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Design and evaluation of microspheres incorporated buccal gel of antihypertensive agent benazepril

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ABSTRACT

The objective of current research is to formulate benazapril microsphere incorporated buccal gel and evaluated. Mucoadhesive microspheres of benazepril prepared using eudragit EPO polymer. Based on maximum drug content (98.94%) and entrapment efficiency (98.79%) exhibited by F10 formulation of benazepril microsphere was chosen as optimised formulation for incorporation into buccal gel of benazepril. The formulation F10 selected was employed for preparation of buccal gel using various polymers like carbopol 934P, HPMC E50LV, poloxamer 407 by mechanical stirring process to develop mucoadhesive buccal gel containing benazepril microspheres. A total of nine formulations were prepared followed by evaluation for pH, viscosity, percent drug content, drug release studies, bioadhesion and accelerated stability studies. The formulation BG6 was chosen as optimized one with maximum release of drug i.e. 99.54% in comparison to pure drug with 38.41% release and subjected to FTIR, SEM and stability studies. The formulation was stable. From all the evaluation studies conducted buccal gel formulated from mucoadhesive microspheres showed that it has potential to deliver benazepril in controlled manner over prolonged time period for buccal use.

Keywords: Benazepril, ACE inhibitor, mucoadhesive microspheres, buccal gel

INTRODUCTION

Microspheres can be described as spherical, solid particles with size ranged from 1 to 1000 µm that can be composed of either polymeric or waxy materials or altered natural products like gums, fats, proteins, waxes. Their large surface to volume ratio is a significant factor in controlling their interfacial properties. They also exhibit colloidal nature as their size decreases. Drug absorption and adverse effects of drugs against GI mucosa is enhanced due tosmaller particle size of microspheres that are distributed throughout the GIT. [1-4]

Even though oral route of drug delivery is most preferred route, it is associated with various restrictions including hepatic first pass metabolism, GI toxicity and degradation in the GI tract. The disadvantages associated with these drug delivery systems gave rise to the need for exploring alternative delivery route. Hence other absorptive mucosae including buccal, sublingual, pulmonary, and transdermal membrane routes are explored as potential sites for drug delivery. Drug delivery by buccal route is employment of buccal mucosa lining the cheeks for drug administration. [5-10]

Benazepril is and ACE inhibitor, which is used to treat high blood pressure, chronic kidney failure, cardiac failure, prevent strokes. It is taken by mouth as tablet and gets converted into benazeprilat, a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. It exhibits activity after 1-2hours of administration, which necessitates need to develop formulation for rapid action through buccal mucosa. [11]

The present study is focused on microspheres; these are micron size polymer particles which employ biodegradable polymers that release the drug for a prolonged duration in controlled manner when they are in proximity to mucin. The microspheres have gained importance for their sustained release of drug over prolonged periods of time in controlled manner.

MATERIALS AND METHODS

Formulation of Benazepril Microspheres

Benazepril microspheres preparedby o/w emulsion solvent evaporation methodemploying eudragit EPO polymer. Different batches were prepared by dissolution of polymer and drug in ethyl acetate-acetone mixture that constituted oil phase. This resultant solution was poured into distilled water containing tween 80 as emulsifying agent (aqueous phase) with continuous stirring. Fine droplets of drug polymer mixture were formed as a process of emulsification that underwent subsequent solidification due to solvent evaporation. The resultant filtered, washed with distilled water for removal of excess oil and later air dried in air oven at 60ºC. Table 1 specifies the various compositions of drug loaded microspheres. [12]

Table 1: Formulation table for preparation of benazepril microspheres

Formulation	Composition				
	Drug (mg)	Eudragit EPO (%)	Ethyl acetate (%)	Acetone (%)	Tween 80 (%)
F1	10	0.5	0.6	4	2
F2	10	1	0.7	4	2
F3	10	1.25	0.8	4	2
F4	10	1.5	0.9	4	2
F5	10	1.75	1	4	2
F6	10	2	1.1	4	2
F7	10	2.25	1.2	4	2
F8	10	2.50	1.3	4	2
F9	10	2.75	1.4	4	2
F10	10	3	1.5	4	2

Evaluation of Microspheres

The formulated microspheres were evaluated for angle of repose [13], bulk density, tapped density, compressibility index (Carr's index) [14], Hausner's ratio and particle size as per the referred methods.

