World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.008

FORMULATION AND DEVELOPMENT OF ENALAPRIL MALEATE FAST DISSOLVING TABLETS BY DIRECT COMPRESSION METHOD AND ITS PHARMACEUTICAL EVALUATION

Shama Parveen*, Jai Narayan Mishra, Dhaneshwar Kumar Vishwakarma and Navneet Kumar Verma

Department of Pharmacy, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur, Uttar Pradesh, India.

***Corresponding Author: Shama Parveen**
Department of Pharmacy, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur, Uttar Pradesh, India.

Article Received on 26/10/2018 **Article Revised on 16/11/2018** **Article Accepted on 06/12/2018**

ABSTRACT

In the project work Enalapril maleate, an anti hypertensive drugs has been formulated into fast dissolving tablets by direct compression method using the different super disintegrates such as croscarmellose and sodium starch glycolate and Excipients like lactose, sucrose magnesium stearate, sodium lauryl sulphate the prepared by the tablets were evaluated for the pre-compression parameter UV Spectroscopy, post compression parameter such as thickness, hardness, friability, drugs contents, weight variation, water absorbance ratio, *invitro* disintegrating time, *invitro* dissolution studies. No chemical interaction between drugs and Excipients was conforming by FTIR study. All the parameter shows good results. Fast dissolving tablets are prepared by direct compression method are results found to be that among of nine formulation as the F9 to be best as its shows in F9 87.10% (direct compression method) maximum drug release respectively. The prepared tablets stability tested at 40^0c having 75% relativity humidity for 1month and found to be stable. Prepared fast dissolving tablets of Enalapril maleate 5 mg was found to be under fasting fed condition.

KEYWORD: Enalapril maleate, fast dissolving tablets (FDTs), superdisintragrants, and lactose.

INTRODUCTION

The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva [1]. The center for drug Evaluation and Research states an ODT to be: "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue."These tablets are distinguished from conventional, sublingual tablets, lozenges and buccal tablets which require more than a minute to dissolve in the mouth. In the literature these are also called orally disintegrating, Orodisperse, Mouth dissolving, Quick dissolving, Fast-melt and rapidly disintegrating tablets and freeze-dried wafers.[2]

Fig No.1.1: Fast dissolving tablets.

Mechanism of Action Enalapril maleate

Enalapril, after hydrolysis to enalaprilate, inhibits 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. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decrease

aldosterone secretion. Although the latter decrease is small, It results in small increases of serum potassium.[3]

MATERIAL AND METHOD

Enalapril maleate obtained as gift sample from aristro pharma pvt. Ltd. (chandigarh, india). Cross carmellose and sodium starch glycolate and other excipient were obtained from locally and use.

Method

Preformulation study

Excipients Compatibility Study by IR spectroscopy

The IR spectra were recorded using IR spectrophotometer. The samples were prepared by mixing the drug and the excipient in 1:1 ratio and the mixtures were stored in closed containers for one week. IR spectrum of the samples was taken using KBr pellet method. The physical mixtures of Enalapril maleate and Excipients were scanned in the wavelength region between 4000 and 400 cm^{-1} and compared to check compatibility of drug with Excipients.[4,5]

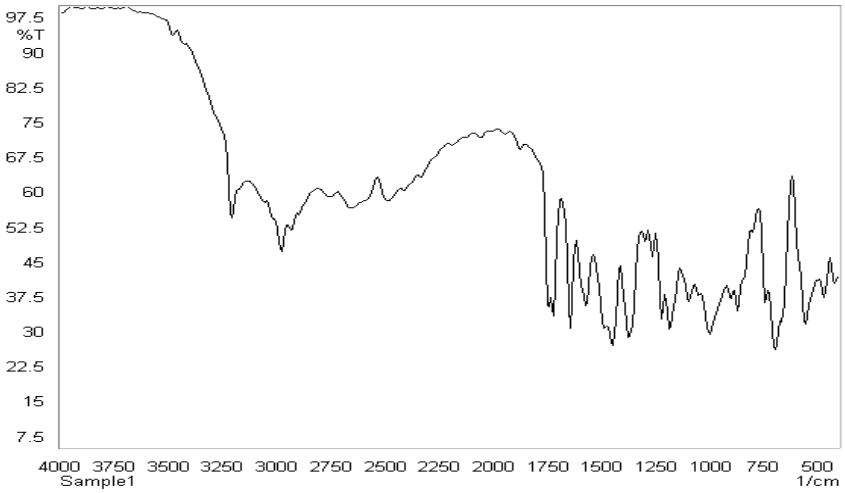

Fig No. 2.1: FTIR of pure Enalapril maleate.

