable devices.

Anti-Hypertensives are the agents that tend to lower the Blood pressure. Antihypertensive drugs have been remarkably improved in the last 50 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive was available. Veratrum and Sodium thiocynate could lower blood pressure but were toxic and difficult to use. The ganglion blockers developed in 1950"s were effective but inconvenient. Reserpine was a breakthrough, but produced mental depression. The therapeutic potential of hydralazine could not be tapped fully because of marked side effects when it was used alone.[5,6]

Guanethidine introduced in 1961 was an improvement on ganglion blockers. The antihypertensives of 1960-70s were Methyldopa, β blockers, thiazide and high ceiling diuretics and clonidine. The status of β blockers and diuretics was consolidated in the 1970s and selective α1 blocker prazosin broke new grounds. The antihypertensives of the 1980-90s are ACE inhibitors and calcium channel blockers. Angiotensin receptor blockers are the latest antihypertensives. With the development of many types of drugs delineation of their long-term benefits, complications and understanding of the principles on which to combine them, hypertension can now be controlled in most cases with minimum discomfort.[5,6]

Depending upon their mechanism of action they are broadly classified as.

- **Angiotensin converting enzyme inhibitors:** Drugs like Benazepril, Enalapril, Captopril, Ramipril.

Benazepril HCL is an ACE inhibitor it is used to treat high blood pressure (hypertension). Lowering blood pressure may lower your risk of a stroke or heart attack.

Hence our work is aimed to prepare controlled release microsphere formulations of Benazepril using different polymers.

MATERIALS AND METHODS

Materials

Benazepril HCl, Xanthan gum was obtained from yarrow chemical products, Mumbai. Chitosan, Sodium lauryl sulphate, Methanol, Dichloromethane, Sodium hydroxide, Dihydrogen ortho phosphate was obtained from S.D fine chemicals limited, Mumbai, India.

Pre-Formulation Studies

Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed for the obtained sample of drug for identification and compatibility studies.

Identification of Pure Drug

The selected pure drug Benazepril was subjected for investigation of physical characterization parameters such as.

IR Spectroscopy

Compatibility study using FT-IR

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug.[7]

Solubility analysis

Pre-formulation solubility analysis was done to select a suitable solvent system to dissolve the drug as well as various excipients used for formulation of microspheres based formulation.[7]

Melting point determination

The melting temperature of drugs was determined using capillary method.

Analytical method used in the determination of Benazepril HCl

The UV spectrophotometric method was developed for the analysis of the drug using Shimadzu 1800 spectrophotometer.

Standard Curve for Benazepril HCl

100 mg of pure drug was accurately weighed in to 100ml volumetric flask and dissolved in small quantity of 0.1 N HCL. The solution was sonicated for 5 min and the volume was make up to the mark with the 0.1 N HCL to

give stock solution-I (1000 µg/ml concentration). 10 ml of stock solution-I was placed in 100 ml volumetric flask and volume was adjusted with methanol to give stock solution-II of 100µg/ml concentration. Stock solution-II was further diluted with methanol to get working standard solution of 5, 10, 15, 20 and 25 µg/ml of 0.1 N HCl to construct Beer's law plot for the pure drug. The absorbance of the solutions was measured at 254 nm using UV-visible spectrophotometer. A graph of concentration VS absorbance was plotted.[8]

Preparation of Benazepril HCl microspheres by solvent evaporation technique

Formulation of Benazepril HCl microspheres

Benazepril HCl microspheres were prepared using Chitosan, Xanthan gum and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then HPMC and Xanthan gum in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding to 40 mg was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of 0.2% (w/v) SLS (sodium lauryl sulphate) at 1500 rpm for 3hrs 30min using a stirrer and heated by a hot plate at 50°C. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature.[9]

Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table 3.

Compression Evaluations

Micromeritic studies[10]

The micromeritic properties of prepared microspheres are characterized by angle of repose, tapped and bulked density, Hausner's ratio, Carr's compressibility index and particle size.

Determination of angle of repose

The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder.

