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Design and In Vivo Evaluation of Quinapril Fast Dissolving Oral Films

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ABSTRACT

In current investigation an attempt has been made to formulate and evaluate Quinapril mouth dissolving films using HPMC 50cps, E5, E15 and in combination of Pullulan by Solvent evaporation method. Sodium starch glycolate acts as a super disintegrating agent and it is shown that as the concentration of the super disintegrates increases the disintegration time decreases. The films were evaluated for weight variation, surface pH, folding endurance, drug content, dissolving time, disintegration time, and in-vitro dissolution studies. Based on the evaluation parameters F17 was to be optimized formulation. The optimized film (F17) showed the more drug release i.e 99.40±5.30% within 7 min, lowest in vitro disintegration time 10 sec. FTIR studies proved no drug polymer interaction takes place. From in vivo bioavailability studies, C_{max} of the optimized formulation F17 was 72.43±0.3ng /ml, was significantly higher as compared to pure drug suspension, i.e., 42.32±0.1ng/ml. T_{max} of optimized formulation was decreased significantly when compared with pure drug (1.00±0.05hr, 2.00±0.1hr), $AUC_{0-\infty}$ 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 Quinapril could be formulated for quick onset of action which is required in the efficient management of hypertension.

Keywords: Quinapril, Mouth dissolving films, Hypertension, Bioavailability studies

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INTRODUCTION

The oral route is one of the oldest routes which are used for conventional and novel drug delivery. The main reason for this route being the highly preferred is ease of administration. FDFs, a new drug delivery system for the oral delivery of the drugs, was developed in late 1970's based on the technology of the transdermal patch. These were developed as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms[1]. Some problems are associated with the OFDF like they are sometime difficult to carry, storing and handling (friability and fragility), these are prepared using the expensive lyophilisation method [2, 3]. To overcome these problems oral films were developed, which are very popular now a days. The concept of oral film was come from confectionary industry [4, 5].Orally fast-dissolving film rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption [6].

Quinapril HCl (marketed under the brand name Accupril by Pfizer) is an angiotensin-converting enzyme inhibitor (ACE inhibitor) used in the treatment of hypertension and congestive heart failure. Due to reduced angiotensin production, plasma concentrations of aldosterone are also reduced, resulting in increased excretion of sodium in the urine and increased concentrations of potassium in the blood. Quinapril HCl is indicated for the treatment of high blood pressure (hypertension) and as adjunctive therapy in the management of heart failure. It may be used for the treatment of hypertension by itself or in combination with thiazide diuretics, and with diuretics and digoxin for heart failure. Quinapril HCl has short half-life 2 hour [7]. The objective of present study is to develop mouth dissolving films of Quinapril for better patient compliance and to provide effective mode of treatment to the impaired and non-cooperative patients suffering from hypertension.

MATERIALS AND METHOD

Materials:

Quinapril was obtained as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. HPMC 50CPS, HPMC E5, HPMC E15, SSG and Pullalan procured from MSN Labs Ltd, Hyderabad, propylene glycol, citric acid, menthol procured from S.D. Fine chemicals, Mumbai.

Methods:

Preparation of Quinapril oral films

It was aimed to prepare fast dissolving oral films Quinapril with the dose of 10 mg per 4 cm^2 film. Film forming polymers like HPMC 50CPS, HPMC E5 , HPMC E15 and Pullalan 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, PG was added and stirring was continued for 30 minutes at 50rpm. Quinapril, Sucralose, citric acid and menthol 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 Quinapril fast dissolving oral films with different HPMC grades and pullalan are shown in Table 1, 2 & 3.

