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R E S E A R C H A R T I C L E

Formulation and Evaluation of Enalapril Oral Dispersible Tablets

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A B S T R A C T

The objective of the present investigation was to formulate and evaluate Enalapril oral dispersible tablets. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. Enalapril is a angiotensin-converting enzyme (ACE) inhibitor, which is used to treatment of renovascular hypertension and symptomatic congestive heart failure. Ten oral dispersible tablets can be formulated by direct compression method by using subliming agents like menthol, camphor, and cross caramellose sodium, sodium starch glycolate, cross povidone as superdisintegrant. The evaluation results revealed that all formulations comply with the specification of official pharmacopoeias and/or standard reference with respect to general appearance, content uniformity, hardness, friability and dissolution. Out of all the formulations, the formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good results for manufacturing the tablets.

Keywords: Enalapril, Oral dispersible tablets, subliming agents, Caramellose, Formulation, Superdisintegrant

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C O N T E N T S

1. Introduction

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the

most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms. Tablets may be defined as the solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods.

Enalapril is a prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is rapidly metabolized in the liver to enalapril following oral administration. Enalapril is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Enalapril may be used to treat essential or renovascular hypertension and symptomatic congestive heart failure. The current investigation is concerned with design and characterization of Enalapril Oral Dispersible tablets to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption, thereby improving the efficacy and better patient compliance.

2. Materials and Method

Materials: The following materials are used to formulation and evaluation of Enalapril oral dispersible tablets.

Table 1: List of Materials

S.No.	Materials	Supplier
1.	Enalapril	Mylan laboratories Ltd, Hyderabad
2.	Menthol	Reachem laboratory chemicals Pvt.Ltd, Chennai
3.	Camphor	Reachem laboratory chemicals Pvt.Ltd, Chennai
4.	Croscarmelose sodium	Merck specialities Pvt.Ltd, Mumbai
5.	Crospovidone	Thermo Fisher scientific India Pvt.Ltd, Chennai
6.	Sodium starch glycolate	Thermo Fisher scientific India Pvt.Ltd, Chennai
7.	Micro crystalline cellulose	Rankem fine chemicals Ltd, New Delhi
8.	Magnesium stearate	Rankem fine chemicals Ltd, New Delhi

Table 2: List of Equipment's

S.No.	Equipments	Manufacturer
1.	Electronic Weighing Balance	Singhla
2.	Hardness Tester	CINTEX Mosanto tester, Mumbai
3.	UV- Spectrophotometer	ELICO SL 210
4.	Friability Test Apparatus	Electrolab EF-2
5.	Hot air oven	Universal hot air oven
6.	Bulk Density Apparatus	Edision
7.	Tablet Compression Machine	CADMACH
8.	Tablet Dissolution apparatus	Lab India
9.	Ultra sonicator bath	Bio-tech India
10.	Digital pH meter	Microprocessor pH stat/Analyser

Formulation Development

Pre formulation studies:

Solubility:

The solubility of a drug may be expressed in number of ways. The U.S. pharmacopoeia and national formularies list the solubility of the drugs as the number of milliliters of solvent in which 1 gram of solute will dissolve. One gm of Enalapril was dispersed in the solvent and based on the following table solubility was determined. The solubility of the drug was determined in water, ethanol and methanol.

Melting point:

Melting point of Enalapril was determined by capillary method. Fine powder of Enalapril was filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt. Melting point of the drug was determined by using Scientek digital melting point apparatus.

Drug polymer compatibility studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Calibration curve of Enalapril in pH 6.8 phosphate buffer:

100 mg of Enalapril was dissolved in 100 ml of water (1000 µg/ml).From the primary stock solution (100 µg/ml), appropriate aliquot i,e., 0.1, 0.2, 0.3, 0.4, 0.5 were transferred to series of 10 ml volumetric flasks and made upto 10 ml with pH 6.8phosphate buffer so as to get concentration of 1,2,3,4 and 5 µg/ml. the absorbance of the solution were measured at 208 nm. This procedure was performed in triplicate to validate calibration curve. A calibration graph was plotted and shown in figure no 1.

Formulation of Enalapril Porous Tablets

By using Direct Compression method:

Porous tablets of Enalapril were prepared by direct compression method employing camphor and menthol as sublimating agents. The concentrations of the above ingredients were optimized as shown in below table on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate enhancing disintegrants and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication.) About 200 mg of the powder mix was weighed accurately and fed into the die of machinery and compressed using 8 mm flat- surface

punches. The hardness of the tablets was adjusted at 4-6 kg/cm^2 using a Monsanto hardness tester.