The diameter of the powder cone was measured and angle of repose was calculated by using the equation.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, h and r are the height and radius of the powder cone respectively.

Different ranges of flowability in terms of angle of repose are given below in the Table 1.

Table 1: Relationship between Angle of Repose (θ) and flow properties.

Angle of Repose (θ)(degrees	Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Determination of bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. An amount of powder blend was introduced in a 100 ml measuring cylinder. Then the weight of powder blend was determined by subtracting the weight of empty measuring cylinder from final weight of measuring cylinder. The cylinder was allowed to fall onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued till no volume change was noted. LBD and TBD were calculated by following formulas;

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}} \quad \text{(a)}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}} \quad \text{(b)}$$

Hausner's ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Table 2: Hausner's ratio.

Sl.No	Hausner's Ratio	Property
1.	0-1.2	Free Flowing
2.	1.2-1.6	Cohesive Flowing

Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$\text{CI} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Particle size determination

The particle size of prepared microspheres were determined by using optical microscopy method.[11]

Morphological study using SEM

The surface morphology of prepared microspheres was determined by using SEM (Hitachi). SEM analysis was used to measure the size and shape of the microspheres.[11]

Percentage yield

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres

was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation.[11]

% Yield = actual weight of product/total weight of excipients and drug × 100

Drug loading and Drug entrapment[11]

Microspheres equivalent to 40 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100 mL volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 258 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas.

$$\% \text{ Drug loading} = \frac{\text{Weight of the drug loaded in the microspheres (DC)}}{\text{Total weight of the microspheres}} \text{ X } 100$$

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present (DC)}}{\text{Theoretical drug load expected}} \text{ X } 100$$

(DC- Actual Drug Content)

***In-vitro* release study**

Dissolution test of Benazepril HCl microspheres was performed by USP II paddle type apparatus. The microsphere containing quantity equivalent to 40 mg of Benazepril HCl were added to USP dissolution apparatus containing 900 mL of 0.1N HCl dissolution media (pH-1.2) at 100 rpm and 37±0.5°C temperature. After 2 hours, 0.1N HCl was replaced with 900 ml of phosphate buffer pH 7.4 as a dissolution medium. 5 mL of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were filtered through a 0.45 µm membrane filter, diluted suitably and assayed spectrophotometrically at 258 nm. The cumulative % drug release was calculated using standard calibration curve.[11]

Further the cumulative amount of Benazepril hydrochloride release from the microspheres at different time intervals were fitted various kinetics model to characterize mechanism of drug release.

Stability Studies

Stability studies are done to understand how to design a product and its packaging such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used. The optimized formulation was subjected for two months stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foil in tightly closed container. They were then stored at 30ºC 65% RH and 40ºC / 75% RH for two months and evaluated for their post-compression studies.

RESULTS AND DISCUSSION

The compatibility studies revealed both drugs and excipients were compatible after FTIR studies, the results shown in Figure 1.

Micromeritic Studies

Various micromeritic properties were evaluated for various parameters such as bulk density, tapped density, % Compressibility index, Hausner's ratio and angle of repose. Bulk density was found in the range of 0.4713-0.5754 g/cm^3 and the tapped density between 0.6126 - 0.7243 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 10.26 -17.94%. The values of angle of repose for all microsphere formulations was found to be in the range of 19.88 - 27.94 which indicated the excellent to good flow properties of prepared microspheres. The results are shown in Table 4.

Particle Size Analysis

Particle size of Benazepril microspheres was determined by optical microscopy by using stage micrometer and ocular micrometer. Average particle size of formulated microspheres is shown in Table 5.

The mean particle size for the microsphere formulations was found to be in range of 152±4.35 µm to 276±5.47µm. Formulation F1 containing Chitosan alone showed 152±4.37 µm size. Formulation containing Chitosan: Xanthan gum in 1:9 ratio showed highest particle size (256±8.44 µm). It was noticed that the particle size of the microspheres increased with increased concentration of Xanthan gum and this may be due to high viscosity of Xanthan gum which increases the droplet size and results in increase in particle size. Formulation containing mixture of Chitosan and Xanthan gum in 9:1 ratio showed lower particle size (F2; 168.77±6.11) which might be low viscosity of Chitosan compared to Xanthan gum.