Table No. 2.1: FTIR of pure Enalapril maleate.

S. NO.	Functional group	Frequency	Reported value
1.	$-CH_3$	1450-1357	1377
2.	-COOH	1440-1400	1445-33
3.	-CH or C-H	3000	2978.09
4.	N-H	3400	3209.55
5.	COO	1765-1720 1290-1180	1747 1188.29

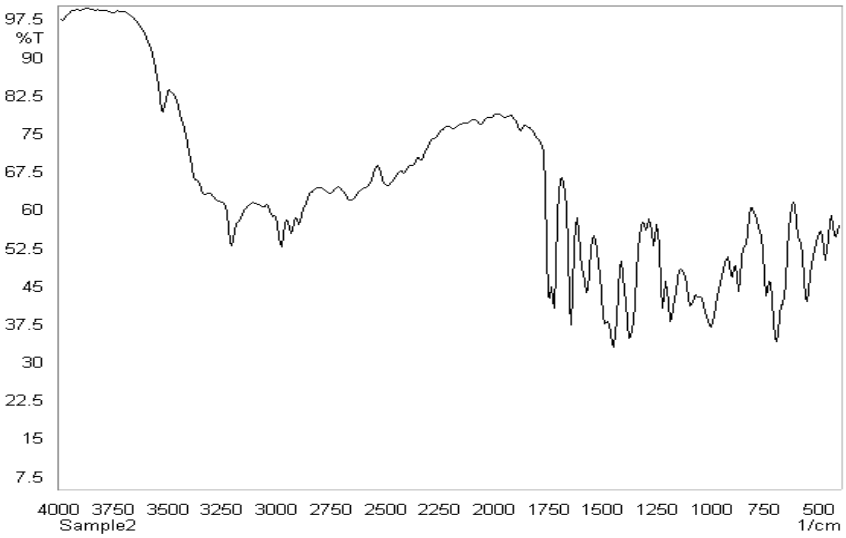

Fig No.2.2: FTIR of drugs + Excipients.

Table No. 2.2: FTIR of drugs + excipient.

S. No.	Functional group	Frequency	Reported value
1.	-OH	3700-300	3525.88
2.	CH_3	1465	1454.33
3.	-O-	702-900	702

4. UV Spectroscopy

a. ʎmax for pure Enalapril maleate in water

Apparatus: UV spectroscopy (semadzu)

The 1 µg/ml sample was prepared and scanned between 200-400nm. The drug showed maximum absorption at 208nm. So the $ʎ_{max}$ of enalapril maleate was found to be 208nm.

Preparation of standard curve for Enalapril maleate

10mg of Enalapril Maleate pure drug was accurately weighed & transferred into a 10ml volumetric flask, dissolved in little quantities of distilled water, then made up to 10ml with water(1000µg/ml). From this solution, 1ml of solution was withdrawn into a 10ml volumetric flask & made up to 10ml with distilled water to get a concentration of 100µg/ml. From this, again pipette out 1ml of solution & diluted to 10ml with distilled water to get a concentration of 10µg/ml. Absorbance of this was measured at 208 nm using UV/VIS spectrophotometer against blank (distilled water).[5]

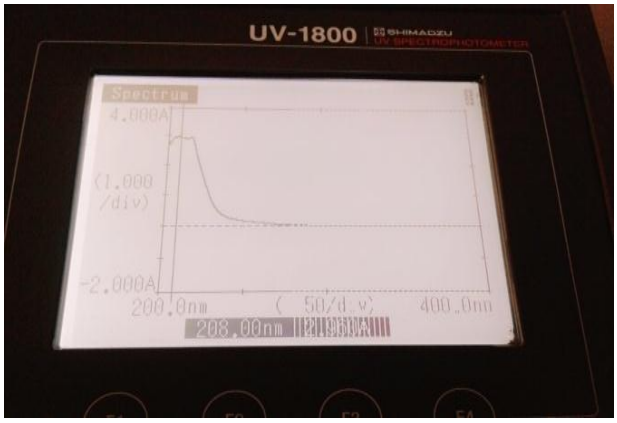

Fig No. 2.3: Standard curve Enalapril maleate in water.

