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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR CHRONOTHERAPEUTIC RELEASE OF BENAZEPRIL

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ABSTRACT

The combination of developments in several technologies, such as microelectronics and micromachineing, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis. Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi developed an electric stimuli induced drug release system using the electrically stimulated swelling /deswelling characteristics of polyelectrolyte hydrogels. They utilized a chemomechanical system, which contained a drug model within the polyelectrolyte gel structure. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.

Keywords: Benazepril, Pulsatile drug delivery system, Release rate.

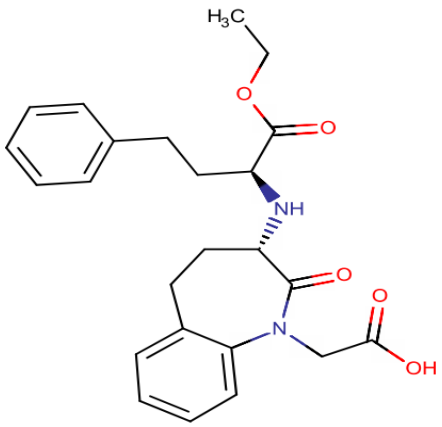
INTRODUCTION

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium [1]. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose [2]. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions [3]. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner [4]. This property is essential to achieve a precisely defined lag time [5].

BENAZEPRIL

Benazepril, brand name Lotensin, is a medication used to treat high blood pressure (hypertension), congestive heart failure, and chronic renal failure. Upon cleavage of its ester group by the liver, benazepril is converted into its active form benazeprilat, a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor [6].

Chemical structure



IUPAC NAME:
2-[(3S)-3-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-2-oxo-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]acetic acid

Chemical Formula: $C_{24}H_{28}N_2O_5$

Molecular weight: 424.49g/mol

Melting point: 49-51°C

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Solubility: Benazepril hydrochloride is a white to off-white crystalline powder, soluble (> 100 mg/mL) in water, in ethanol, and in methanol.

Pharmacology [7]
Indication: For the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

Pharmacodynamics: Benazepril, an angiotensin-converting enzyme (ACE) inhibitor, is a prodrug which, when hydrolyzed by estarases to its active Benazeprilat, is used to treat hypertension and heart failure, to reduce proteinuria and renal disease in patients with nephropathies, and to prevent stroke, myocardial infarction, and cardiac death in high-risk patients. Benazepril and Benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. 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.

Mechanism of action: Benazeprilat, the active metabolite of Benazepril, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II. As angiotensin II is a vasoconstrictor and a negative-feedback mediator for renin activity, lower concentrations result in a decrease in blood pressure and stimulation of baroreceptor reflex mechanisms, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Benazeprilat may also act on kininase II, an enzyme identical to ACE that degrades the vasodilator bradykinin.

Absorption: Peak in plasma within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract.

Metabolism: Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Benazepril and benazeprilat may be conjugated to glucuronic acid prior to urinary excretion.

Route of elimination: Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (i.e., biliary) excretion accounts for approximately 11%-12% of benazeprilat excretion in healthy subjects.

Half life: 10-11 hours

The rational of this study is to design and evaluate an oral site-specific, pulsatile drug delivery system containing Benazepril, which can be targeted to colon in a pH and time dependent manner. In the present research work, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach. A pulsatile 'Tablet in tablet' dosage form, taken at bed time with a programmed release.Start of drug release immediately from the outer tablet so that attack of heart diseases can be prevented in the night hours then we will have a lag time then the drug will be released from the inner tablet slowly then, can prevent a sharp increase in the incidence of heart disesses.