Table 1: Formulation Trails Using HPMC 50 CPS

Ingredients	F1	F2	F3	F4	F5	F6
Quinapril (mg)	158.95	158.95	158.95	158.95	158.95	158.95
HPMC 50 CPS	150	200	250	300	350	400
Pullalan	100	110	130	160	150	140
Propylene glycol	30	30	30	30	30	30
Citric acid	80	80	80	80	80	80
Sucralose	40	40	40	40	40	40
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
SSG	4	4	4	8	8	8
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Formulation Trails Using HPMC E5

Ingredients	F7	F8	F9	F10	F11	F12
Quinapril (mg)	158.95	158.95	158.95	158.95	158.95	158.95
HPMC E5	100	200	250	300	375	450
Pullalan	100	120	140	160	180	200
PG	30	30	30	30	30	30
SSG	10	10	10	12	12	12
Citric acid	80	80	80	80	80	80
Sucralose	40	40	40	40	40	40
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 3: Formulation Trails Using HPMC E15

Ingredients	F13	F14	F15	F16	F17	F18
Quinapril (mg)	158.95	158.95	158.95	158.95	158.95	158.95
HPMC E15	125	175	200	250	400	350
Pullalan	100	120	140	160	180	200
Propylene glycol	30	30	30	30	30	30

Citric acid	80	80	80	80	80	80
Sucralose	40	40	40	40	40	40
SSG	14	15	14	16	18	16
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Evaluation of quinapril 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 Surface pH [8], Weight variation[9], Thickness [10], Folding Endurance [11], Morphological properties, Moisture content, % Drug content and content uniformity [12], Percent elongation[13], Tensile strength [14], *In vitro* Disintegration time, *In vitro* Dissolution studies and *in vivo* studies on rabbits.

***In vitro* disintegration studies**

Test was performed using disintegration test apparatus. 4 cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute. Time required by the film, when no traces of film remain above the gauze was noted [15].

***In vitro* dissolution studies**

The *in-vitro* dissolution studies were conducted using 900 ml of 0.1 N HCl (pH 1.2). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm^2) was placed on a stainless-steel wire mesh with sieve opening 700µm. The film sample placed on the sieve was submerged into dissolution media. Aliquots (5 ml) of the dissolution medium were withdrawn at regular time intervals and the same amount was replaced with the fresh medium and filtered through 0.45µm Whatman filter paper and was analyzed spectrophotometrically at 259 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches [16].

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 [17].

Drug Excipient Compatibility Studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method [18].

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

quinapril 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 Chromatographic analysis of quinapril in plasma was achieved on a µ-bondapack C18 column (150×4.6 mm, 5µ) mobile phase containing Methanol: Water (80:20) was used. The flow rate was 1.0 ml/min and effluent was monitored at 232 nm. The retention time (min) for quinapril and hydrochlorothiazide (internal standard) were (3.6, 2.2)

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 Quinapril oral films

It was aimed to prepare fast dissolving oral films of Quinapril with the dose of 10 mg per 4 cm^2 film. Total 18 formulations were prepared using three different polymers, HPMC 50 CPS, HPMC E5, HPMC E15 and maltodextrin, the resulting films were shown in figure 1.

Figure 1: Preparation of Quinapril Films

Physical Characterization of films:

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 50CPS, E5, E15 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 Quinapril

Weight variation, transparency and thickness of all the formulations were found to be within the limits and results were depicted in Table 4. Formulation F17 was found to be optimized one on the basis of evaluation parameters.

Table 4: Evaluation parameters of Quinapril mouth dissolving films

Formulation Code	Weight (mg)	Transparency	Thickness (mm)	Disintegration time(sec)
F1	23±0.56	Clear	0.236±0.04	15±0.74
F2	24±0.94	Clear	0.269±0.19	18±0.81
F3	21±0.47	Clear	0.233±0.06	14±0.74
F4	22±0.34	Clear	0.257±0.19	17±0.81
F5	25±0.22	Clear	0.240±0.09	18±0.81
F6	23±0.31	Clear	0.268±0.18	15±0.74
F7	21±0.47	Clear	0.249±0.15	13±0.72
F8	22±0.59	Clear	0.254±0.06	14±0.74
F9	24±0.94	Clear	0.216±0.07	15±0.74