Scanning Electron Microscopy (SEM)

The shape and surface morphology of prepared Benazepril HCl microsphere was done by scanning electron microscope. Image obtained from SEM analysis of microsphere samples revealed that all microspheres

prepared were smooth, almost spherical in shape and non porous.

The microspheres containing higher concentration of Xanthan gum were smooth, spherical and slightly aggregated particles when compared with the microspheres of Benazepril with higher concentration of Chitosan which were porous, rough, grossly, discrete spherical. Scanning electron photomicrographs of the formulations F2 and F10 are shown in Figure 2.

Drug Loading, Drug Entrapment and Percentage yield

Formulation F1 and F11 containing Chitosan and Xanthan gum alone respectively showed less entrapment capacity. Formulation F10 containing 9:1 ratio of Xanthan gum: Chitosan showed highest entrapment. As the Xanthan gum concentration was increased, the percentage drug loading decreased and percentage entrapment efficiency was increased due to increase viscosity of the Xanthan gum. The entrapment efficiency was increased with higher Xanthan gum concentration and this may be due to the diffusion of drug into the aqueous phase because of decrease in interfacial tension by Xanthan gum between drug and aqueous phase.

The percentage drug loading of all formulation was ranged between 48.54±0.13 and 97.78±0.01% and the entrapment efficiency is between 68.3±0.11 and 95.9±0.22%. Percentage yield of different formulation F1 to F11 were calculated and the yield was found in the range of 89.21%-52.68%. The percentage yield was higher for formulation F1 which contains Chitosan alone. Percentage loading was decreased gradually when the concentration of Xanthan gum was increased. The results of drug loading capacity and entrapment efficiency are shown in Table 6.

***In-vitro* drug release studies**

Dissolution studies on all the eleven formulations of Benazepril microspheres were carried out using a USP dissolution apparatus. Dissolution test was carried out first 2 hours with 0.1N HCl (pH 1.2) and after 2 hours experiment was conducted by using pH 7.4 phosphate buffer as the dissolution medium. The *in-vitro* drug release data of different formulations are shown in Table 7 and Figure 3. The cumulative percent drug release was found to be in the range of 64.56% to 94.86% at the end of 12 hours. First 4 hours the cumulative % of drug release from prepared microsphere was higher than drug release was slower. This might be the fact that gradually microspheres start swelling which in turns controls the drug release from the microsphere formulations. The cumulative drug release depends upon the combination of polymer used. Formulation F1 and F11 showed less than 65% of drug released at the end 12 hours, whereas formulation containing 9:1 ratio of Chitosan and Xanthan gum showed 94.86% drug release at the end of 12 hours. The increased density of the polymer matrix at higher concentrations Chitosan results in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at this ratio and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

Stability studies results

The formulations subjected to the stability studies and the evaluation parameters performed after the study period was no significant changes with respect to the initial observations. Hence prepared formulation was physicochemically stable throughout study period.

Table 3: Formulation of Benazepril HCL Microspheres.

Formulation Code	Chitosan (Mg)	Xanthan gum (mg)	Benazepril HCl (mg)	Dichloromethane (ml)	Methanol (ml)	Sodium lauryl sulphate (mg)
F1	1000	--	40	10	10	200
F2	900	100	40	10	10	200
F3	800	200	40	10	10	200
F4	700	300	40	10	10	200
F5	600	400	40	10	10	200
F6	500	500	40	10	10	200
F7	400	600	40	10	10	200
F8	300	700	40	10	10	200
F9	200	800	40	10	10	200
F10	100	900	40	10	10	200
F11	--	1000	40	10	10	200

Table 4: Micromeritic properties of Benazepril mucoadhesive microspheres.

