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Preparation and in vivo evaluation of oral films containing benazepril

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ABSTRACT

Mouth dissolving film (MDF) is a better alternate to oral disintegrating tablets due to its novelty, ease of use, and the consequent patient compliance. The present investigation highlights the formulation and evaluation of mouth dissolving films of Benazepril. It was prepared by solvent casting method using HPMC and maltodextrin as film forming polymer. The prepared films were subjected for *in vitro* evaluation tests like thickness, folding endurance, surface pH, morphological properties, moisture content, %Drug content and content uniformity, tensile strength, percent elongation, *In vitro* disintegration time, in vitro dissolution studies and stability studies. The in vitro disintegration time and dissolution time of the optimized formulation (F15) was found to be 9 seconds and 99.45 % within 7 min respectively. FTIR studies showed no drug polymer interaction takes place. From in vivo bioavailability studies, C_{max} of the optimized formulation F15 was 105±0.4ng /ml, was significantly higher as compared to pure drug suspension, i.e., 82±0.1ng/ml. T_{max} of optimized formulation was decreased significantly when compared with pure drug (1.00±0.2hr, 2.00±0.3hr), $AUC_{0-\infty}$ and AUC_{0-t} for optimized solid dispersion formulation was significantly higher ($p<0.05$) as compared to marketed product. These results revealed that fast dissolving films of Benazepril could be formulated for quick onset of action which is required in the efficient management of hypertension.

Keywords: Benazepril, HPMC, Hypertension, Mouth dissolving films, Pharmacokinetics.

INTRODUCTION

Fast dissolving drug delivery systems such as Mouth dissolving films are novel dosage forms that disintegrate or dissolve within the oral cavity. They have emerged as a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but to all age group people. (Kulkarni PK et., al 2011). These systems may offer superior clinical profiles with potential oral mucosal absorption, thus increasing the drug bioavailability with respect to oral administration. The rapid disintegration system of these FDOF's is mainly because of formulation modifications i.e. by the use of super-disintegrant and sugar-based ingredients.(Aggarwal J et., al 2011) [2, 10]. Owing to large surface area of the film formulation, there is greater

disintegration and dissolution in the oral cavity. As the drug is absorbed through buccal mucosa, first pass metabolism is avoided thus enhancing the bioavailability. Films prove to be advantageous in case of dysphagic patient. As compared to orally disintegrating tablets the films are less fragile and hence provide ease of transportation (Upreti K et., al 2014) [19]. Hydroxy propyl methyl cellulose is the water soluble swellable polymer which was used as a film forming agents at low viscosity. There are several preferred grades of HPMC film formers few of them are HPMC 15CPS, HPMC E5LV and HPMC E 15LV. These polymers were easily soluble in the water and gives viscous clear solution (Corniello CM 2006, Sweetman SC. 2007) [6].

Benazepril and benazeprilate inhibit angiotensin-converting enzyme (ACE) in human subjects and animals (Bhushan et., al 2016) [5]. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-rennin hypertension (Mahendran et., al 2010) [11].

MATERIALS AND METHODS

Materials

Benezapril was obtained as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. HPMC 15 CPS, HPMC E5 LV, PEG 400, Mannitol, Citric acid and Maltodextrin were procured from MSN Labs ltd, Hyderabad. Amaranth procured from Oxford Laboratory, Mumbai. SLS, Menthol, PG and PVPK 30 were procured from SD fine ltd, Mumbai.

Methods

Preparation of Benazepril oral films

It was aimed to prepare fast dissolving oral films of Benezapril with the dose of 20 mg per 4 cm^2 film. Film forming polymers like HPMC 15CPS, HPMC E5 LV, HPMC E15LV and maltodextrin were weighed accurately, added to a small amount of water in a small beaker, covered with an aluminium foil and soaked for 24 hours to ensure complete hydration. Then, PEG 400 and PG was added and stirring was continued for 30 minutes at 50rpm. Benazepril, Mannitol, citric acid and amaranth were dissolved in sufficient quantity of water and added to the polymer mixture. This film forming solution was then stirred well to obtain a homogenous solution. Dry and clean Petridish was selected and the solution was poured into it. Drying was carried out at 45°C in a hot air oven for 6 hours. The Petridish was then removed and left aside to cool down to room temperature. The film was then peeled carefully using surgical scalpel by making a small incision in the film on one side of the Petridish. Small films of 4 cm^2 were cut from one big film and packed primarily in aluminium foil and secondarily in a self- sealing polythene bag to ensure least moisture penetration and the resulting films were evaluated. The composition of Benezapril fast dissolving oral films with different HPMC grades are shown in **Table 1, 2, 3.**

Evaluation of Benezapril Fast Dissolving Oral Films

Physical characterization of FDOFs

Physical characterization of FDOFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity.