F10	25±0.22	Clear	0.238±0.07	18±0.81
F11	23±0.44	Clear	0.242±0.09	13±0.72
F12	22±0.59	Clear	0.265±0.19	16±0.75
F13	25±0.64	Clear	0.237±0.04	15±0.74
F14	21±0.47	Clear	0.238±0.04	16±0.75
F15	23±0.44	Clear	0.255±0.06	14±0.74
F16	24±0.94	Clear	0.245±0.62	18±0.81
F17	20±0.30	Clear	0.248±0.13	10±0.67
F18	22±0.34	Clear	0.251±0.06	12±0.70

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

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

Table 5: Evaluation parameters of Quinapril mouth dissolving films

Formulation Code	Drug Content (%)	Moisture content (%)	Folding Endurance (count)	Surface pH
F1	97.68±0.62	4.50±0.38	110±2	6.74±0.3
F2	96.61±0.60	4.32±0.29	104±2	6.66±0.4
F3	95.45±0.58	4.29±0.24	103±3	6.78±0.4
F4	92.18±0.50	3.99±0.68	99±1	6.81±0.4
F5	93.67±0.52	3.19±0.10	101±2	6.85±0.6
F6	92.61±0.50	4.12±0.20	98±1	6.66±0.3
F7	91.23±0.49	3.98±0.68	101±2	6.79±0.4
F8	96.13±0.60	4.64±0.48	104±3	6.35±0.3
F9	97.14±0.62	4.48±0.35	107±1	6.48±0.4
F10	96.54±0.60	3.01±0.09	110±2	6.55±0.4
F11	95.54±0.58	4.20±0.24	108±1	6.58±0.4
F12	97.32±0.62	3.42±0.30	111±2	6.69±0.4
F13	95.42±0.58	3.85±0.54	115±2	6.72±0.3
F14	97.68±0.62	3.99±0.68	101±3	6.78±0.4
F15	96.14±0.60	4.01±0.09	104±1	6.66±0.3
F16	92.14±0.50	4.29±0.24	110±2	6.74±0.3
F17	98.13±0.69	4.20±0.24	122±4	6.91±0.2
F18	93.67±0.52	4.66±0.50	109±2	6.81±0.2

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

***In vitro* disintegration studies**

The disintegrating time of all the formulations was ranges from 10 to 17sec. The disintegration time of optimized formulation (F17) was found to be 10 sec, which was very less and desirable for quick onset of action (figure 2 and table 4).