Formulation Code	Bulk Density ($g/cm^{3)}$	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.5426±0.015	0.6126±0.005	12.65±1.21	1.158±0.023	21.93±0.23
F2	0.4987±0.028	0.6814±0.014	14.24±1.32	1.156±0.051	24.74±0.14
F3	0.5233±0.015	0.7243±0.008	10.26±1.27	1.183±0.011	27.94±0.13
F4	0.4713±0.009	0.6446±0.015	11.74±1.34	1.131±0.019	23.81±0.14
F5	0.5318±0.013	0.6183±0.001	12.36±1.04	1.121±0.020	24.67±0.26
F6	0.5168±0.012	0.7136±0.012	13.56±1.02	1.156±0.010	27.08±0.16
F7	0.4576±0.016	0.7228±0.018	12.47±1.21	1.122±0.031	23.61±0.54
F8	0.5754±0.011	0.6845±0.012	15.24±1.03	1.229±0.013	24.54±1.07
F9	0.5438±0.016	0.6412±0.014	15.35±0.84	1.183±0.026	25.12±1.11
F10	0.558±0.0130	0.6743±0.018	17.94±1.34	1.122±0.03	19.88±0.14
F11	0.5418±0.013	0.6643±0.075	15.94±1.34	1.129±0.02	22.±430.16

Table 5: Particle Size of Benazepril Microspheres.

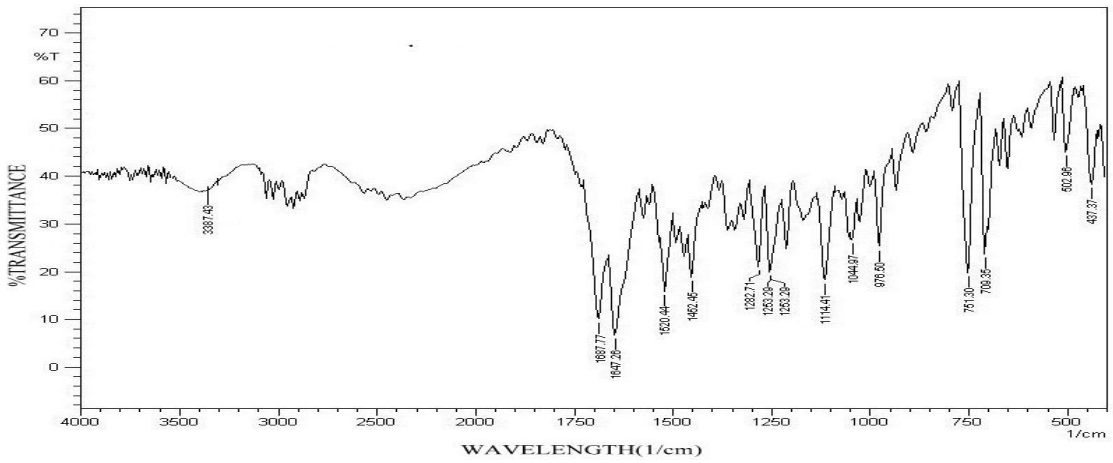
Formulation code	Average particle size (µm)±SD
F1	152.8±8.35
F2	168.3±6.11
F3	176.6±9.42
F4	198.8±7.14
F5	210.9±10.73
F6	223.6±12.24
F7	240.2±8.69
F8	247.3±11.46
F9	253.9±12.51
F10	256.6±8.44
F11	276.2±5.47

Table 6: Drug Loading and Drug Entrapment of Microspheres.