The prepared films were subjected for in vitro evaluation tests like weight variation (Talele Swati G et., al 2015) [17], thickness (Kumar V et., al 2011) [11], folding endurance(Anjum Pathan et., al 2016), surface pH (Mital S et., al 2012) [11], morphological properties, moisture content, % Drug content and content uniformity (Nafee N. A et al., 2003) [13], tensile strength (Agarwal GP and Seth AK, Saini TR. 1985) [1], percent elongation (Peh KK and Wong FC. 1999), In vitro disintegration time, in vitro dissolution studies and stability studies.

In vitro disintegration studies

The disintegration time is the time when a film starts to break or disintegrate. The dissolution time

is the time when the film completely dissolves. The in vitro disintegration and dissolution time of fast-dissolving films was determined visually in a glass dish of 25 ml distilled water with swirling every 10 S. (Alka Tomar et al., 2012) [3]

In vitro dissolution studies

The dissolution profile of quick release films of Benazepril was carried out in USP basket type apparatus containing 900 ml of Phosphate buffered saline pH 7.4. The film was placed in the basket, maintained at 37 ± 0.5°C and the agitation speed was 50 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at regular time intervals and the same amount was replaced with the fresh medium. Samples were analysed spectrophotometrically at 241 nm and the cumulative percentage of drug release was calculated (Hiroyoshi S et al., 2009.) [8]

Moisture Content

The patches were weighed and kept in a desiccators containing calcium chloride at 40^{o}C for 24 hr. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight. . (Tanwar YS et al., 2007) [18]

Drug Excipient Compatibility Studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method (Ivory AA et al., 2004, Dinge A and Nagarsenker M) [7].

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

SEM studies

The surface characteristics of film were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

Stability studies

The stability study of the optimized fast-dissolving films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The patches were characterized for the drug content and other parameters during the stability study period.

Pharmacokinetic Study

Animal Preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^{0}C, RH 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

In vivo Study design

Rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were anaesthetized with intravenous injection of pentobarbital in a dose of 25mg/kg then positioned on table with the lower jaw supported in a horizontal position and the FDF contains Benezapril was carefully placed on the rabbit tongue. The marketed drug was administered orally to group B with equivalent to animal body weight.

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00 & 24.00h after dosing. Blood samples were collected in heparinised tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml

of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200 µ1 of 70 % of acetonitrile and 30% water was injected for HPLC analysis.

For HPLC an Inertsil ODS 3V, 250x4.6 mm, column with 5 µm particle size and in this method, chromatographic separation was achieved using a LiChrospher 60 RP column at 25°C, The sample was analysed using Triethylamine: Acetonitrile: Methanol in the ratio of 50:25:25(pH adjusted to 3.0 with Orthrophosphric acid) as a mobile phase at a flow rate of 2.0ml/min and detection at 235nm. The retention time for Amlodipine (Internal Standard) and Benazepril hydrochloride was found to be 16.999 and 12.550 min respectively, (Bharat Kumar D , Jitendra patel, Pranati Chhatoi , Shabana Begum, Suddhasatya Dey (2011). Analytical Method Development and Validation of Amlodipine and Benazepril hydrochloride in combined dosage form by RP-HPLC, *International Journal of Chemical and Pharmaceutical Sciences*, April., 2 (1): 26-10**)**

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Preparation of Benezapril oral films

It was aimed to prepare fast dissolving oral films of Benezapril with the dose of 20 mg per 4 cm^2 film. Total 18 formulations were prepared using three different polymers like HPMC 15 CPS, HPMC E5LV and maltodextrin, the resulting films were shown in **Figures 1.**