% Drug Content

Drug content analysis was done using a double beam UV-Visible Spectrophotometer (UV-1800, Shimadzu, Japan). The experiment was performed by preparing working solution in concentration rage of 0.5 µg/ml, 1 µg/ml, 2 µg/ml, 4 µg/ml, 6 µg/ml and 8 µg/ml from standard stock solution of 50 µg/ml in using phosphate buffer saline pH 6.8 followed by measurement of absorbance of the solutions at 240nm. Drug content was determined by calculation of concentration from the absorbance via a standard curve [15]

Drug Entrapment Efficiency

5mg of benazepril microspheres crushed by use of mortar and pestle was weighed followed by suspension in 1/10N HCl (25ml) for about 24h which was then filtered. Of this filtrate, 1ml was withdrawn and subjected to UV analysis at 240nm after dilution to

10ml. calculation of drug entrapment efficiency was done using following formula with table 3 specifying the data.[16]

In Vitro Drug release Profile

In vitro drug release studies were performed using USPbasket-type dissolution rate test apparatus (LABINDIA, DISSO-2000, and Mumbai, India). Microspheres that were weighed accurately were taken in 500 ml of o.1N HCl at100rpm maintaining temperature constant (37±1ºC). At pre-set time intervals 2 m withdrawal of aliquots was done simultaneously replacing with an equal volume of fresh pre warmed dissolution medium maintaining sink condition throughout the experiment. [17]

Formulation of Microspheres Incorporated Buccal Gel

Benazepril loaded microcapsules are optimized based on drug entrapment efficacy, drug content and drug release study. The optimized formulation from the microspheres formulation is utilized in the formulation of buccal gel. Initially methyl paraben and propyl paraben are dissolved in water at 80ºC, then accurately weight amount of polymer (poloxamer 407, carbopol 934P, HPMC E50LV) is dispersed in water maintained at 40ºC with constant stirring using mechanical stirrer at 1200 rpm for 30min. The microsphere containing benazepril drug was dissolved in PEG 400followed by addition toabovewith through mixing. Parabens solution is added and finally the pH is adjusted using triethanolamine and stirred slowly until a clear homogenous gel is obtained [18]. (Table2-4)

Table 2: Composition of microspheres incorporated benazepril gel with poloxamer 407 as polymer

	Poloxamer 407 (mg)	Methyl paraben %W/W	Propyl paraben %W/W	PEG400 (%)	Sodium saccharin (ml)	Triethanolamine %W/W
BG1	250	0.15	0.05	1	0.1	Qs
BG2	500	0.15	0.05	2	0.1	Qs
BG3	750	0.15	0.05	3	0.1	Qs

Table 3: Composition of microspheres incorporated benazepril gel with carbopol 934p as polymer

	Carbopol 934p (mg)	Methyl paraben %W/W	Propyl paraben %W/W	PEG400 (%)	Sodium saccharin (ml)	Triethanolamine %W/W
BG4	250	0.15	0.05	1	0.1	Qs
BG5	500	0.15	0.05	2	0.1	Qs
BG6	750	0.15	0.05	3	0.1	Qs

Table 4: Composition of microspheres incorporated benazepril gel with HPMC E50LV

	HPMC E50LV (mg)	Methyl paraben %W/W	Propyl paraben %W/W	PEG400 (%)	Sodium saccharin (ml)	Triethanolamine %W/W
BG7	250	0.15	0.05	1	0.1	Qs
BG8	500	0.15	0.05	2	0.1	Qs
BG9	750	0.15	0.05	3	0.1	Qs

Evaluation of Microspheres Incorporated Buccal Gel

Surface PH of the Gel

A digital glass rod pH meter is used for gel surface pH measurementby placing the electrode near to the gel and equilibrates for one min. if the formulation is acidic or basic it causes irritation to the mucosal lining hence measuring the surface pH is significant in formulation of bio adhesive gel [19].