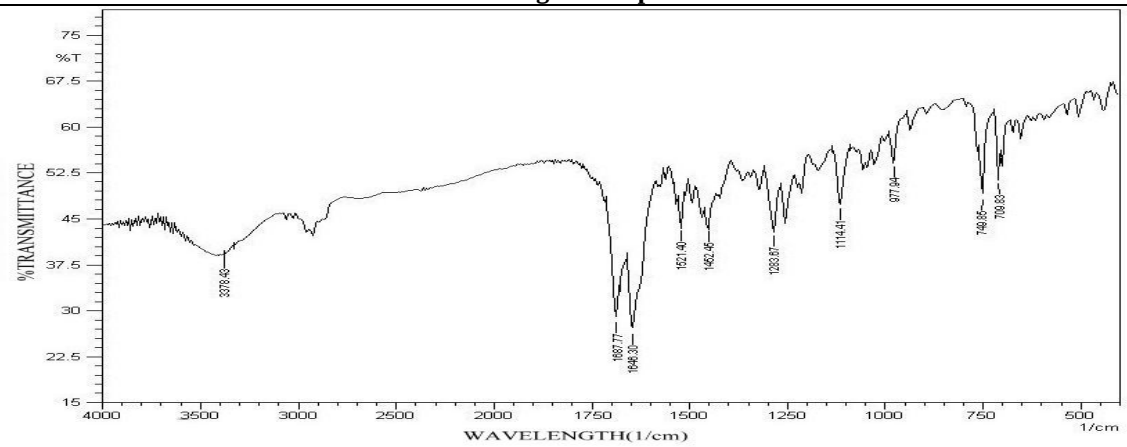
Formulation Code	Percentage Drug Loading (%)	Percentage Drug Entrapment (%)	Percentage yield (%)
F1	48.54	68.30	89.21
F2	97.78	82.48	86.38
F3	68.81	90.40	79.53
F4	71.73	78.12	75.88
F5	77.88	83.62	71.20
F6	82.86	91.44	69.98
F7	85.44	78.88	65.14
F8	76.32	84.94	63.56
F9	63.12	92.48	58.91
F10	59.74	95.90	54.44
F11	52.30	70.71	52.68

Table 7: *In-vitro* drug release for Benazepril Microspheres formulation.

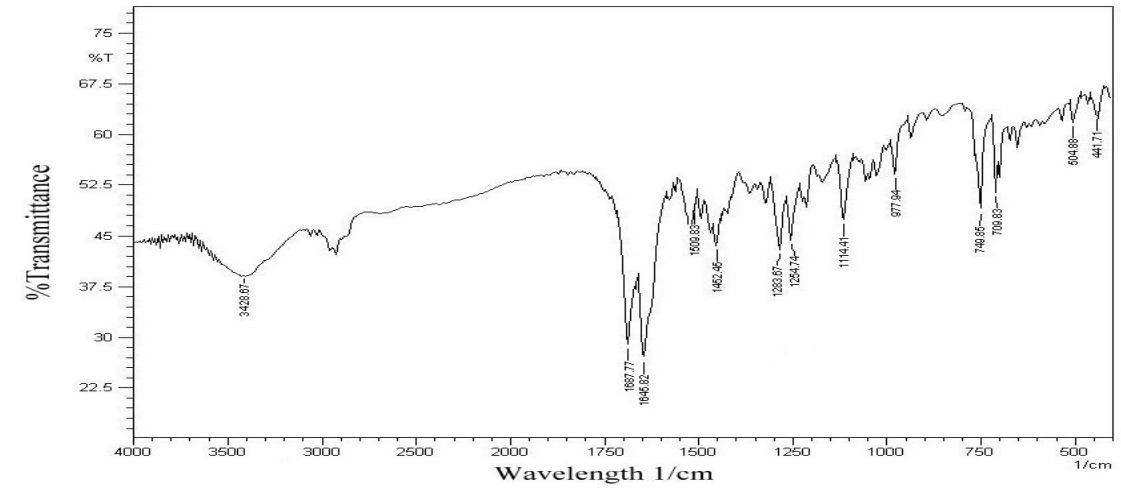
Time (hrs)	Cumulative % drug release of formulations										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	16.47	14.38	13.46	14.98	14.10	13.18	13.76	13.11	12.59	11.04	10.50
2	30.18	28.25	24.70	27.55	24.83	24.15	22.94	20.56	18.37	19.37	20.37
3	42.46	40.38	38.74	40.62	38.35	36.87	36.29	31.90	27.50	27.50	28.50
4	58.84	55.46	53.12	51.82	50.65	48.18	47.74	46.58	45.34	42.34	35.87
5	64.30	59.43	57.58	58.01	56.21	54.06	53.49	51.41	46.98	47.85	41.05
6	71.29	66.85	64.34	65.64	62.73	61.74	57.50	55.28	54.47	50.47	48.76
7	75.94	71.81	68.53	71.26	68.47	65.93	62.78	60.49	60.86	56.52	52.54
8	79.84	76.52	72.25	73.72	71.58	68.71	70.18	68.52	57.41	60.41	55.41
9	83.23	80.14	74.31	77.16	74.69	71.18	75.26	72.76	62.50	62.50	57.50
10	85.01	81.89	75.53	80.59	77.93	73.68	77.39	74.84	65.57	65.57	59.57
11	86.89	83.11	77.04	82.43	79.85	74.81	80.61	77.60	68.83	69.83	61.83
12	88.38	94.86	78.29	84.30	81.12	75.90	82.32	79.72	74.69	72.69	64.56