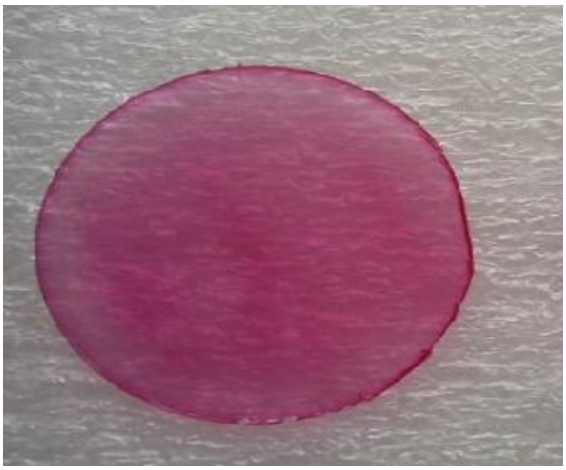

Figure 1: Preparation of oral mouth dissolving films of Benezapril

Physical Characterization of films

Physical characterization of FDOFs was carried out by visual inspection and the following results were observed.

The films were evenly colored and no migration of color was observed. The increased thickness of film is attributed to the increase in the amount of HPMC 15 CPS, HPMC E5LV and blend of polymers. All formulations were found to be excellent in film forming property, non-tacky, thin, flexible and easy to peel. The films obtained from all the formulations had smooth surface on either side.

Evaluation of fast dissolving oral films of Benezapril

Thickness & Weight variation

Weight variation, transparency and thickness of all the formulations were found to be within the limits and results were depicted in Table 4. Formulation F15 was found to be optimized one on the basis of evaluation parameters.

Drug content, moisture content, folding endurance and pH was found to be within the limits and the results are summarized in **Table 5**.

In vitro disintegration studies

The disintegrating time of all the formulations was ranges from 9 to 19sec. The disintegration time of optimized formulation (F15) was found to be 9 sec, which was very less and desirable for quick onset of action (**Table 4 & Figure 2**).

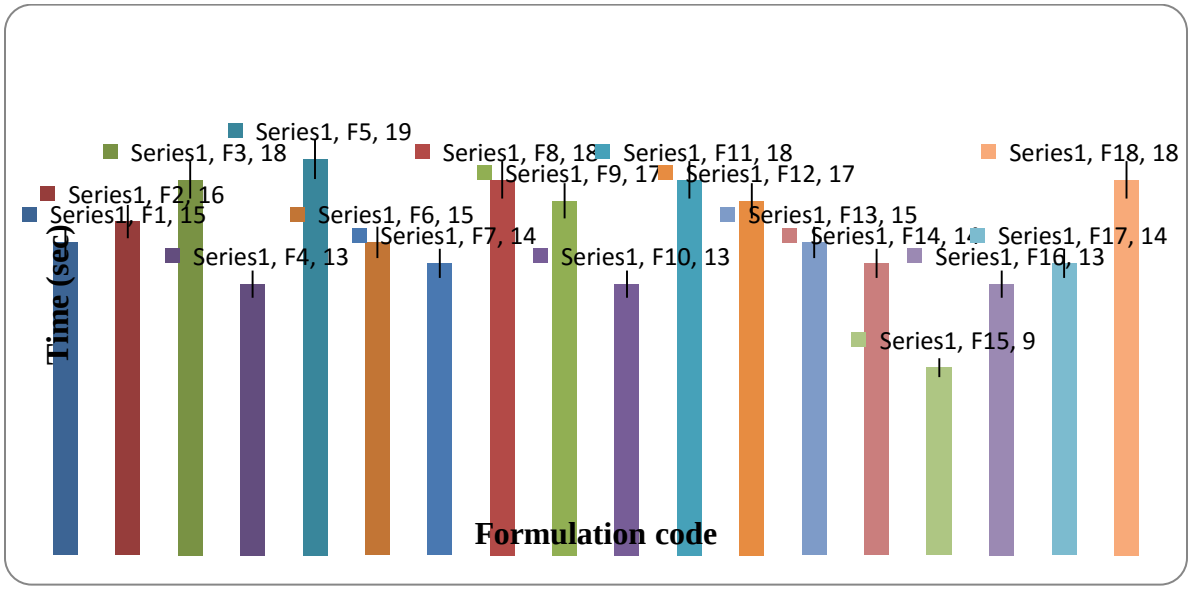

Figure 2: *In vitro* disintegrating time of all Formulations F1-F18

Tensile strength and Percent Elongation

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation at break. Results revealed thatoptimized formulation (F15) showed better tensile strength (11.8 g/cm^2) and moderate % elongation (9.6) (**Table 6**).