Evaluation of Tablets

Pre-compression parameters:

Angle of Repose: 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. The angle of repose has been used to characterize the flow properties of solids.

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

Where:

θ = angle of repose; h = height in cms; r = radius in cms

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.

Bulk density = weight of powder / Bulk volume

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

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[19]. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Hausner's Ratio:

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

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

Post compression tablets:

Organoleptic properties of tablets:

Organoleptic properties such as taste, color, odour, were evaluated. Ten tablets from each batch were randomly selected and tested for taste, color, odour and physical appearance**.**

Thickness: The thickness of individual tablets of 6 numbers were measured with vernier calipers, it permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within ± 5% variation of standard value.

Hardness:

The tablet hardness of different formulations was measured using the Monsanto hardness tester for 6 tablets. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge on the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it.

Weight Variation Test: Twenty core and coated tablets with coat were selected at random and individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specifications.

In vitro Disintegration time: The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

Drug Content Uniformity Assay

Ten tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of phosphate buffer pH 6.8, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with phosphate buffer pH 6.8. Absorbance of this solution was measured at 208nm using phosphate buffer pH 6.8as blank and content of drug was estimated.

In vitro Dissolution studies:

Dissolution of the tablet of each batch was carried out using USP type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 500ml of phosphate buffer pH 6.8used as dissolution medium and the temperature of the medium was set at 37 ± 0.5^{0}C. 5 ml of sample was withdrawn at predetermined time interval of 5min., 10min., 15min, 20min,25min,30min, 35min and 40min. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV-visible spectrophotometer at 208 nm using buffer solution as blank solution.The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.

3. Results and Discussion

Organoleptic properties: Organoleptic properties such as taste, color, odour were evaluated and the results are within the standards. The drug is showing solubility in methanol and in water.

Analytical method: The absorbance of the Enalapril solution were measured at 208 nm. A calibration curve was plotted. The results were shown in table 5 and fig 1.

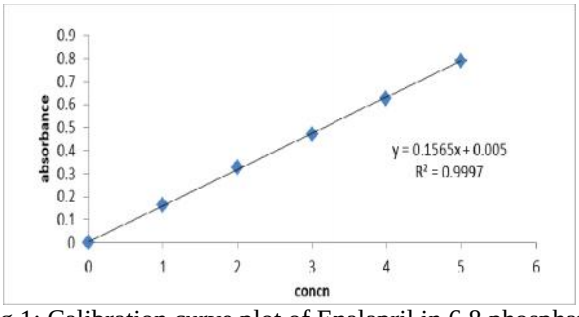

Fig 1: Calibration curve plot of Enalapril in 6.8 phosphate buffer

Pre- Compression Parameters:

All the formulations prepared by direct compression method showed the angle of repose less than 34, which reveals good flow property. The bulk density and tapped density for all formulation (F1 – F10) varied from 0.442 - 0.485 gm/cm^3 and 0.501 - 0.593 gm/cm^3 respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F10) blend range from 15.5- 19.1 and 1.10-1.28 respectively, shows fair flow properties. The results are shown in the (Table.6).

Post compression parameters: Post compression parameters like hardness, drug content, weight variation and disintegration tests are performed to the porous tablets for before drying and after drying. All the parameters are present in within the specified limits. The results were shown in table 7 & 8.

***In-vitro* Dissolution studies:** Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media (pH 6.8phosphate buffer) for 40 minutes. At the end of 30 minutes almost total amount of the drug is released (i.e 100%), from the formulation prepared by the direct compression method with 8% Cros carmellose sodium. F1,F2,F3,F4 and F5 formulations didn't show much effect on the Disintegration time i,e., 1min, 42sec respectively and dissolution time 100% in 40min and 99% in 35min respectively.F6 showed good disintegrating time i.e.,18sec and dissolution of 100% in 30min. F7,F8,F9 and F10 formulations didn't show much effect on the Disintegration time i,e., 45sec,28sec and 19sec respectively, dissolution time of 99% in 40min,100% in 40min and 100% in 35min respectively. The results given in table 9.