A. Pure drug Benazepril HCl



B. Drug with Chitosan



C. Benazepril HCl microsphere formulation

Figure 1: FTIR studies of drug Benazepril HCl, drug with excipient and formulation.

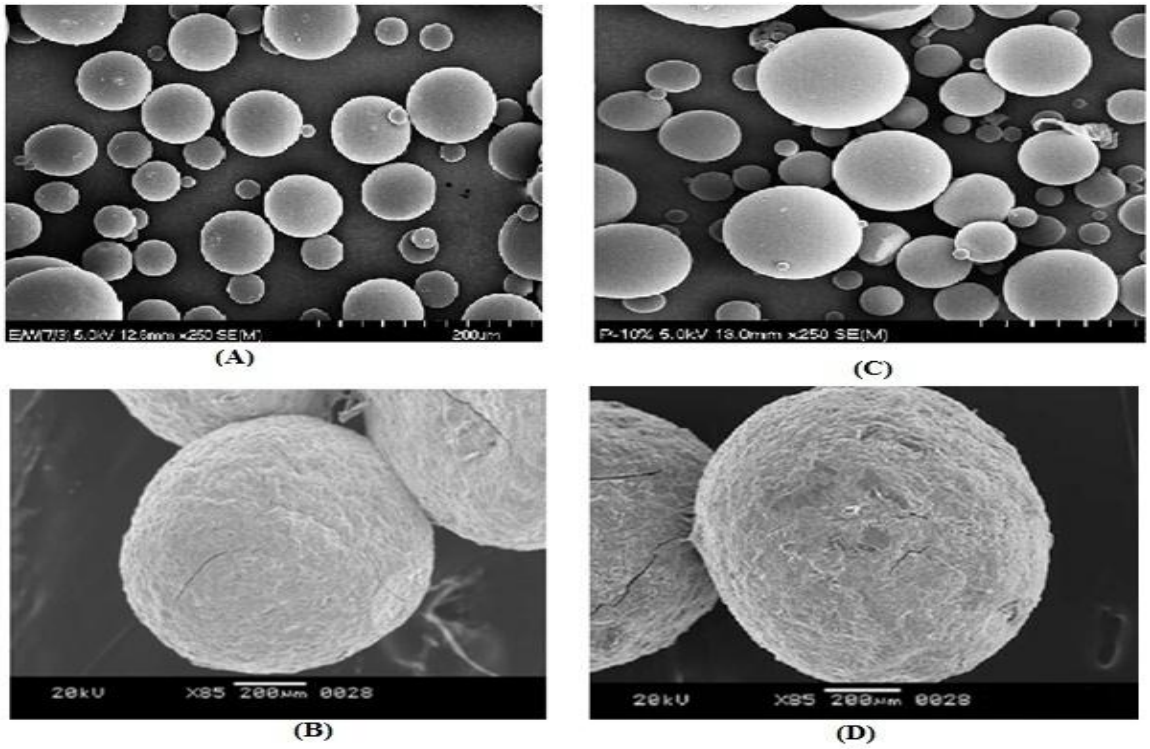


Figure 2: SEM images of F2 and F10 formulation (A) and (B) are images of F2 formulation, (C) and (D) are images of F10 formulation.

