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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF BENAZEPRIL

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ABSTRACT

The purpose of this research is to prepare enteric coated tablets consisting of disintegrants and Benazepril by direct compression method and to evaluate their quick disintegration and release properties. To the optimized formulation enteric coat is usually given by various enteric polymers. The effect of various excipients and process variables on the particle morphology, micromeritics properties, *In vitro* release behavior was studied.

INTRODUCTION

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. 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. Benazeprilat may also act on kininase II, an enzyme identical to ACE that degrades the vasodilator bradykinin.

METHODOLOGY

Preparation of buffers:

a) Preparation of 0.1 N Hcl Solutions: 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.

II. 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
- 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 formulation (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

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

RESULTS AND DISCUSSION

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.

Standard Calibration graph values of Benazepril in 0.1N Hcl at 235 nm: Standard plot of Benazepril plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis.

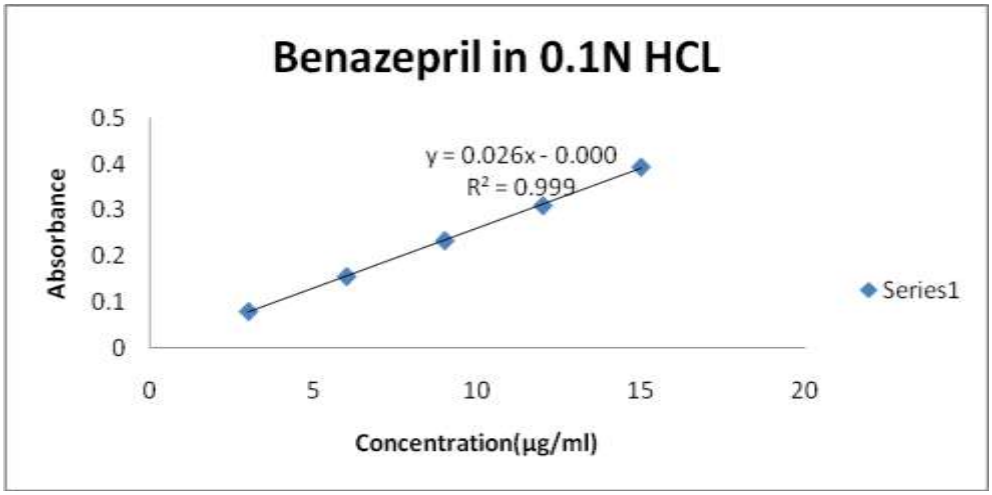
Construction of Standard calibration curve of Benazepril in 6.8 phosphate buffer:

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.

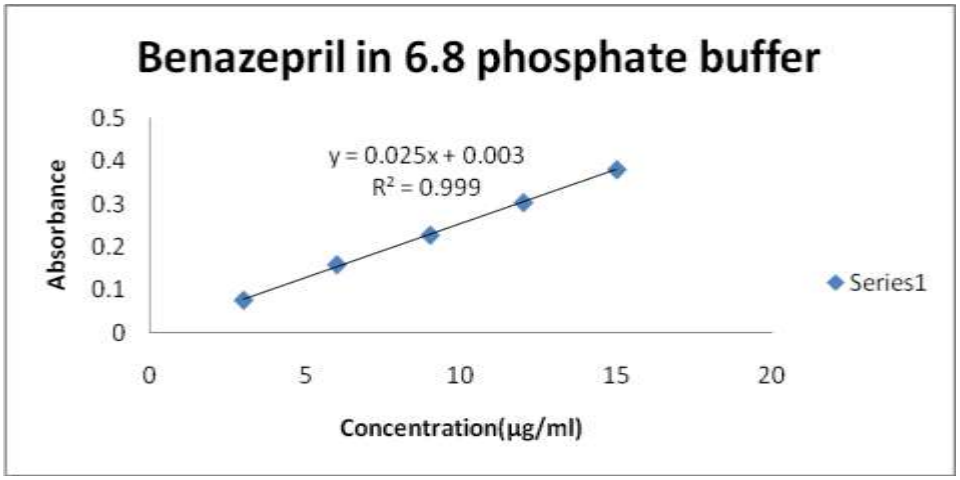
Pre Compression studies

Inference: The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table: 14. 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).