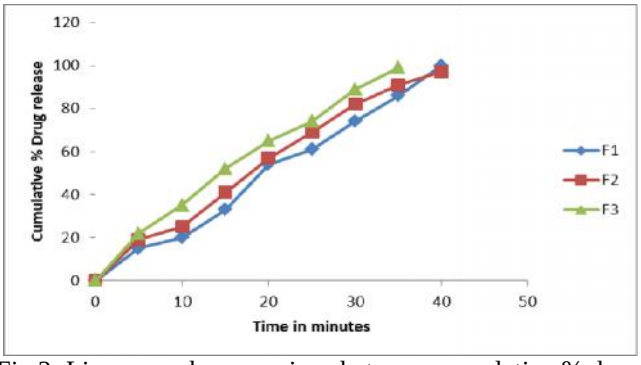

Fig 2: Linear graph comparison between cumulative % drug release for formulations (F1- F3)

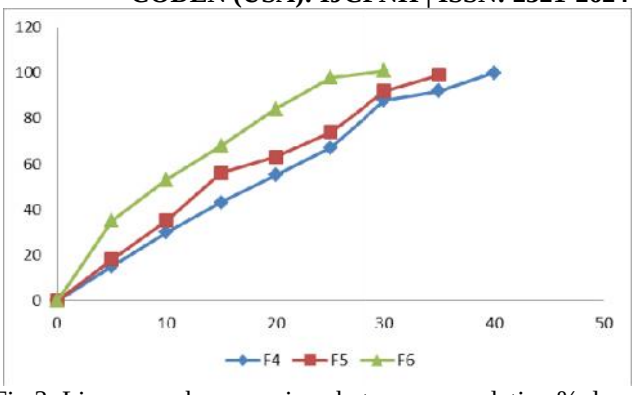

Fig 3: Linear graph comparison between cumulative % drug releases for formulations (F4 - F6)

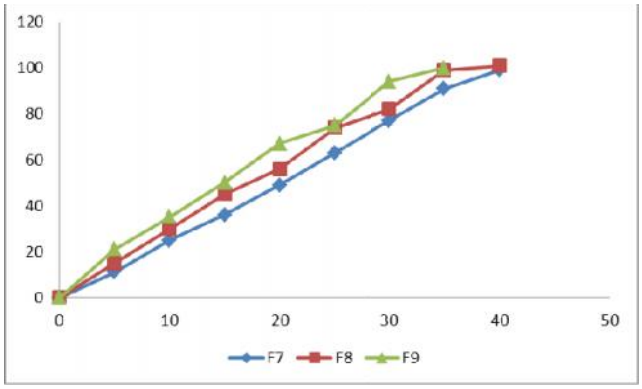

Fig 4: Linear graph comparison between cumulative % drug releases for formulations (F7- F9)

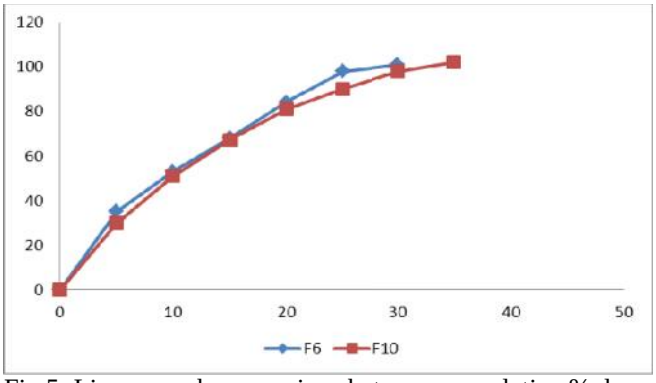

Fig 5: Linear graph comparison between cumulative % drug releases for formulations (F6 & F10)

Table 3: Formulation design of Enalapril Oro Dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Enalapril	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Menthol	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	-
Camphor	-	-	-	-	-	-	-	-	-	20mg
MCC	150	146	142	150	146	142	150	146	142	142
SSG	8mg	12mg	16mg	-	-	-	-	-	-	-
CCS	-	-	-	8mg	12mg	16mg	-	-	-	16mg
CP	-	-	-	-	-	-	8mg	12mg	16mg	-
Mg.stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total weight	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