In-vitro drug dissolution study of formulation batches F1 to F18

The cumulative % drug release for the formulations F1 to F18 are graphically represented in **Figure 3-5**.The optimized formulation (F15) shows highest Percent of drug release 99.45±5.30 by the end of 7 min (**Figure 3-5**).

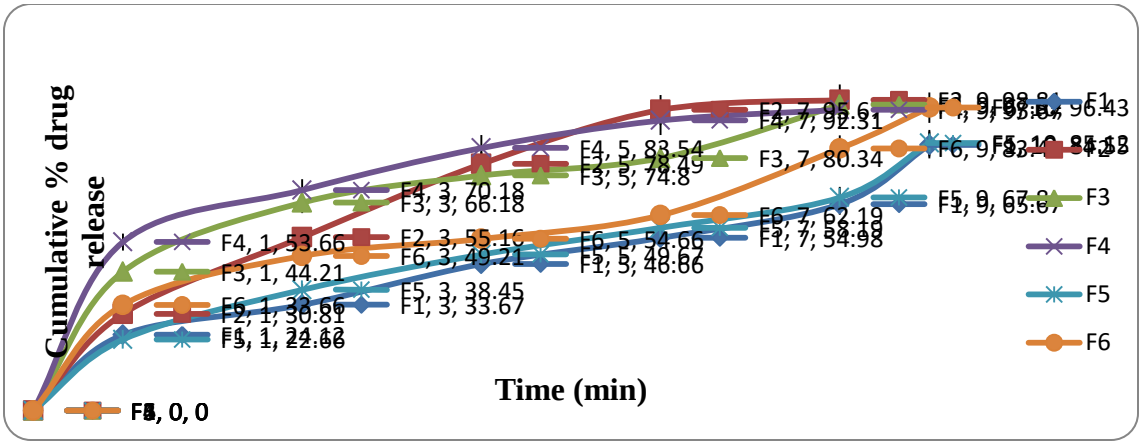

Figure 3: Cumulative % drug release of Formulation F-1 to F-6

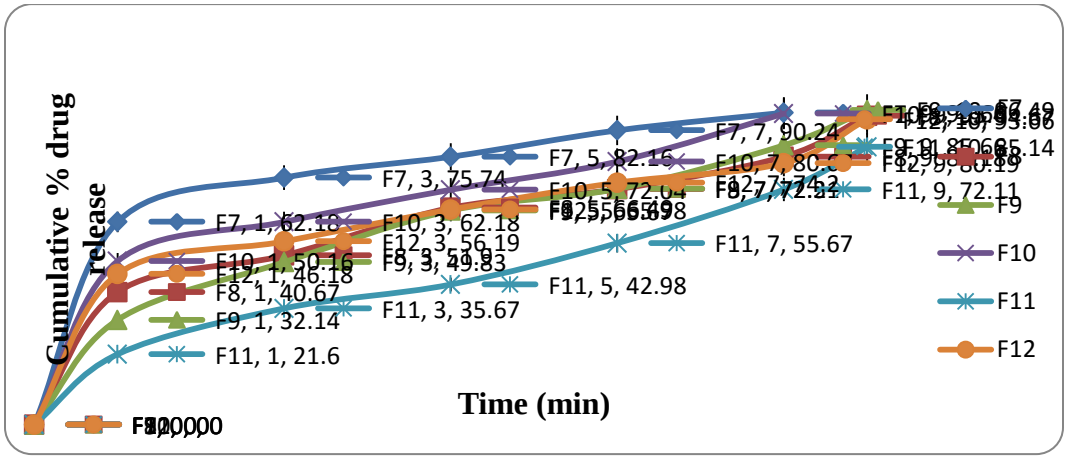

Figure 4: Cumulative % drug release of Formulation F-7 to F-12

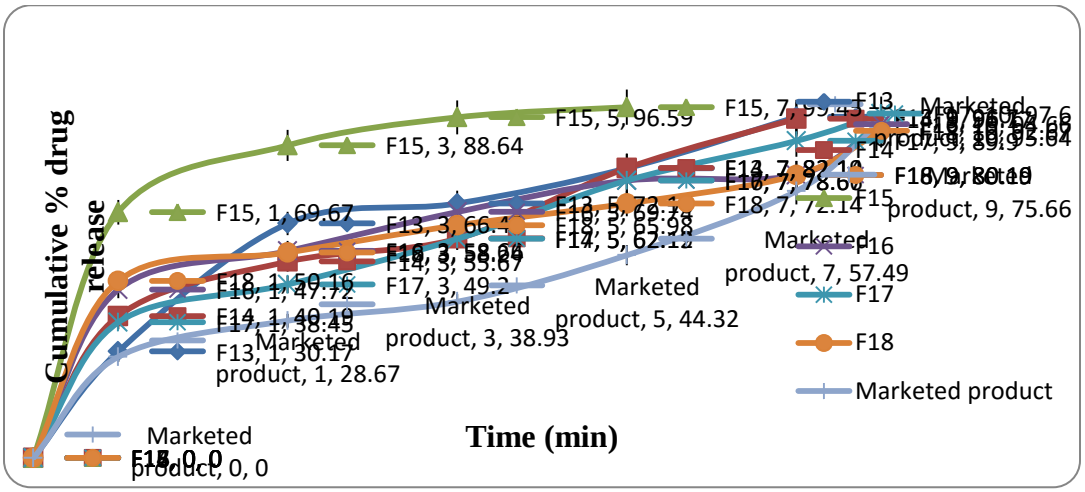

Figure 5: Cumulative % drug release of Formulation F-13 to F-18

Drug Excipient Compatibility Studies by FTIR

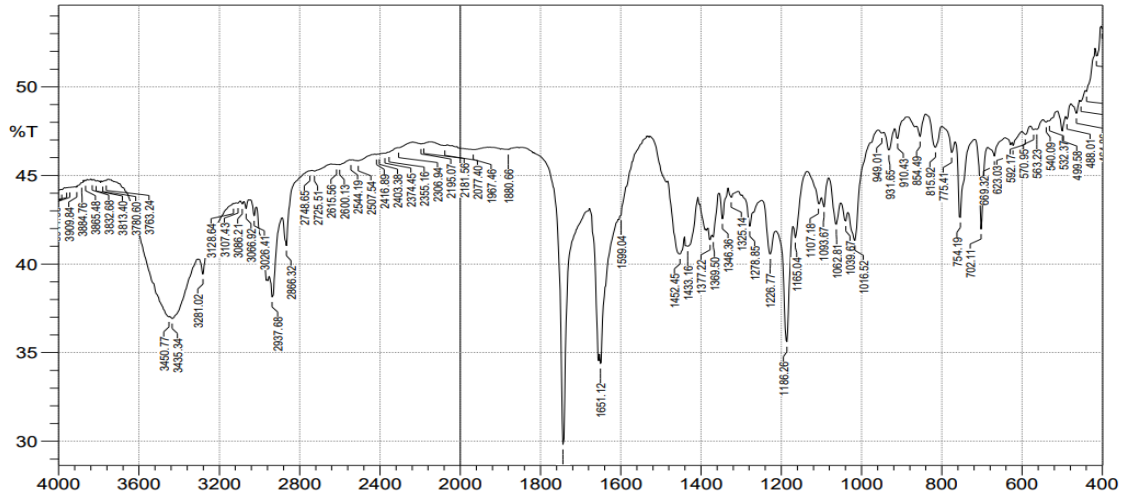

Figure 6: FTIR Spectroscopy of Benezapril Pure Drug

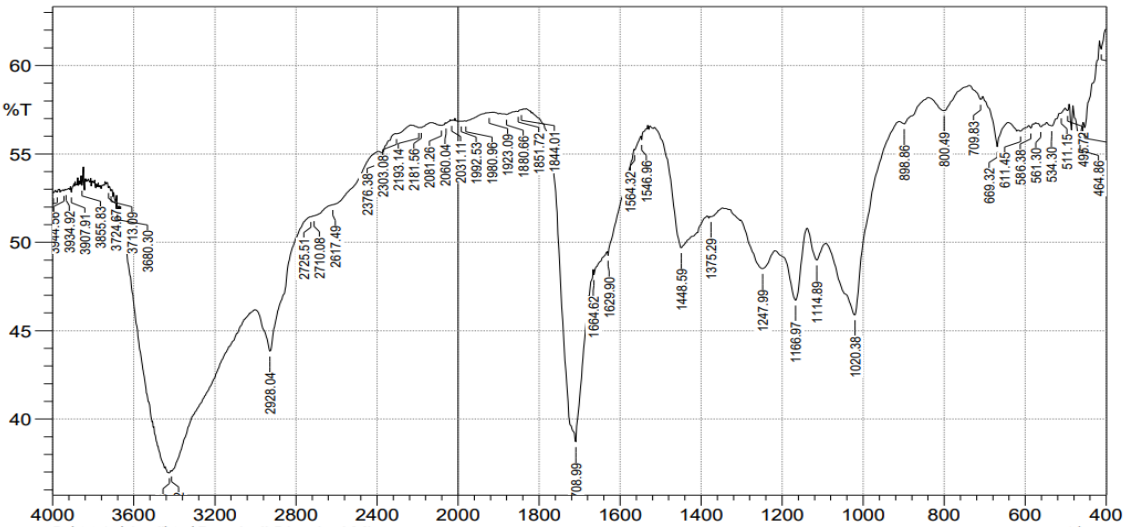

Figure 7: FTIR Spectroscopy of Benezapril optimized mouth dissolving film (F15)

The presence of characteristic absorption bands of Benezapril pure drug **(Figure 6)** and the optimized film containing **Benezapril** (**Figure 7**) suggest that there is no interaction takes place between the drug and excipients used in the formulation.