Table No. 2.3: Standard calibration curve in water.

S.No.	Concentration	Absorbance
1.	0	0
2.	0.1	0.126
3.	0.2	0.235
4.	0.3	0.329
5.	0.4	0.429
6.	0.5	0.528
7.	0.6	0.621

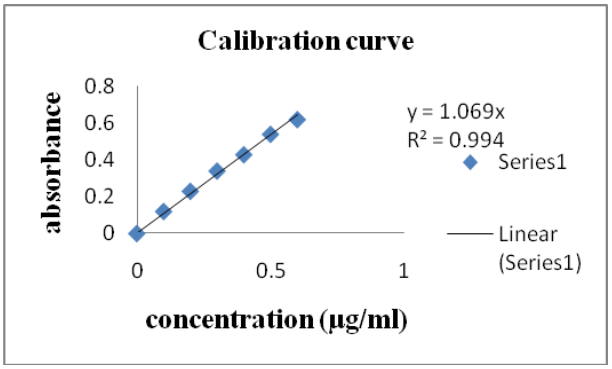

Fig. No. 2.4: Calibration graph of Enalapril maleate in water.

b. Standard curve in phosphate buffer pH 6.8

Preparation of phosphate buffer pH 6.8

Dissolve 28.80 g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in sufficient water to produced 1000 ml. [6]

$ʎ_{max}$ for pure Enalapril Maleate in phosphate buffer 6.8

The 10 µg/ml sample was prepared and scanned between 200-400nm. The drug showed maximum absorption at 212nm. So the $ʎ_{max}$ of Enalapril Maleate was found to be 212 nm.

Preparation of standard curve

10mg of Enalapril Maleate pure drug was accurately weighed & transferred into a 10ml volumetric flask, dissolved in little quantities of phosphate buffer 6.8,then made up to 10ml with phosphate buffer 6.8 (1000µg/ml). From this solution, 1ml of solution was withdrawn into a 10ml volumetric flask & made up to 10ml with 6.8phosphate buffer to get a concentration of 100µg/ml. From this, again pipette out 1ml of solution & diluted to 10ml with 6.8 phosphate buffer to get a concentration of 10µg/ml. Absorbance of this was measured at 212 nm using UV/VIS spectrophotometer against blank (6.8phosphate buffer).[6]

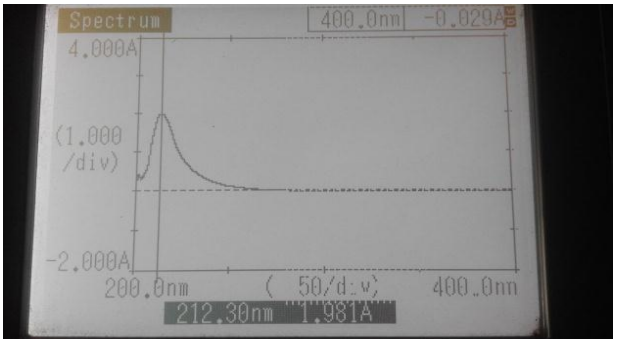

Fig No. 2.5: Spectra of Enalapril Maleate in phosphate buffer.

Table No. 2.4: Standard calibration curve in phosphate buffer.