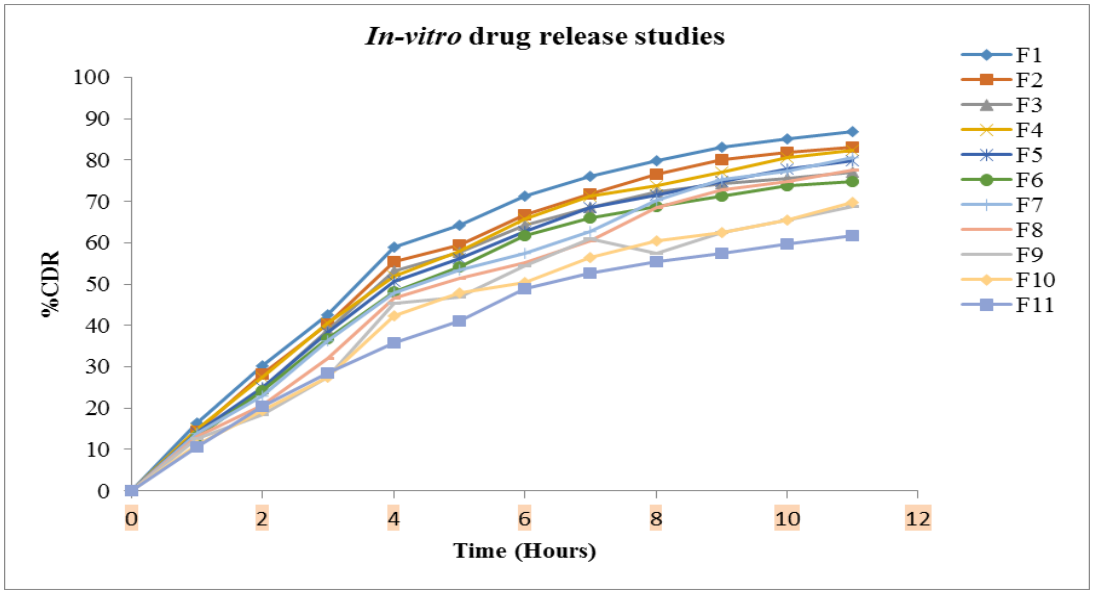


Figure 3: Comparative cumulative percentage drug profile of Benazepril HCl Microspheres.

CONCLUSIONS

The study reports a novel attempt to formulate microspheres of the Benazepril HCl by using natural gums like Chitosan and Xanthan gum as polymers, Sodium lauryl sulfate as permeation enhancer. Total eleven batches of Benazepril HCl microspheres were prepared by solvent evaporation method. Various types of evaluation parameters were assessed, with a view to obtain controlled release of Benazepril HCl. FTIR studies results showed that there was no any chemical interaction between drug and excipients. The precompression properties results of all the formulations were found to be within the standard limits and indicate prepared microspheres showed excellent to good flow properties. Micromeritic studies results showed that the mean particle size of the prepared microspheres was within the range of 152 to 276µm. SEM analysis of the microspheres results clearly showed that Chitosan containing microspheres were smooth, spherical and slightly aggregated particles when compared with the microspheres of Xanthan gum which were porous, rough, grossly, discrete spherical. Drug entrapment and

practical yields were optimum depend upon the polymer used. As the concentration of Xanthan gum was increased the % drug entrapment was increased and loading decreased due to increase in the viscosity of the solution. Cumulative percentage drug release was conducted for 12 hours and results showed formulation F2 containing 9:1 ratio of Chitosan: Xanthan gum showed highest percentage of drug release at the end of 12 hours. As the concentration of Xanthan gum was increased drug release was retarded. The overall curve fitting into various mathematical models was found to be on an average. The formulations F1 to F11 were fitted to Higuchi kinetic model and the drug release from the formulation was by non-fickian diffusion mechanism. Based on the results of drug release studies, formulation F2 was selected for short term stability studies and results showed that there was no significant change in the drug entrapment, and *in-vitro* drug release characteristics of the microspheres. Thus, the formulated mucoadhesive microspheres seem to be a potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention in stomach and increasing the bioavailability of drug.

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