Scanning electron microscopy

SEM of **Benezapril** mouth dissolving film shows the rough and uneven surface with circular pits with the absence of particles suggesting the presence of the drug in dissolved state in the polymer HPMC. They further ensure the loss of crystallinity when formulated as a film comprising amorphous HPMC (**Figure 8**).

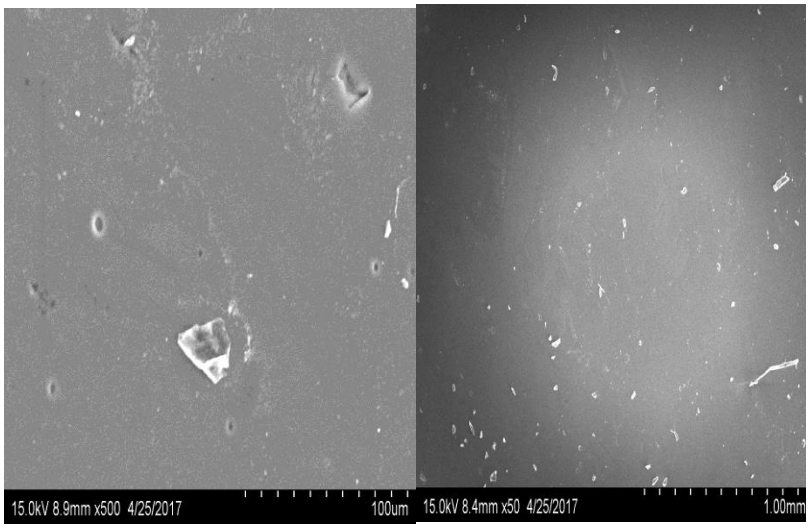

Figure 8: Scanning electron micrograph of Benezapril optimized mouth dissolving films

Stability Studies for optimized formulation

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Disintegrating time, drug content and In vitro drug release studies were performed for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation F15 is stable and retained their original properties with minor differences.

Pharmacokinetic studies

Pharmacokinetic parameters comparison for Benezapril optimized film and marketed Product

The bioavailability parameters for the both test film and reference standard are summarized in **Table 12**. Mean time to reach peak drug concentration (T_{max}) was 1.00±0.5h and 2.0±0.1h for the optimized and commercial formulations, respectively, while mean maximum drug concentration (C_{max}) was 105±0.4ng/ml and 82±0.1ng/ml, respectively. C_{max} was significantly increased when compared with marketed product. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0-\infty}$ infinity for film formulation was higher (420.46±1.14ng. h/ml) than the marketed Product 316.11±1.12ng. h / ml. Statistically, AUC_{0-t} of the Film formulation was significantly higher ($p<0.05$) as compared to Marketed formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Benezapril from Film formulation as compared to the Marketed Product.

Table 12: Comparison of pharmacokinetic parameters of Benezapril between the film and marketed Product in Rabbits (mean ± SD, n = 6).