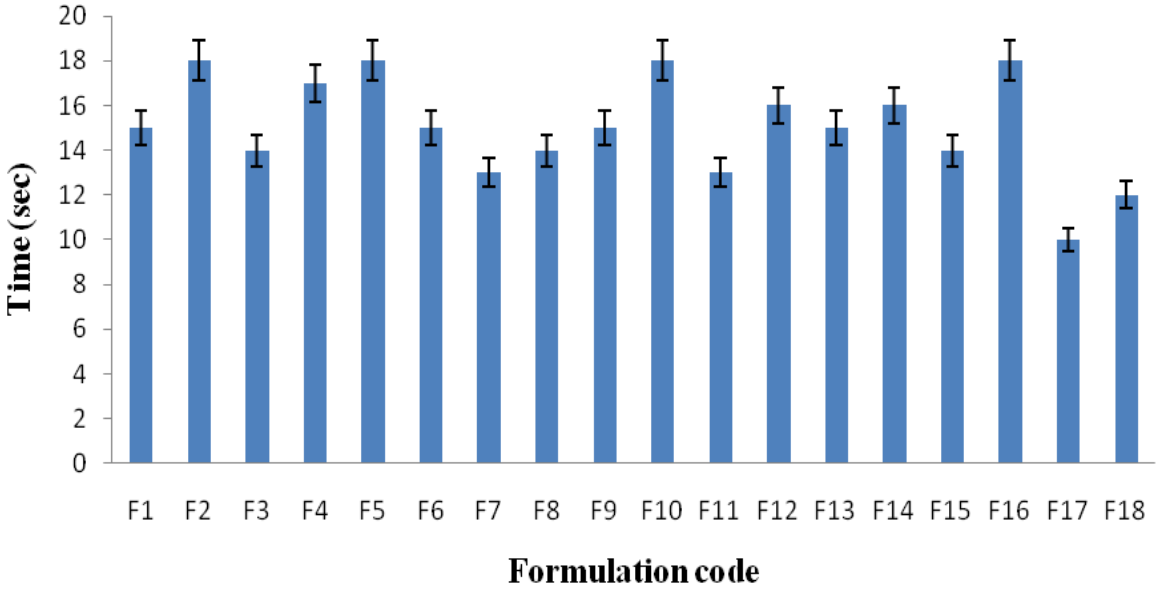


Figure 2: *In vitro* disintegrating time of all Formulations F1-F18

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 (F17) showed better tensile strength (11.9 g/cm^2) and moderate % elongation (9.8) (Table 6).