Viscosity Study

The viscosity is measured using Brookfield viscometer using T shape spindle (No: S63) varied rpm and calculated as follows [20]

Viscosity (cps)=(300/N)X observed reading

Where, N = rpm

Estimation of Drug Content

The formulations containing 20mg of drug transferred to volumetric flask, dissolved in 0.1N HCl and the volume to made up to 10ml using 0.1NHCl. Absorbance values are noted at 240nm followed by calculation of drug concentration form standard calibration curve [21]

Bio Adhesion Study

Goat buccal tissue is used for this study. A section of buccal tissue of goat was taken in a manner that its mucosal side was placed onto the glass vial and tightly secured with rubber band, two such vials were prepared and on one of the vial connected to balance benazepril gel is applied and other placed on a height adjustable pan. The weights were slowly increased tilltwo vials remained attached. Bioadhesive force (g) which is the minimal weights by which the two mucosal layers get detached is determined [22].

In-Vitro Drug Release

In-vitro drug release studies for benazepril gel was done using 37°C using 0.1NHCl as dissolution medium. Transfer of accurately weighed gel containing benazepril equivalent to 10mg was performedinto a receptor division of Franz diffusion cell. Gentle pushing down of the gel onto the cellophane membrane was done to ensure all the gel encounters membrane. This was followed by addition of 1ml of 0.1NHCl to the reservoir chamberfor wetting gel. The receiving compartment is magnetically stirred at 37°C. 2ml of the sample was withdrawn at regular intervals of time and the same was replenished with fresh dissolution media. The withdrawn sample is estimated for drug release spectrophotometrically at 240nm [23]

Ex-Vivo Permeation Studies of Drug Through Buccal Mucosa

The procedure for this study s similar to in-vitro drug release study conducted in Franz diffusion cell, except the goat buccal tissue is used in ex-vivo studies. Freshly excised goat tissue was used in these studies, within 2hour of removal. The underlying tissues were removed using surgical scissors and the basal membrane was retained, and washed thoroughly, examined for integrity and stored at 4°C for 24 hours before using for the ex-vivo study. The permeation studies was also studied using Franz diffusion cell and 20mg equivalent quantity of the gel is placed on the buccal mucosa tissue and 0.1NHCl was used as medium for the study and remaining procedure is similar to that followed in vitro study

Characterization of Microspheres Incorporated Buccal Gel of Benazepril

Fourier Transform Infrared Spectroscopy (FTIR)

Recording of FTIR spectra of pure drug, physical mixture and optimized formulations were done using Fourier transform Infrared spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was one cm^{-1}[24]

Sem Studies

Scanning electron microscopy (SEM) (HITACHI, S-3700N) was employed for studying the shape and morphology of the microspheres by taking pictures at an appropriate magnification. [24].

Stability Studies

Six month Accelerated stability study of the optimized formulation was carried out under different conditions as per ICH guidelines in astability chamber at 40°C /75 % RH. Bioadhesive gel incorporated with benazepril was characterized for the Percent drug content, pH and viscosity during this period [25].

RESULTS AND DISCUSSIONS

Preparation of Benazepril Microspheres

Benazepril microspheres were prepared as shown in Figure 1.

Fig 1: Benazepril microspheres

Evaluation of Microspheres

Micromeritic Properties

The bulk and tapped densities of all the formulations were 0.45g/cc to 0.53 g/cc and 0.52g/cc to 0.57 g/cc respectively (table 5). A satisfactory angle of repose was observed for all formulations with F10 showing a value of 25.74 that is indicative of excellent flow property.