Table 4: Drug – Excipients Compatibility Studies

S. No	Composition Details	Initial	Observation			
			Storage Condition Duration			
			40^{O} C/75% RH			60^{O}C
			1M	2M	3M	1M
1	Enalapril	White Crystalline powder	NCC	NCC	NCC	NCC
2	Enalapril + Mentol	White Crystalline powder	NCC	NCC	NCC	NCC
3	Enalapril+ Camphor	White Crystalline powder	NCC	NCC	NCC	NCC
4	Enalapril+ Croscarmellose Sodium	White Crystalline powder	NCC	NCC	NCC	NCC
5	Enalapril+ Crospovidone	White Crystalline powder	NCC	NCC	NCC	NCC
6	Enalapril+ Sodium Starch Glycolate	White Crystalline powder	NCC	NCC	NCC	NCC
7	Enalapril+ Magnesium Stearate	White Crystalline powder	NCC	NCC	NCC	NCC
8	Enalaril+Micro Crystalline cellulose	White Crystalline powder	NCC	NCC	NCC	NCC

NCC = No Characteristic Change

Table 5: Calibration curve of Enalapril

S.No	Concentration in µg/ml	Absorbance
1	0	0
2	1	0.165
3	2	0.325
4	3	0.471
5	4	0.627
6	5	0.789

Table 6: Evaluation of tablet blend for formulations (F1 – F10)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose
F1	0.464	0.574	1.23	19.1	29.47
F2	0.423	0.501	1.16	15.5	27.63
F3	0.456	0.542	1.22	15.8	25.54
F4	0.467	0.559	1.25	16.4	26.23
F5	0.485	0.593	1.10	18.2	27.21
F6	0.460	0.556	1.21	17.2	30.38
F7	0.478	0.575	1.24	16.8	28.46
F8	0.450	0.554	1.28	18.7	25.71
F9	0.442	0.537	1.27	17.6	31.82
F10	0.467	0.559	1.25	16.4	26.23

Table 7: Evaluation of porous Tablets for Formulations (F1 – F10) Before Drying

Formulation	Hardness (kg/cm2)	Weight (mg)	Thickness (mm)	Disintegration time (min)	Drug content (%)
F1	6.0	201	2.4	6	98.2
F2	6.1	198	2.4	5min 24sec	98.72
F3	6.2	201	2.6	4min	98.4
F4	6.0	202	2.5	5min 45sec	98
F5	6.2	203	2.4	4min 34sec	98.44
F6	6.1	198	2.4	2min 21sec	100.8
F7	6.2	201	2.5	5min 32sec	98.2
F8	6.0	201	2.5	4min	98.4
F9	6.1	203	2.4	2 min17sec	99.32
F10	6.1	198	2.4	2min 28sec	98

Table 8: Evaluation of porous Tablets for Formulations (F1 – F10) after drying

Formulation	Hardness (kg/cm2)	Weight(mg)	Thickness (mm)	Disintegration time (sec)	Drug content (%)
F1	3.5.0	181	2.4	1min 14sec	98.2
F2	3.7	179	2.4	47sec	98.72
F3	3.9	182	2.6	38sec	98.4
F4	3.8	183	2.5	1min	98
F5	3.7	184	2.4	42sec	98.44
F6	3.6	183	2.45	18sec	100.8
F7	3.6	181	2.5	45sec	98.2
F8	3.9	183	2.5	28sec	98.4
F9	3.8	184	2.4	19sec	99.32
F10	3.7	183	2.4	22sec	98

Table 9: In-Vitro Release Profile of Enalapril from formulations F1-F10

Time (min)	Cumulative % drug release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
5	15	19	22	15	18	35	11	15	21	30
10	20	25	35	30	35	53	25	30	35	51
15	33	41	52	43	56	68	36	45	50	67
20	54	57	65	55	63	84	49	56	67	81
25	61	69	74	67	74	98	63	74	75	90
30	74	82	89	88	92	100	77	82	94	98
35	86	91	99	92	99		91	99	99	100
40	100	97		100			99	100		

4. Conclusion

The present research done with an aim to design an porous oral dosage of Enalapril and evaluation of the tablets for various parameters including in vitro drug release studies. Enalapril Oro dispersible tablets were formulated by using microcrystalline cellulose as filler, camphor and menthol as subliming agents, crospovidone, SSG and CCS as super disintegrant, and magnesium stearate as lubricant. The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, thickness, weight variation, hardness and drug content. The formulation F6 containing 8% of CCS and 10% of menthol showed disintegration time of 18seconds after drying. Menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters viz: Hardness, Thickness, Weight variation and drug content were also found to be within limits. The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good results for manufacturing the tablets.

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