Table 6: Tensile Strength and Percent Elongation

Formulation Code	Tensile Strength (G /Cm^2)	Percent Elongation (%)
F17	11.9	9.8

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

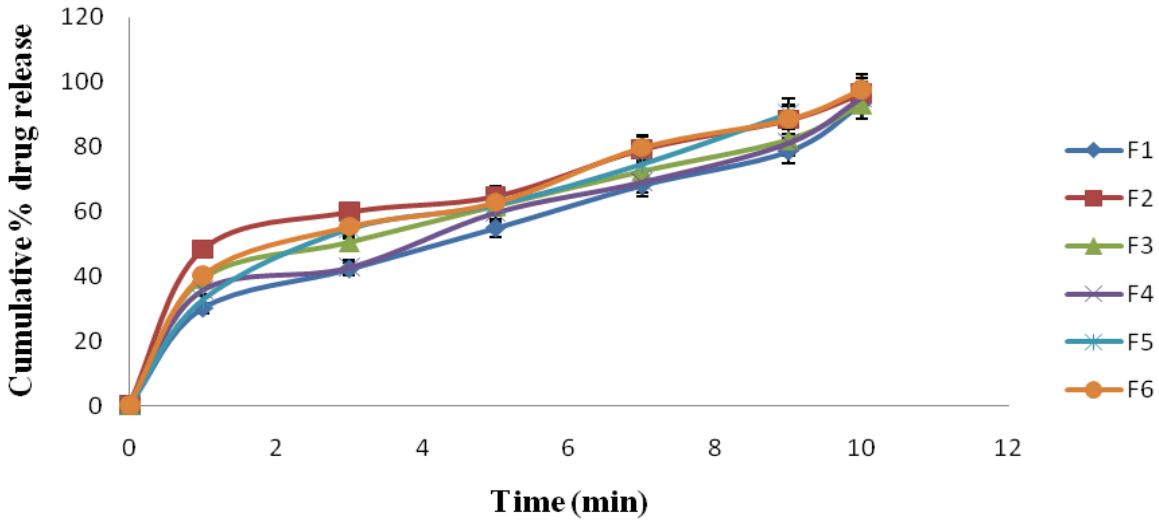


Figure 3: Cumulative % Drug Release for formulation F1-F6

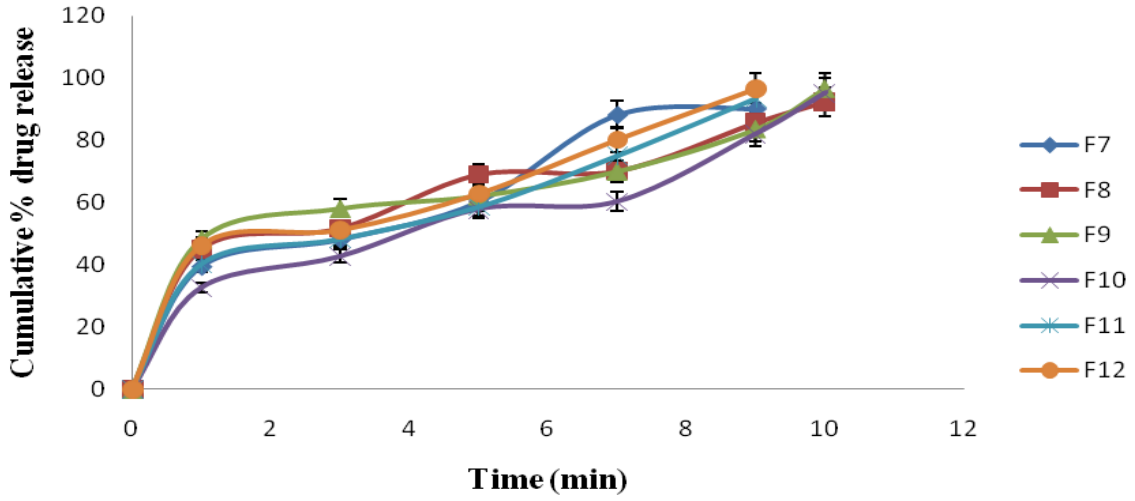


Figure 4: Cumulative % Drug Release of formulation F7-F12

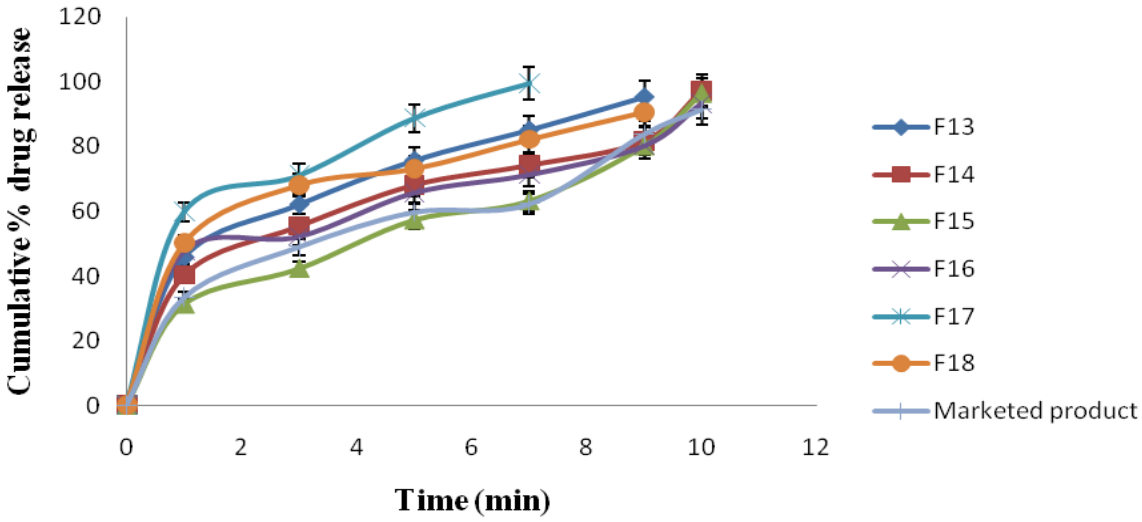


Figure 5: Cumulative % Drug Release of formulation F13-F18

The cumulative % drug release for the formulations F1 to F18 are graphically shown in figures 3-5. The optimized formulation (F17) shows fast and highest Percent of drug release 99.10±4.32by the end of 7 min when compared with marketed product of 81.32 within 10 min.