The compressibility index values ranged 9to14 %. The Hausner`s ratio values ranged from 1.10to1.14 %. These findings indicated that the all the batches of formulations exhibited good flow properties.

Table 5: Micromeritic properties of microspheres of benazepril

Micrometric Properties	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's index	Hausner's Ratio	Angle of repose (Ɵ)
F1	0.49±0.72	0.53±0.86	12.48±0.73	1.12±0.95	32.74±0.83
F2	0.46±0.87	0.57±0.36	11.39±0.36	1.11±0.48	30.83±0.87
F3	0.53±0.56	0.50±0.27	13.79±0.83	1.13±0.84	29.76±0.53
F4	0.50±0.98	0.56±0.36	14.47±0.36	1.14±0.83	29.74±0.84
F5	0.49±0.73	0.53±0.87	11.87±0.36	1.12±0.96	28.83±0.88
F6	0.46±0.88	0.57±0.37	10.48±0.74	1.10±0.49	27.76±0.54
F7	0.53±0.57	0.50±0.28	12.19±0.37	1.13±0.85	27.74±0.85
F8	0.50±0.99	0.56±0.37	13.46±0.84	1.14±0.84	26.83±0.89
F9	0.49±0.74	0.53±0.88	13.47±0.37	1.12±0.97	26.76±0.55
F10	0.45±0.89	0.52±0.38	9.37±0.37	1.10±0.50	25.74±0.86

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Particle Size, % Entrapment Efficiency and Drug Content

All the formulations particle size was in micron range with F10 having a least value of 412 µm (table 6). All the formulations exhibited entrapment efficiency and drug content greater than 90 % with highest values exhibited by formulation F10 which was about 98.79% entrapment efficiency and 98.94% drug content.

Table 6: Particle size, % entrapment efficiency and drug content of microspheres of benazepril formulations (F1-F10)

Formulation code	Particle size (µm)	Entrapment efficiency (%)	Drug content (%)
F1	743±0.14	80.19±0.63	91.35±0.26
F2	634±0.36	82.45±0.74	92.42±0.24
F3	522±0.22	88.23±0.86	93.47±0.68
F4	535±0.51	91.45±0.25	91.37±0.75
F5	721±0.42	93.66±0.36	93.24±0.76
F6	814±0.37	94.59±0.25	94.46±0.64
F7	765±0.75	95.73±0.38	95.63±0.75
F8	685±0.21	96.67±0.18	96.24±0.64
F9	524±0.12	96.53±0.62	96.42±0.65
F10	412±0.65	98.79±0.16	98.94±0.47

Above parameters are communicated as Average ± Standard Deviation; (n=3)

In-Vitro Drug Release of Benazepril Microspheres

The dissolution for the benazepril microspheres was conducted in USP 1 basket type dissolution apparatus using 0.1N HCl. It was observed from the results that as the polymer concentration was increased the release was also sustained and increases linearly from F1-F10. All the formulations exhibited more than 90% of drug release by the end of 12hours in comparison to pure drug that released only 38.41% by the end of 12 hours. Formulation F10 exhibited maximum percent drug release of 99.42% owing to the highest concentration of polymer used in it. Taking all the evaluation parameters into consideration F10 was considered as optimised formulation. Hence it is used in further studies for the formulation of microspheres incorporated buccal gel of benazepril**.** (Figure2)