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

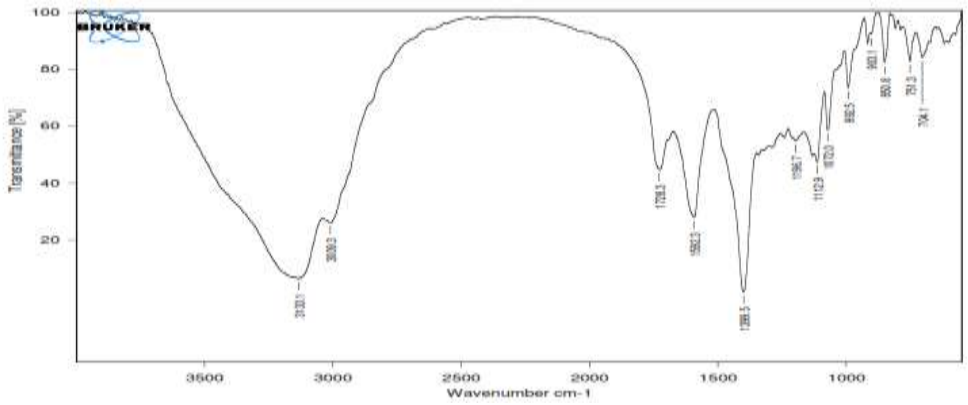


CONCENTRATION (µg/ml)	ABSORBANCE
3	0.076
6	0.159
9	0.228
12	0.304
15	0.381



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

Evaluation of Tablets: IR graph for Benazepril



Post compression studies: Pre compression studies of Benazepril core tablets

Table: Post compression studies of Benazepril core tablets

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

➢ **Table: Post compression studies of Benazepril core tablets**

% weight variation	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 single batch of 20 tablets

Table : Precompression 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

Inference:

The blends prepared for direct compression of tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table: 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 25.35-34.96˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

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

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 %.

***IN VITRO* DISSOLUTION STUDIES OF BENAZEPRIL COMPRESSION COATED TABLETS**:

Table: 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

Note: 5 ml of sample was with draw at each time point & replace the same volume of 6.8 phosphate buffer preheated to 37± 0.5 ºC

Table: Dissolution data of Benazepril colon targeted Tablets

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

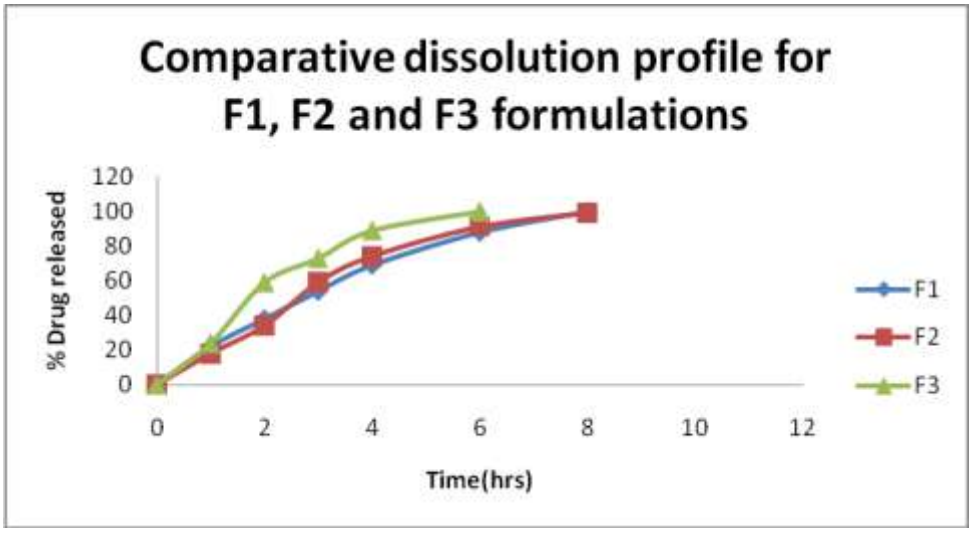


Figure: Comparative dissolution profile for F1, F2 and F3 formulations

Table: 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

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.

SUMMARY AND 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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