S.No.	Concentration(µg/ml)	Absorbance
1.	0.0	0.0
2.	0.1	0.050
3.	0.2	0.102
4.	0.3	0.150
5.	0.4	0.199
6.	0.5	0.244
7.	0.6	0.292

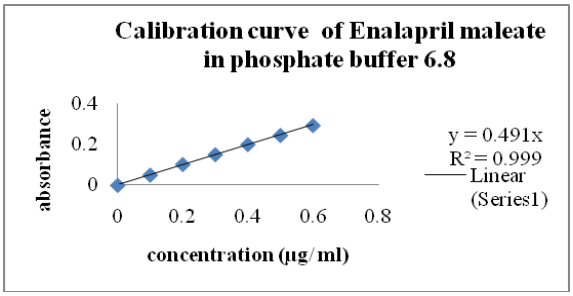

Fig. No. 2.6: Calibration graph of enalapril maleate in phosphate buffer 6.8 pH.

Table No. 2.5: Pre-compression parameter of powder blend (direct compression method).

Formulation code	Bulk density (gm/ml)±SD	Tapped density (gm/ml)±SD	Angle of repose(◦) ±SD	Carr index(%)±SD	Hausner's ratio±SD
F1	0.39±0.0059	0.45±0.0022	27.88±1.29	12.9±1.12	1.15±0.02
F2	0.40±0.0060	0.47±0.0018	30.00±1.66	14.93±1.34	1.18±0.03
F3	0.37±0.0038	0.40±0.0032	27.75±1.03	6.41±1.21	1.07±0.04
F4	0.39±0.0037	0.44±0.0023	33.57±0.38	12.23±1.41	1.14±0.04
F5	0.41±0.0028	0.49±0.0039	35.34±0.45	16.31±1.61	1.19±0.02
F6	0.50±0.0083	0.60±0.0041	28.60±3.88	16.7±1.53	1.20±0.03
F7	0.43±0.0055	0.51±0.0044	25.74±1.80	16.94±1.58	1.20±0.04
F8	0.43±0.0024	0.51±0.0036	27.95±2.26	15.00±2.23	1.18±0.04
F9	0.43±0.0058	0.52±0.0058	32.85±1.45	18.34±2.02	1.22±0.02

Formulation Development

By Direct compression method

The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrants and optimization of concentration of superdisintegrants. The main criteria for fast dissolving tablets is to disintegrate or dissolve rapidly in oral cavity in 15-60 seconds, without need of water and should have pleasant mouth feel. The super disintegrate (croscarmellose, and Sodium Starch Glycolate) were used to formulate the tablets. All the ingredients as shown in Table 1 were co-ground in a pestle and motor and then lactose and magnesium stearate were added and mixed for 10 minutes. All the ingredients were passed through # 60-mesh separately. The mixed blend of drug-excipient was compressed using a single punch tablet machine.[7,8]

Table No. 2.6: Formulation of Enalapril maleate fast dissolving tablet (Direct compression method).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
ENM	5	5	5	5	5	5	5	5	5
Crosscarmellose	10	15	20	25	28	30	35	38	40
SSG	40	38	35	30	28	26	25	22	20
Mg. stearate	100	100	100	100	100	100	100	100	100
Lactose	50	50	50	50	50	50	50	50	50
Sucrose	120	120	120	120	120	120	120	120	120
SLS	30	30	30	30	30	30	30	30	30
Starch(20%conc)	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of the Fast Dissolving tablets (FDT)

Quality control tests for FDTs of all formulations were performed, and the average values were calculated. All the tablets were evaluated for different parameters as weight variation, hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and *in vitro* dissolution study.

Tablet thickness

The thickness of three tablets from each batch was determined using a Vernier caliper. The thickness was measured in centimeters.

Weight Variation

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance (Shimadzu). The individual weighed is then compared with average weight for the weight variations.

Hardness

The strength of tablet is expressed as tensile strength (kg/cm2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation

batch were tested randomly and the average readings were noted.

Friability

Friability of the tablets was determined using Roche Friabilator. This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula,

% Friability = (Initial weight - Loss in weight) / Initial weight*100

Friability below 1% was considered as acceptable.

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10mg of Enalapril maleate was dissolved in 100 ml of phosphate buffer solution, pH 6.8., filtered, diluted suitably and analyzed for drug content at 212 nm using UV-Visible spectrophotometer (Shimadzu1700, Tokyo, Japan).