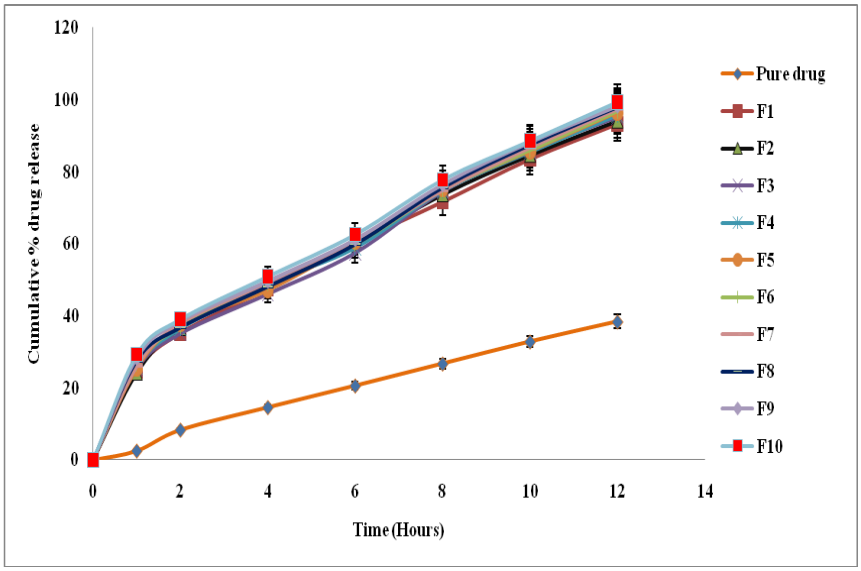


Fig 2: Comparative dissolution profile of benazepril pure drug and benazepril microspheres (F1-F10)

Preparation of Benazepril Buccal Gel

The microsphere incorporated buccal gel is shown in Figure 3.

Fig 3: Benazepril microspheres incorporated buccal gel

Evaluation of Microspheres Incorporated Buccal Gel

The pH of all formulations of benazepril gel from BG1-BG9 showed fairly neutral pH of approximately 6.02–7.01 over the 6 htest period which is indicative of gel pH in range of that of saliva (pH 5.8–7.1) (table 7) Viscosity of prepared gel formulations was between 358-534 cps. Formulations prepared from carbopol-934P polymer with microspheres prepared from solvent evaporation technique showed high viscosity and gels prepared from poloxamer407 polymer showed lowest viscosity. The percentage drug content of the prepared gel formulations was within the range of 95.03- 99.45% with highest exhibited by BG6.

Bioadhesive strength was conducted with the goat buccal mucosa. Fair bio-adhesion values were obtained for all prepared gels (BG1-BG9) in between 14.34-18.94 g. of those, formulation resulting from Carbopol-934P polymers depicted maximum bio-adhesive property owing to higher degree of polymer cross-linking and a high cohesive force between buccal mucosa and polymer.

Table 7: Evaluation parameters of benazepril gel

Formulation	Surface pH	Viscosity(cps)	%Drug content	Bioadhesive strength (g)
BG1	6.02±0.76	430±0.37	95.37±0.48	14.89±0.35
BG2	6.67±0.31	378±0.82	96.36±0.52	15.83±0.42
BG3	6.31±0.35	358±0.82	98.67±0.31	16.48±0.57
BG4	6.11±0.76	439±0.41	97.45±0.49	14.94±0.38
BG5	6.54±0.74	522±0.82	98.78±0.41	16.83±0.62
BG6	6.87±0.76	534±0.41	99.45±0.49	18.94±0.38
BG7	6.05±0.21	501±0.48	95.03±0.31	15.32±0.86
BG8	6.48±0.64	378±0.13	96.99±0.48	16.63±092
BG9	6.92±0.52	436±0.8	97.5±0.41	17.34±0.63

Above parameters are communicated as Average ± Standard Deviation; (n=3)

In-Vitro Release Studies

The drug release was showing sustained release for increased duration in a controlled manner for 12hours. Franz diffusion study conducted for drug release showed good results and all the formulations released the drug in controlled manner when compared to the marketed formulation tablet with drug release only 38.41%. The drug release is attributed to the polymer used which swells when coming in contact with the dissolution media and results in slow release of the drug, the enhancement in drug release is attributed to the microsphere formulation which is micron in size and provide good space for easy absorption thereby enhancing the drug release and bioavailability. BG6 was the final optimized formulation with drug release of 99.54%containing Carbopol 934p polymer in high concentration. The results are depicted in figure 4.