MATERIALS AND METHODS

Analytical Method Development

Preparation of buffers

a) Preparation of 0.1 N Hcl Solution

0.1N Hcl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water

b) Preparation of 6.8 pH phosphate buffer solution

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted up to 1000ml to get 0.2M sodium hydroxide solution. 50 ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-mL volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

Preparation of Standard Calibration Curve for Benazepril

a) Standard solution of Benazepril by using 0.1 N Hcl

100mg of drug is dissolved in 100ml of methanol. This is first stock solution.10ml of 1st stock solution is diluted with 100ml of 0.1N Hydrochloric acid buffer. This is 2nd stock solution. Now from 2nd stock, various concentrations of 3ug/ml, 6ug/ml, 9ug/ml, 12ug/ml and 15ug/ml were prepared by using same 0.1 N Hydrochloric acid buffer. Blank was also prepared with same buffer composition except the drug. All the samples were analyzed at 235 lambda max with respect to the blank.

b) Standard solution of Benazepril by using 6.8 phosphate buffer Solution

100mg of drug is dissolved in 100ml of methanol. This is first stock solution.10ml of 1st stock solution is diluted with 100ml of 6.8 buffer. This is 2nd stock solution. Now from 2nd stock, various concentrations of 3ug/ml, 6ug/ml, 9ug/ml, 12ug/ml and 15ug/ml were prepared by using same 6.8 buffers. Blank was also prepared with same buffer composition except the drug. All the samples were analyzed at 235 lambda max with respect to the blank.

Formulation of Benazepril PDDS tablets

Preparation of core Tablets

- All the excipients except Talc &Aerosil were cosifted through # 40 ASTM & blended in a poly bag for 10 min
- To the above mixture # 60 ASTM passed Talc & Aerosil were added & lubricated by blending in a poly bag for 5 min

Preparation of coating layer

- All the excipients except Mg.stearate were cosifted through # 40 ASTM & blended in a poly bag for 10 min
- To the above mixture # 60 ASTM passed Mg.stearate was added & lubricated by blending in a poly bag for 5 min

Compression coating of core tablet

- Prepared coating layer was used for shell formation.
- Press coating of tablet was performed. Half the amount of powder from every formulations (one by one) was filled into the die to form a powder bed. In center core, tablet formulation is placed. Over this remaining half of the granules was filled intodie and contents were compressed using concave punches of 10 mm diameter. Hardness of tablet was maintained between 6‑8 kg/ cm^2.

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following Pre, post compression quality control studies and dissolution studies [8]

A) Pre Compression studies

1. Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

2. Density

a) Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder/ Bulk volume.

$$D_b = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b) Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder. Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula .

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f)$$

M = mass of the powder

V_f = tapped volume of the powder.

3. Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

Compressibility index = 100 x

- $\frac{\text{Tappeddensity - Bulk density}}{\text{Tappeddensity}}$

4. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{TappedDensity}}{\text{Bulk Density}}$$

B) Post compression studies

1. General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\%\text{weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{Average weight}} \times 100$$

3. Thickness: Thickness of the tablets (n=3) was determined using a Vernier calipers.

4. Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was

taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\%Friability = [(W_1-W_2)/W_1] \text{ X } 100$$

Where, W_1= weight of tablets before test,
W_2 = weight of tablets after test

6. Assay Procedure

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg ofmodel drug a 10 ml volumetric flask. Add approximately 6ml of 0.1N HCl and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer. Calculate the quantity in mg of model drug Hydrochloride in the portion taken by the formula

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

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7. *In vitro* Dissolution Study

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 2 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =235 nm using a UV-spectrophotometer (Lab India). Then remove the 0.1N Hcl and replace with 6.8 phosphate buffer and continue the dissulotion with the above procedure from 2^{nd} hour.

C) *In vitro* Release Kinetics Studies

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t.$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slowrelease tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$Log\ C = Log\ C_o - kt/2.303$$

Where C is the amount of drug dissolved at time t,
C_o is the amount of drug dissolved at t=0 and
k is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line.Will be linear if the release obeys the first order release kinetics.

3 Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent[20].