Wetting time & water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5 cm) containing 6 ml of phosphate buffer solution, pH 6.8. A tablet was placed on the paper and time required for complete wetting was measured using a stop watch. The wetted tablet was then weighed. Water absorption ratio (R)was determined using following equation,

$$R = \frac{Wa - Wb \times 100}{Wa}$$

Wa = Weight of tablet after water absorption,
Wb = Weight of tablet before water absorption

Wetting time

***In vitro* disintegration time**

10 ml of phosphate buffer solution, pH 6.8 was placed in a petridish of 10 cm diameter. The tablet was then carefully positioned in the center of the petridish and the time required for the tablet to completely disintegrate into fine particles was noted.

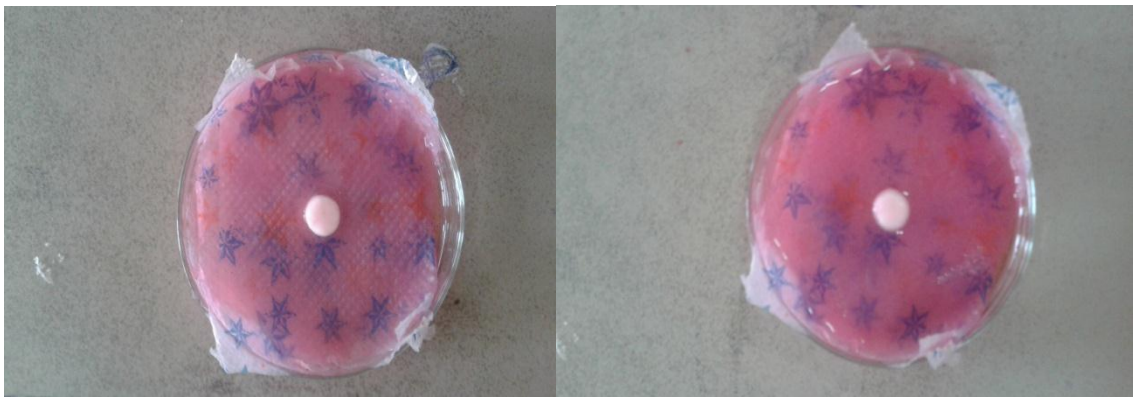

Fig No. 2.5: Wetting time study.

***In- vitro* disintegration time**

In-vitro disintegration times for Fast dissolving tablets of Enalapril maleate were determined using USP disintegration test apparatus with 900 ml of phosphate buffer solution, pH 6.8 as medium maintained at a temperature of 37 } 2°C. The time in seconds taken for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

In-vitro Dissolution Study

The release rates of Enalapril maleate from fast dissolving tablets were determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer 6.8, at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at regular intervals of 1 mins for 30mins. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whitman filter. Absorbance of these solutions was measured at 212 nm using UV Spectrophotometer. Cumulative percentage of drug release was then calculated.

Stability studies

In order to determine the change in *In-vitro* release profile on storage, stability studies of optimized batch i.e., F9 was carried out at40°C in a humidity chamber having 75% RH. Samples were withdrawn at regular intervals of 15 days during the study of 30 days. Formulation is evaluated for change in *In-vitro* drug release pattern, hardness, wetting time, weight variation, percent drug content.[9,10,11]

Table No. 2.7: Evaluation of fast dissolving tablet of Enalapril maleate (Direct compression method).

Evaluation parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness(mm)±SD	4.71±0.040	4.5±0.039	4.56±0.05	4.87±0.045	5.01±0.049	4.83±0.042	4.87±0.042	4.53±0.050	4.44±0.044
Hardness (kg/cm^2)±SD	3.83±0.12	3.71±0.31	3.56±0.25	3.56±013	3.49±0.23	3.42±0.37	3.41±0.34	3.20±0.06	3.09±0.10
%Friability ±SD	0.52±0.18	0.60±0.14	0.62±0.19	0.58±0.11	0.59±0.16	0.59±0.14	0.64±0.10	0.68±0.10	0.19±0.18
Disintragration time (sec) ± SD	98.16±0.61	96.11`0.42	90.51±0.23	88.20±0.23	87.86±0.82	86.52±0.41	78.52±0.84	71.69±0.76	69.60±0.63
Wetting (sec)±SD	40.22±0.25	38.90±0.11	37.45±0.20	36.65±0.24	36.75±0.35	36.25±0.53	35.90±0.47	35.78±0.58	35.11±0.22
Water absorption a ratio	141.68±0.56	149.27±0.78	156.34±0.81	150.65±0.45	148.36±0.78	155.28±0.91	180.91±0.78	193.69±0.54	209.65±0.89
Content uniformity(%)±SD	99.27±0.63	96.99±0.55	99.81±0.35	98.85±0.20	97.81±0.44	98.92±0.87	69.97±0.38	98.64±0.29	99.69±0.63