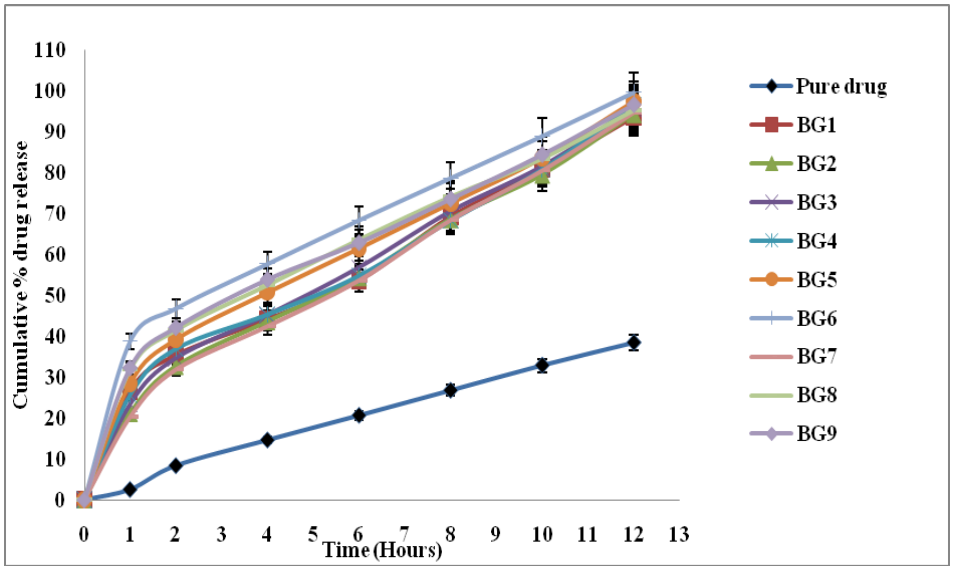


Fig 4: Comparative in-vitro drug release profile of benazepril microspheres incorporated buccal gel formulation BG1-BG9, and pure drug.

Ex-Vivo Permeation Studies of Drug Through Buccal Mucosa

The drug permeation through buccal mucosa was is given in table 8. Results show that with increase in polymer concentration the drug permeation also increases with highest value of 98% observed for BG6. (Table 8)

Table 8: The drug permeated through buccal mucosa

Formulation	Drug permeated (%)
BG1	93.26
BG2	94.57
BG3	96.27
BG4	96.73
BG5	97.12
BG6	98.73
BG7	94.53
BG8	96.3
BG9	97.53

Characterization of Microspheres Incorporated Buccal Gel of Benazepril

FTIR Studies

Negligible drug-polymer interaction was indicated by FTIR spectra of benazepril pure drug (figure 5), and the optimized formulation (figure 6) as indicated by presence of similar characteristic bands or peaks in the spectrum of pure drug and that of formulation. Benazepril pure drug displayed the principal peaks at 3281.02 cm^{-1} due to acid O-H stretching, N-H stretching around 2937.68 cm^{-1}, aromatic C-H stretching is at 2866.32 cm^{-1}, acid C = O stretching around 1599.04 and C-O stretching around 1186.26 cm^{-1}.