4. Peppa's-Korsemeyer equation (Power Law)

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$$Mt/M_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t
M_α is the amount released at time α,
M_t/M_α is the fraction of drug released at time t,
K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value[21].the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Table 1. List of equipments

S. No.	Name of the Equipment	Model
1	Electronic Weighing Balance	Scale-Tec
2	Friabilator	Roche Friabilator Electrolab, Mumbai
3	Compression Machine	CMD(CADMACH)
4	Tablet Hardness Tester	Pfizer Hardness Tester, Mumbai
5	UV	Labindia UV 3000+
6	Dissolution Apparatus	Electrolab TDT-08L
7	Vernier Callipers	CD-6"CS

Table 2. Formulation of core tablets

Ingredients	Weight in mg
Benazepril	10
Crosspovidone	12
Lactose	46
Starch	30
Talc	1
Aerosil	1
Total weight (mg)	100

Table 3. Preparation of coating layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
MCC	128	128	128	192	192	192	256	256	256
HPMC K100M	70	--	--	105	--	--	140	--	--
EUDRAGIT RS 100	--	70	--	--	105	--	--	140	--
PEO	--	--	70	--	--	105	--	--	140
MG. Stearate	2	2	2	3	3	3	4	4	4
Total Weight (mg)	200	200	200	300	300	300	400	400	400

Table 4. Angle of repose limits - Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 5. Compressibility index limits - Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 6. Weight variation tolerance for uncoated tablets - Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 7. Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl.upto 2hrs and 6.8 phosphate buffer 3hr-12hr
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1, 2, 3, 4, 6, 8, 10 and 12hrs
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	235 nm

Table 8. Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

RESULTS AND DICUSSION

Table 9. Standard Calibration graph values of Benazepril in 0.1N Hcl at 235 nm

Concentration (µg/ml)	Absorbance
3	0.079
6	0.155
9	0.233
12	0.309
15	0.393

Table 10. Standard Calibration graph values of Benazepril 6.8 phosphate buffer at 235 nm

Concentration (µg/ml)	Absorbance
3	0.076
6	0.159
9	0.228
12	0.304
15	0.381

Table 11. Pre compression studies of Benazepril core tablets

Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
0.37	0.41	9.75	1.1	11.14

Table 12. Post compression studies of Benazepril core tablets

% weight vaiation	Thickness± SD n=3 (mm)	%*friability	%Drug Content± SD n=3	Hardness (Kg/cm^2) Avgwt hardness ± SD n=3
Pass	3.03±0.05	0.132	99.6±1.5	3.63 ±0.057

*Test for Friability was performed on singlebatch of 20 tablets

Table 13. Pre compression studies of Benazepril Colon targeted tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	32.73
F2	0.39	0.48	18	1.23	34.96
F3	0.50	0.58	13	1.16	28.58
F4	0.44	0.50	12	1.1	27.92

F5	0.37	0.41	9.75	1.1	25.35
F6	0.37	0.41	9.75	1.1	33.14
F7	0.36	0.39	7.6	1.0	27.03
F8	0.41	0.45	8.8	1.0	31.85
F9	0.39	0.48	18	1.23	28.96

Table 14. Post compression studies of Benazepril coating tablets

Formulation Code	% weight vaiation	Thickness (mm)	% friability	%Drug Content	Hardness (Kg/cm^2)
F1	Pass	5.03±0.15	0.143	98.9 ±2.3	5.62 ±0.057
F2	Pass	4.93±0.05	0.110	100.2± 1.7	5.72 ±0.1
F3	Pass	5.06±0.11	0.142	101.3 ±1.2	5.56 ±0.057
F4	Pass	5.06±0.15	0.151	102.3 ±1.7	6.03 ±0.115
F5	Pass	5.03±0.057	0.62	100.1 ±1.2	6.00 ±0.1
F6	Pass	5.1±0.1	0.154	100.7 ±1.1	6.63 ±0.057
F7	Pass	4.99±0.03	0.23	99.3 ±2.2	5.97 ±0.14
F8	Pass	5.15±0.12	0.19	100.2± 1.4	5.83 ±0.11
F9	Pass	5.04±0.11	0.17	99.7 ±1.3	5.98 ±0.12

*Test for Friability was performed on single batch of 20 tablets

Table 15. Dissolution profile

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1 N HCL and 6.8 Phosphate buffer
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1, 2, 3, 4, 6, 8 and 10hrs
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	235nm

Table 16. Percentage of drug release

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	**0**	0
1	22	18	24	5	14	12	1	**1**	1
2	38	34	59	9	24	28	3	**2**	2
3	54	59	73	28	39	52	15	**5**	5
4	69	74	89	48	57	61	20	**13**	15
6	88	91	100	69	73	78	31	**42**	21
8	100	99		78	92	88	48	**68**	31
10				88	100	99	68	**97**	40