Drug excipient compatibility studies by FTIR

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

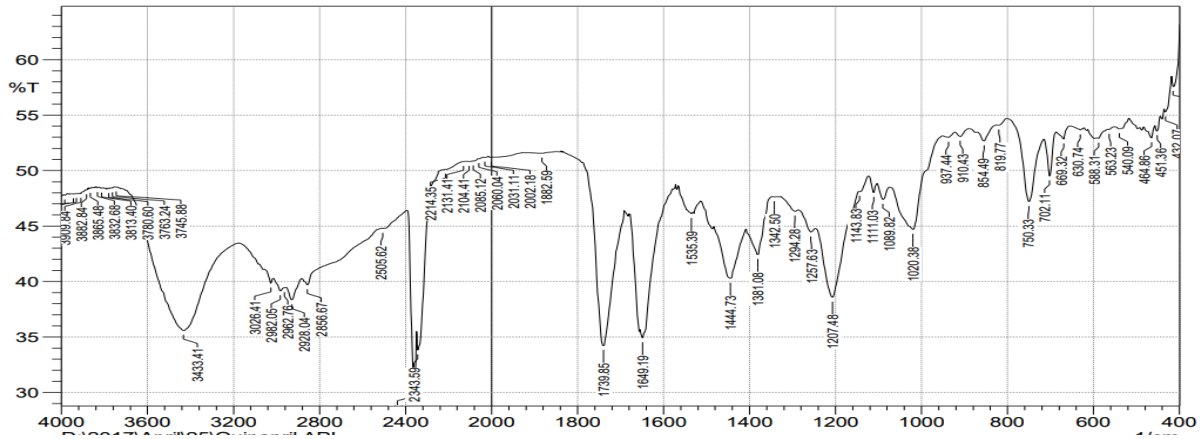


Figure 6: FTIR Spectroscopy of Quinapril Pure Drug

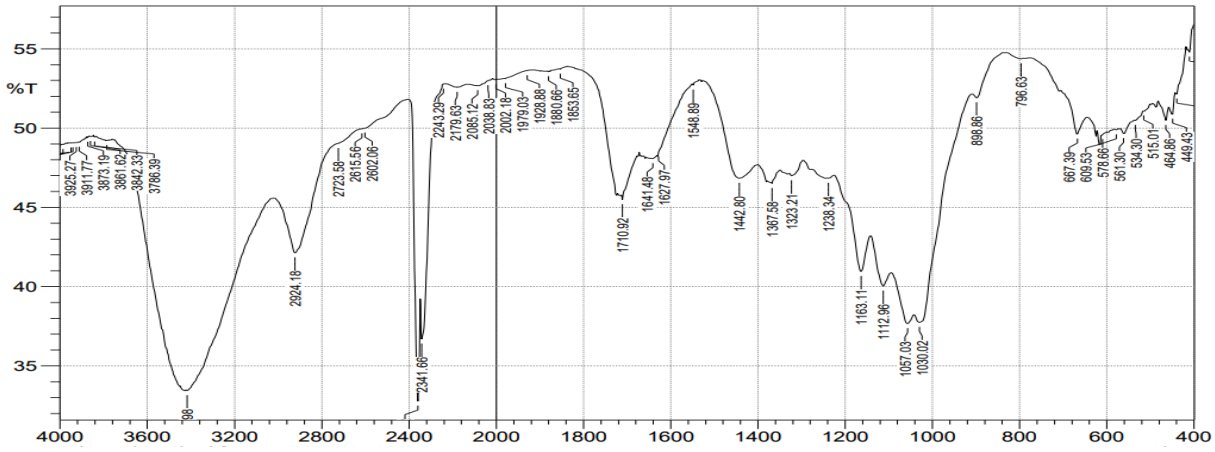
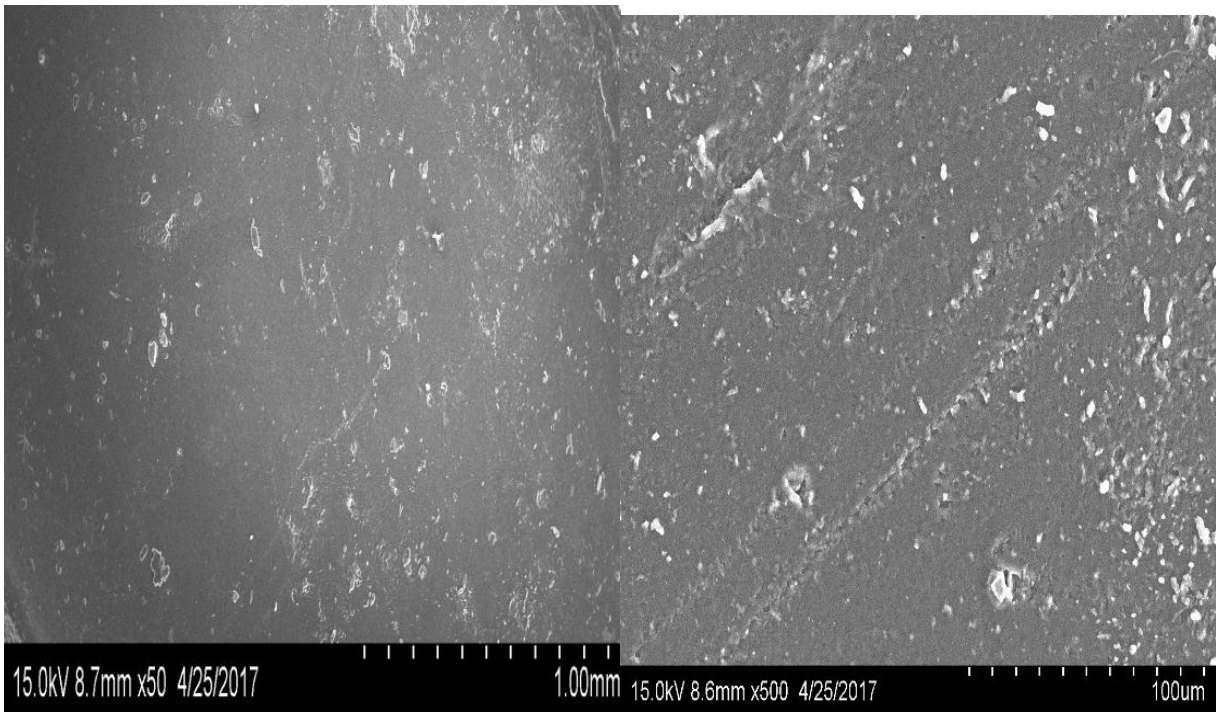


Figure 7: FTIR Spectroscopy of Quinapril optimized mouth dissolving film (F17)

Scanning electron microscopy:

SEM of Quinapril 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 (figures 8 (a) and (b)).



8 (a) **8 (b)**

Figures 8 (a) and (b): Scanning electron micrograph of Quinapril optimized mouth dissolving films

Stability Studies for optimized formulation

Optimized formulation (F17) 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 F17 is stable and retained their original properties with minor differences.

Pharmacokinetic parameters comparison for quinapril optimized film and marketed Product:

Mean time to reach peak drug concentration (T_{max}) was 1.00±0.5h and 2.00±0.1h for the optimized and commercial formulations, respectively, while mean maximum drug concentration (C_{max}) was 72.43±0.3ng/ml and 42.32±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 (337.42±0.144ng. h/ml) than the marketed Product 269.31±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 quinapril from Film formulation as compared to the Marketed Product (table 7).

Table 7: Comparison of pharmacokinetic parameters of quinapril between the film and marketed Product in Rabbits (mean ± SD, n = 6).