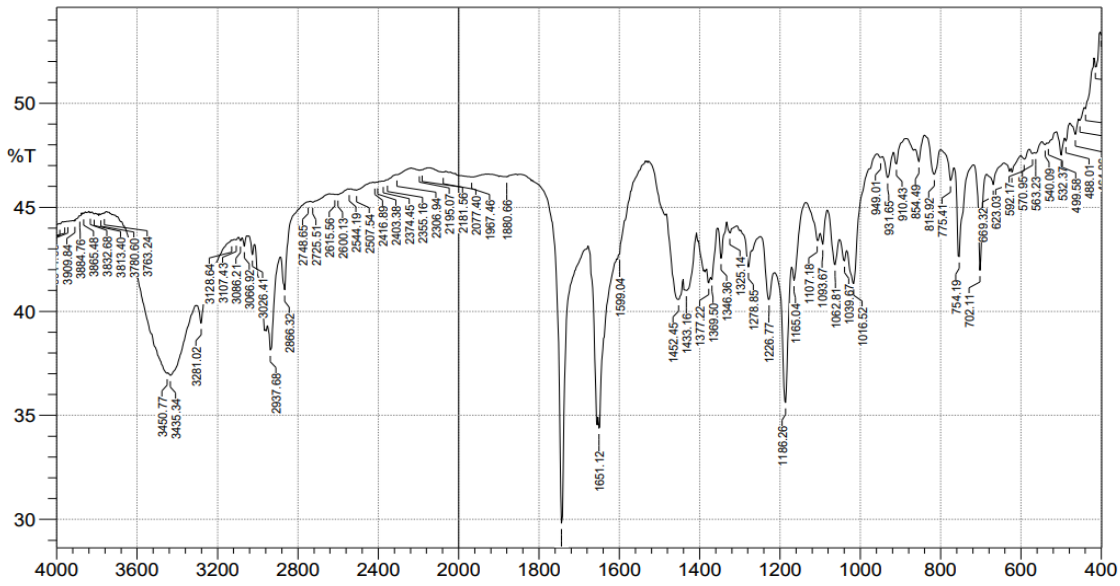


Fig 5: FTIR Spectroscopy of Benazepril Pure Drug

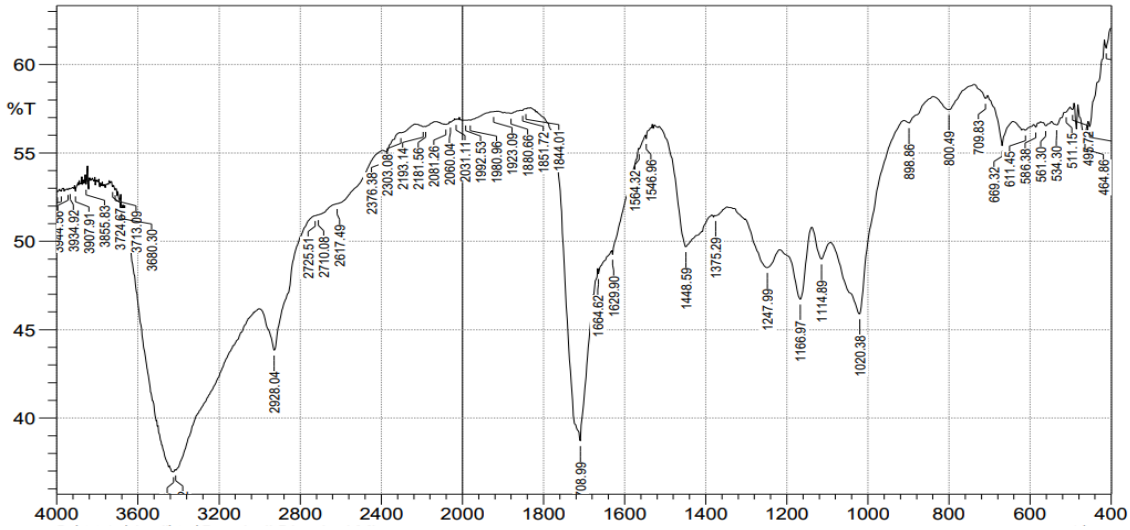
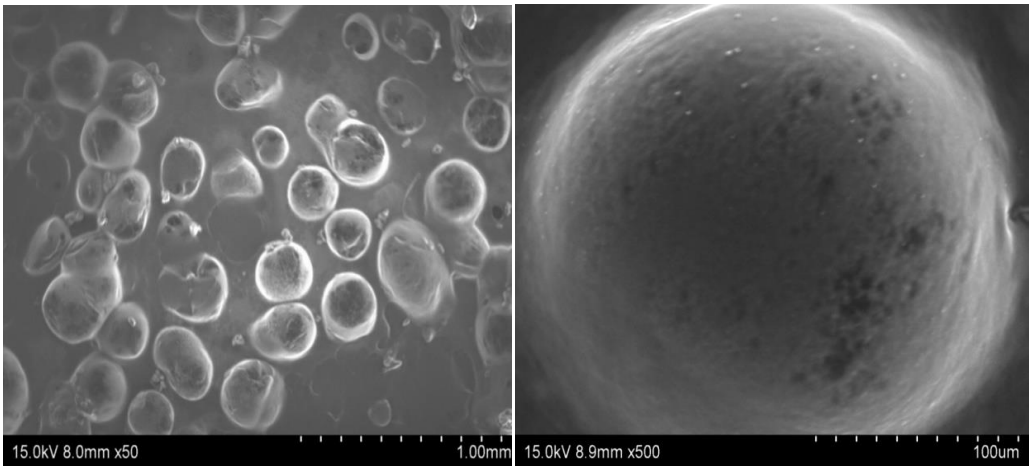