Table 17. R^2 and 'n' result table

Formulation Code	R^2 values				'n' value
	Zero order	First order	Higuchi	Peppas	
F1	0.978	0.994	0.987	0.996	0.789
F2	0.964	0.980	0.975	0.980	0.947
F3	0.951	0.983	0.980	0.926	0.797
F4	0.976	0.982	0.943	0.943	1.350
F5	0.986	0.966	0.973	0.985	0.894
F6	0.965	0.996	0.978	0.945	0.901
F7	0.987	0.957	0.901	0.961	1.853
F8	0.964	0.852	0.847	0.971	2.167
F9	0.986	0.982	0.903	0.966	1.724

Figure 10: Standard calibration curve of Benazepril in 0.1N Hcl at 235 nm

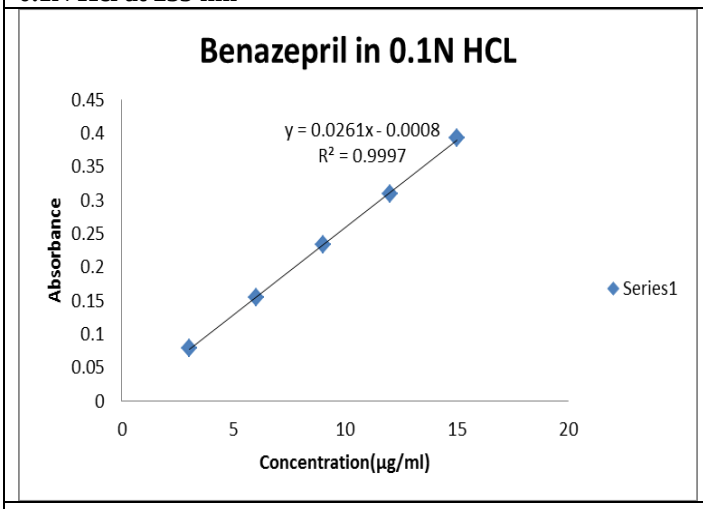


Figure 11: Standard calibration curve of Benazepril in 6.8 phosphate buffer at 235nm