Pharmacokinetic Parameters	Quinapril optimized formulation (F17)	Marketed Product
C_{max} (ng/ml)	72.43±0.3	42.32±0.1
AUC_{0-t} (ng. h/ml)	281.78±1.74	180.46±1.16
$AUC_{0-\infty}$ (ng. h/ml)	337.42±0.14	269.31±1.12
T_{max} (h)	1.00±0.5	2.00±0.1
$t_{1/2}$ (h)	2.05 ± 0.51	4.06 ± 0.01

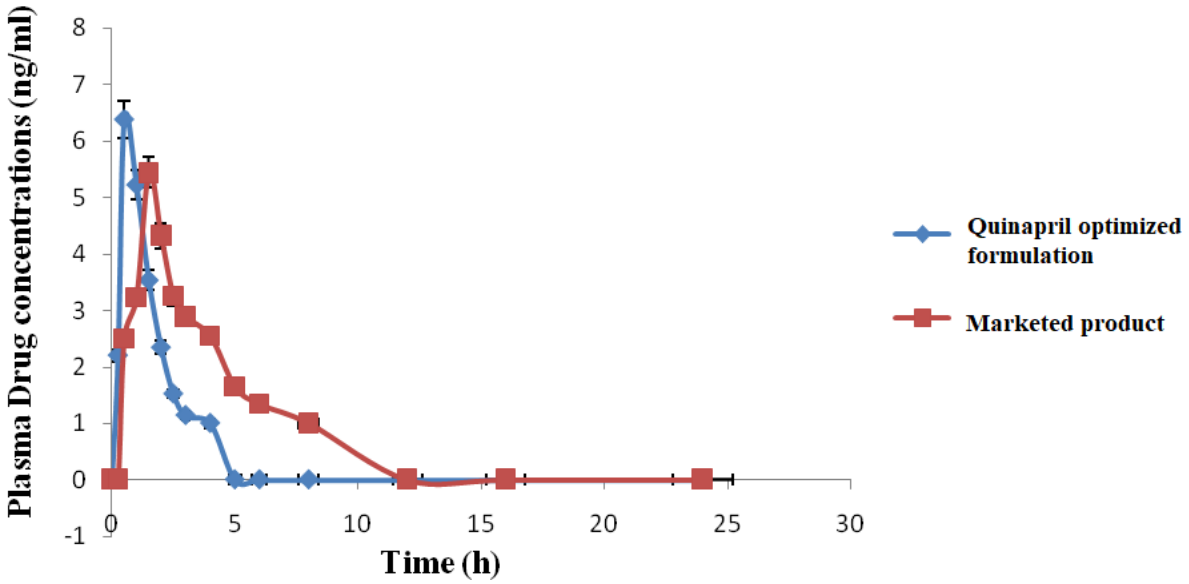


Figure 9: Plasma concentration–time curves for the Quinapril optimized formulation and marketed product

CONCLUSION:

Based on the encouraging results, the fast-dissolving films of Quinapril can be considered suitable for the treatment of Hypertension. Quinapril mouth dissolving films using HPMC 50cps, E5, E15 and in combination of Pullulan was prepared by Solvent evaporation method. Sodium starch glycolate acts as a super disintegrating agent and it is shown that as the concentration of the super disintegrates increases the disintegration time decreases. The films were evaluated for weight variation, surface pH, folding endurance, drug content, dissolving time, disintegration time, and in-vitro dissolution studies. Based on the evaluation parameters F17 was to be optimized formulation. The optimized film (F17) showed the more drug release i.e 99.40±5.30% within 7 min, lowest in vitro disintegration time 10 sec. FTIR studies proved no drug polymer interaction takes place. From in vivo bioavailability studies, C_{max} of the optimized formulation F17 was 72.43±0.3ng /ml,

was significantly higher as compared to pure drug suspension, i.e., 42.32±0.1ng/ml. T_{max} of optimized formulation was decreased significantly when compared with pure drug (1.00±0.05hr, 2.00±0.1hr), $AUC_{0-\infty}$ 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 Quinapril could be formulated for quick onset of action which is required in the efficient management of hypertension. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

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