Fig 6: FTIR Spectroscopy of Benazepril formulation

Scanning Electron Microscopy

SEM of benazepril buccal gel (figure 7A,7B) shows the smooth and even surface with the absence of particles suggesting the presence of the drug in dissolved state in the polymer Carbopol 934p.



A **B**

Fig 7: A and B- Benazepril buccal gel SEM

Stability Data

Accelerated stability studies conducted for the final optimized formulation at 40°C /75 % RH for 6 months and evaluated for %drug content, viscosity and surface pH. All the data was found to be within limits and the formulation was stable (table 9).

Table 9: Accelerated stability data at 40°C /75 % RH for 6 months

Retest time for optimized formulation (BG4)	%Drug release	%Drug content
0	99.54±0.64	99.45±0.49
30	99.01±0.15	99.01±0.37
60	98.76±0.78	98.74±0.25
90	98.45±0.35	98.54±0.62
180	98.09±0.25	98.07±.47

Above parameters are communicated as Average ± Standard Deviation; (n=3)

CONCLUSION

To treat hypertension, microspheres incorporated buccal gel of benazepril was formulated and evaluated. The mucoadhesive microspheres were being prepared following o/w emulsion solvent evaporation technique by varying concentrations of ethyl eudragit EPO polymer, ethyl acetate andtween 80. Ten such formulations prepared and evaluated for micrometric parameters, drug dissolution and stability studies. Formulation F10 possessing bulk density of 0.45 g/ml), tapped density of 0.52 g/ml, optimal angle of repose (25.74), CI value of 9.37, Hausner's ratio of 101 was chosen optimal. These findings indicated that the all the batches of formulations exhibited good flow properties. The particle size of F10 is least (412 µm) maximum entrapment efficiency (98.79%) and maximum drug content of 98.94%. The dissolution profile of all formulations indicates All the formulations exhibited more than 90% of drug release by the end of 12 h when compared to pure drug which released only 38.41% by the end of 12 h. Formulation F10 showed highest drug release of 99.42%owing to the highest concentration of polymer used in it.

Hence F10 is chosen for incorporation into buccal gel using various polymers.Nine formulations of microspheres incorporated buccal gel(BG1-BG9) prepared and evaluated. The result showed that all the formulations had good bioadhesive values. The formulation prepared from carbopol-934P polymer showed the highest bio adhesive property when compared to other formulations which may be due to greater polymeric crosslinking structure and greater cohesive force between polymeric gel and buccal mucosal membrane. BG6 was the final optimized formulation with drug release of 99.54% containing carbopol 934p polymer in high concentration.

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