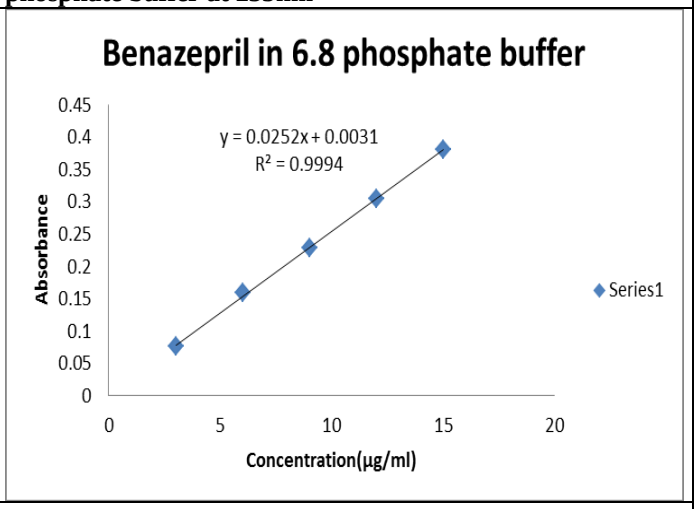


Figure 1. Comparative dissolution profile for F1, F2 and F3 formulations

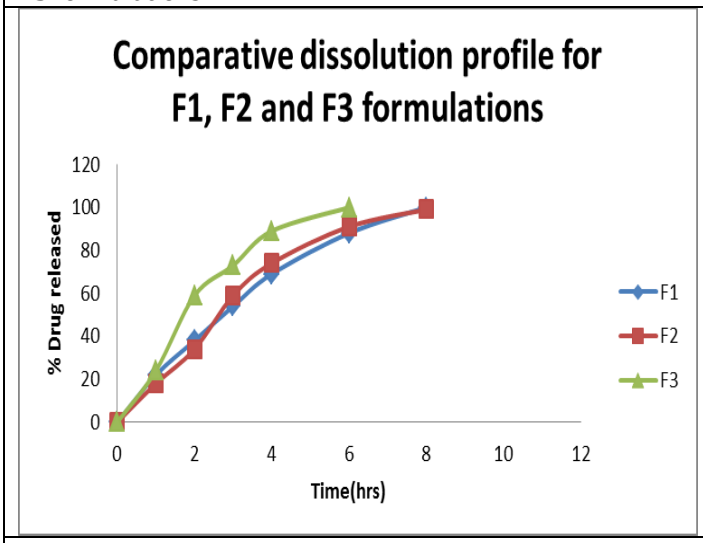


Figure 2. Comparative dissolution profile for F4, F5 and F6 formulations

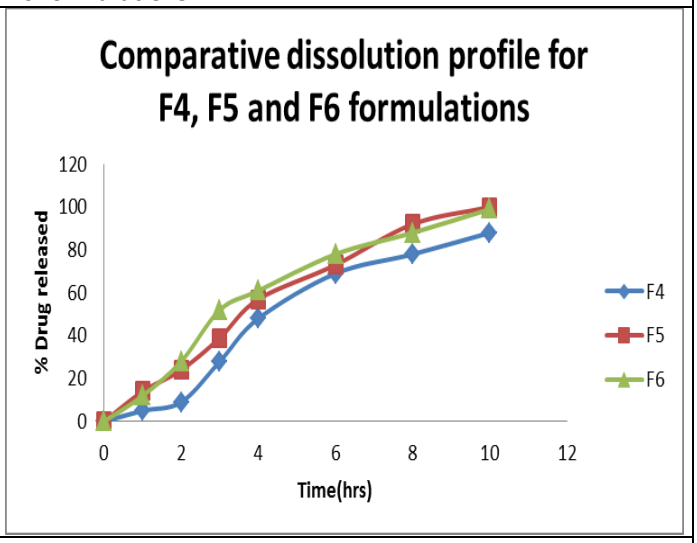