Pharmacokinetic Parameters	Optimized formulation	Marketed Product
C_{max} (ng/ml)	105±0.4	82±0.1
AUC_{0-t} (ng. h/ml)	318.88±1.74	246.47±2.16
$AUC_{0-\infty}$ (ng. h/ml)	420.46±1.14	316.11±1.12
T_{max} (h)	1.00±0.5	2.0±0.1
$t_{1/2}$ (h)	2.053 ± 0.5	3.364 ± 0.1

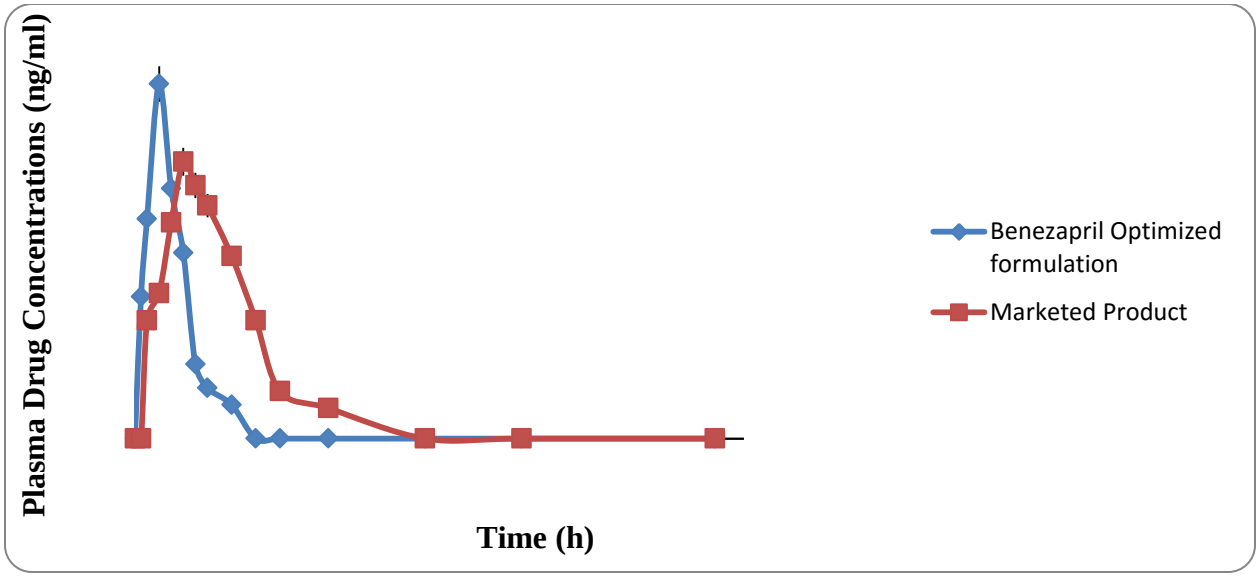

Figure : Figure 12: Plasma concentration–time curves for the benazepril optimized formulation and marketed product

Table 1: Formulation Trails Using HPMC 15 CPS

INGREDIENTS	F1	F2	F3	F4	F5	F6
Benezapril drug (mg)	317.9	317.9	317.9	317.9	317.9	317.9
HPMC 15 CPS (mg)	100	150	200	250	300	350
Maltodextrin (mg)	110	130	150	170	190	210
PEG 400 (mg)	25	25	25	25	25	25
SLS (mg)	-	25	-	25	-	25
Mannitol (mg)	50	50	50	50	50	50
Citric acid (mg)	15	15	15	15	15	15
Menthol (mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distill water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Formulation Trails Using HPMC E5LV

INGREDIENTS	F7	F8	F9	F10	F11	F12
Benezapril drug (mg)	317.9	317.9	317.9	317.9	317.9	317.9
HPMC E5LV (mg)	100	150	200	250	300	350
PG (mg)	20	25	20	25	20	25
Maltodextrin (mg)	100	110	120	130	140	150
PVP K 30 (mg)	-	25	-	25	-	25
Mannitol (mg)	50	50	50	50	50	50
Citric acid (mg)	15	15	15	15	15	15
Menthol (mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distill water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 3: Formulation Trails Using HPMC E5LV

INGREDIENTS	F13	F14	F15	F16	F17	F18
Benezapril drug (mg)	317.9	317.9	317.9	317.9	317.9	317.9
HPMC E5LV (mg)	150	175	200	250	300	350
Maltodextrin (mg)	100	110	135	110	120	125
PEG 400 (mg)	25	25	25	25	25	25
SLS (mg)	-	20	-	25	-	30
PVP K 30 (mg)	20	-	30	-	25	-
Mannitol (mg)	50	50	50	50	50	50
Citric acid (mg)	15	15	15	15	15	15
Menthol (mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distill water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 4: Evaluation parameters of Benezapril mouth dissolving films