Figure 3. First order plot for F1, F2 and F3 formulations

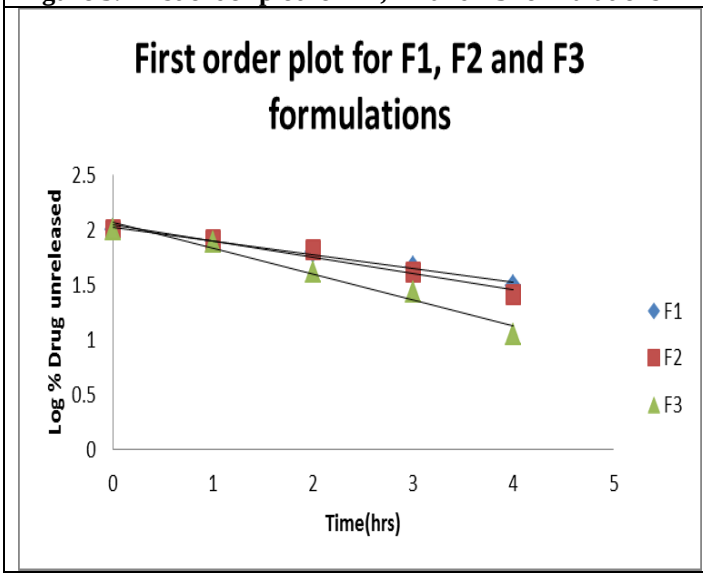


Figure 4. Higuchi plot for F1, F2 and F3 formulations

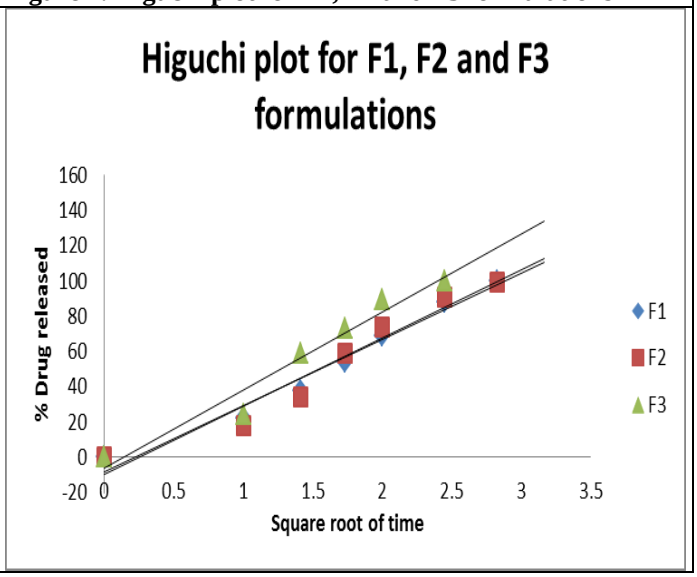


Figure 5. IR graph for Benazepril

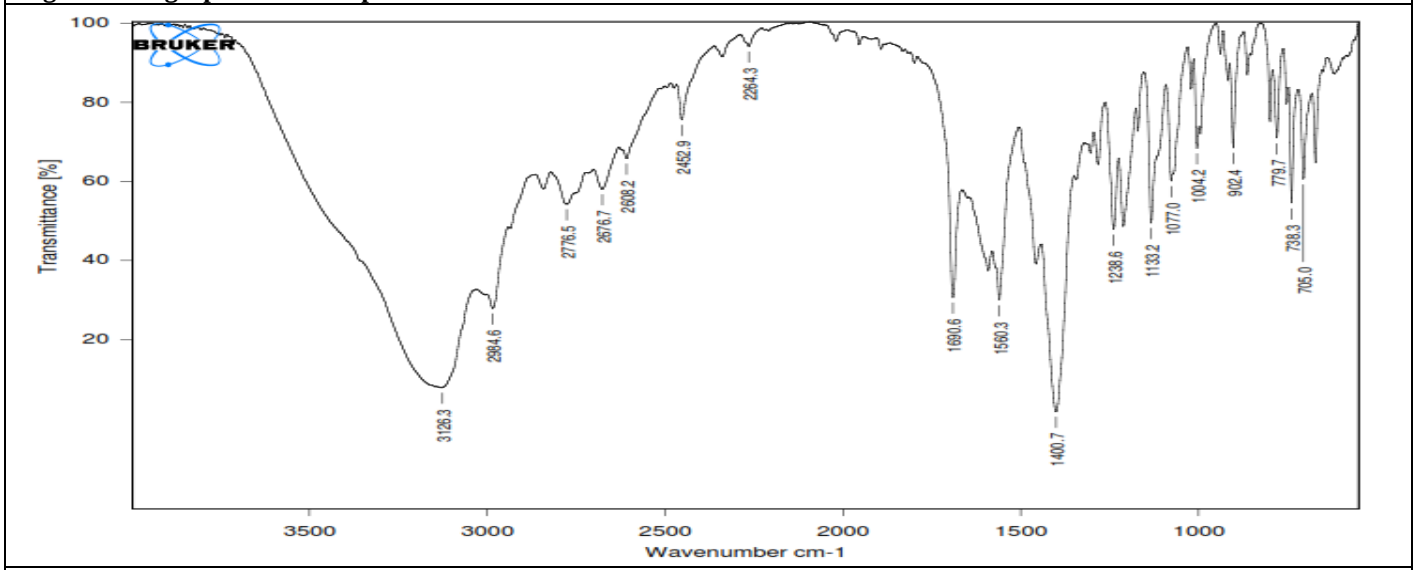
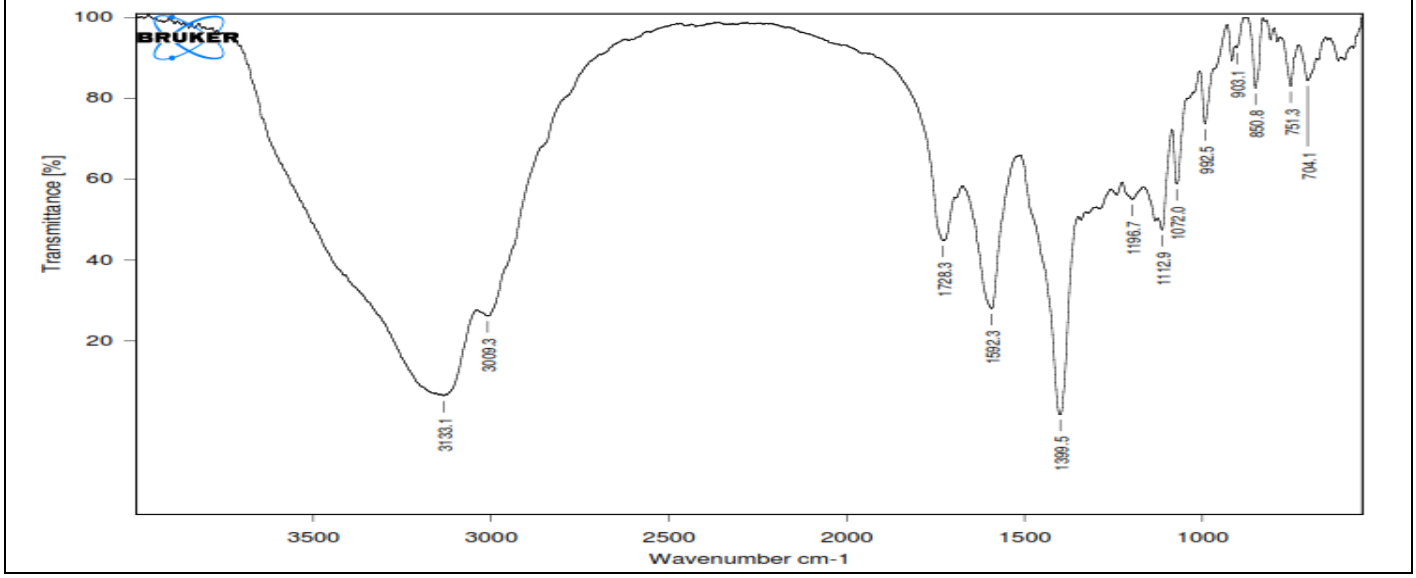