Formulation Code	Weight variation (mg)	Transparency	Thickness (mm)	Disintegration time (sec)
F1	21±0.51	Clear	0.215±0.06	15±0.35
F2	23±0.59	Clear	0.235±0.06	16±0.35
F3	24±0.60	Clear	0.254±0.05	18±0.36
F4	20±0.49	Clear	0.227±0.07	13±0.24
F5	21±0.51	Clear	0.248±0.09	19±0.36
F6	23±0.59	Clear	0.237±0.07	15±0.36
F7	24±0.60	Clear	0.246±0.06	14±0.29
F8	23±0.59	Clear	0.215±0.06	18±0.36
F9	20±0.49	Clear	0.218±0.09	17±0.36
F10	23±0.59	Clear	0.223±0.04	13±0.24
F11	20±0.49	Clear	0.225±0.06	18±0.36
F12	24±0.60	Clear	0.228±0.09	17±0.36
F13	21±0.51	Clear	0.234±0.05	15±0.35
F14	23±0.59	Clear	0.240±0.02	14±0.24
F15	**22±0.58**	**Clear**	**0.249±0.10**	**9±0.20**
F16	25±0.62	Clear	0.245±0.06	13±0.24
F17	24±0.60	Clear	0.251±0.02	14±0.24
F18	21±0.51	Clear	0.261±0.02	18±0.36

Values are expressed in mean± SD (n=3)

Table 5: Evaluation parameters of Benezapril mouth dissolving films

Formulation Code	Drug Content (%)	Moisture content (%)	Folding Endurance (count)	Surface pH
F1	95.20±0.58	3.51±0.30	95±1	6.79±0.5
F2	96.42±0.60	3.81±0.50	94±2	6.78±0.4
F3	97.89±0.62	3.90±0.60	95±2	6.87±0.4
F4	94.40±0.56	4.50±0.29	98±1	6.81±0.2
F5	95.15±0.58	4.69±0.48	99±4	6.67±0.4
F6	96.62±0.60	4.98±0.69	96±1	6.62±0.3
F7	95.54±0.58	4.25±0.24	98±2	6.85±0.6
F8	97.31±0.62	3.99±0.68	105±1	6.72±0.3
F9	94.32±0.56	3.01±0.09	102±2	6.79±0.4
F10	93.67±0.52	3.52±0.33	105±1	6.81±0.2
F11	97.61±0.62	3.33±0.29	105±2	6.85±0.6

F12	96.62±0.60	3.68±0.47	104±1	6.53±0.3
F13	97.60±0.62	3.85±0.54	106±3	6.58±0.4
F14	98.61±0.64	4.01±0.09	110±1	6.80±0.4
F15	**99.80±0.69**	**4.18±0.20**	**118±4**	**6.93±0.5**
F16	92.45±0.50	4.32±0.29	98±1	6.60±0.1
F17	94.41±0.56	3.51±0.30	105±2	6.78±0.4
F18	95.60±0.58	3.90±0.60	91±2	6.81±0.2

Values are expressed in mean± SD (n=3)

Table 6: Tensile Strength and Percent Elongation

FORMULATION CODE	TENSILE STRENGTH (g /cm^2)	PERCENT ELONGATION (%)
F15	11.8	9.6

CONCLUSION

The present research work was aimed to formulate and evaluate mouth dissolving films of benazepril. The film was prepared by solvent casting method using different grades of HPMC and maltodextrin as film forming polymer. The prepared films were subjected for *in vitro* evaluation tests like thickness, folding endurance, surface pH, morphological properties, moisture content, %Drug content and content uniformity, tensile strength, percent elongation, *In vitro* disintegration time, in vitro dissolution studies and stability studies. The in vitro disintegration time and dissolution time of the optimized formulation (F15) was found to be 9 seconds and 99.45 % within 7 mints respectively. FTIR studies showed no drug polymer interaction takes place. From in vivo bioavailability studies, C_{max} of the optimized formulation F15 was 105±0.4ng /ml, was significantly higher as compared to pure drug suspension, i.e., 82±0.1ng/ml. T_{max} of optimized formulation was decreased significantly when compared with pure drug (1.00±0.2hr, 2.00±0.3hr), $AUC_{0-\infty}$ and AUC_{0-t} for optimized films was significantly higher ($p<0.05$) as compared to marketed product. These results revealed that fast dissolving films of Benazepril could be formulated for quick onset of action which is required in the efficient management of hypertension.

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