Figure 6. IR graph for Best formulation F2



1. Construction of Standard calibration curve of Benazepril in 0.1N HCl

The absorbance of the solution was measured at 235nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table no 13. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 3 to 15 µg/ml.

Inference: The standard calibration curve of Benazepril in 0.1N HCl showed good correlationwith regression value of 0.999.

2. Construction of Standard calibration curve of Benazepril in 6.8 phosphate buffer

The absorbance of the solution was measured at 235nm, using UV spectrometer with 6.8 phosphatebuffer as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 3 to 15 µg/ml.

Inference: The standard calibration curve of Benazepril in 6.8 phosphate buffer showed good correlation with regression value of 0.999.

Pre Compression studies

Pre compression studies of Benazepril core tablets

Inference

- The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets.
- The bulk density and the tapped density for all formulations were found to be almost similar.

- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be 11.14 which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Pre compression studies of Benazepril Colon targeted tablets

Inference

- The blends prepared for direct compression of tablets was evaluated for their flow properties; the results for the blends of compression tablets.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends.

The angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies of Benazepril coating tablets

Inference

- The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.
- The thickness of tablets was found to be between 4.9-5.2 mm.
- The hardness for different formulations was found to be between 5.56 to 6.63 kg/cm^2, indicating satisfactory mechanical strength.
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

R^2 and 'n' result

Inference

- Among the different control release polymers Eudragit RS100 was showing highest drug release retarding capacity
- F8 was showing the satisfactory results and having better sustainability
- When we plot the release rate kinetics for best formulation f2 was following zero order because correlation coefficient value of zero order is more than first order value.
- F8 formulation diffusion exponent n value is n > 0.89 so they are following Super Case II transport.

CONCLUSION

From the experimental data, it can be concluded that Eudragit RS100 was respectively showed better pulsatile drug release of Benazepril. When drug: polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, content uniformity and *in vitro* drug release. Formulation F8 gave better-controlled drug release and in comparison to the other formulations. The most probable mechanism for the drug release pattern from the formulation was Super Case II transport.

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