Table No. 2.8: % Drug release profile of fast dissolving tablets Enalapril maleate.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	14.73	19.13	16.71	23.42	17.48	20.01	23.42	13.52	28.15
2	19.57	23.53	25.4	37.5	26.94	28.48	34.52	28.15	37.14
3	26.5	26.5	35.63	42.56	38.16	37.5	39.37	42.34	46.52
4	31.56	34.31	40.63	47.52	45.31	43.66	45.31	47.51	54.65
5	35.3	41.24	47.4	43.78	47.84	45.31	52.35	57.29	58.39
10	47.73	47.71	53.56	57.29	54.76	54.76	58.72	64.55	61.8
15	53.56	50.15	58.39	61.36	58.39	58.39	65.76	68.29	64.99
20	56.41	57.25	63.12	67.3	65.65	63.67	69.72	69.72	76.1
25	65.65	62.79	69.5	73.9	72.14	74.56	74.67	78.3	83.8
30	67.52	68.62	74.23	75.54	76.76	77.2	78.3	86.33	87.1

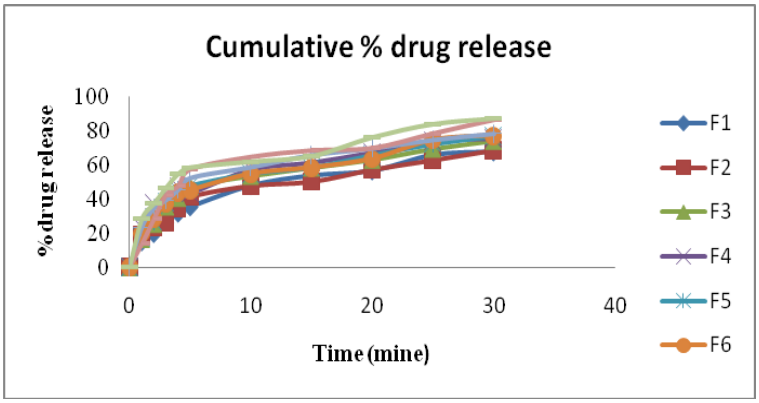

Fig No.2.6: In-vitro drug release profile of fast dissolving tablets Enalapril maleate.

Table No. 2.9: Accelerated stability study of optimized formulation MD6 at 40^{0C}/75%RH for one month.

Period	Hardness(kg/cm^2)	Disintegration time(sec)	Wetting time(sec)	Drug content (%)	%drugs release
0Day	3.09±0.10	69.60±0.65	35.11±0.18	99.69±0.03	86.33
15 day	3.07±0.09	68.58±0.56	33.12±0.12	99.57±0.04	85.95
30 day	3.02±0.4	67.48±0.47	31.15±0.10	98.97±0.09	85.31

RESULT AND DISCUSSION

Preformulation study

In Preformulation studies various characteristic of drug such as identification analytical method, micromeritics, solubitities study, loss on drying and partition coefficients were evaluated. The results for these studies are shown in table no.3.1.

Table No. 3.1: Results preformultion study.

S. No.	Preformulation Study	Results
1.	**Organoleptic properties** Description: State: Colour: Odour: Taste:	 White crystalline powder White Odourless Bitter

2.	**Identification** a. UV absorption maxima b. TLC c. Melting point d. Infra-red spectra	 208, 212 R_f =0.56 143-144^{oC} No change spectra
3.	**Assay of Drugs**	98.5 to101.5% (Standard as per IP)
4.	**Calibration Curve** a. In water b. In phosphate buffer P^H 6.8	 λmax y =1.069x λmax y =0.491x
5.	**Micromeriticas** a. Bulk density b. Tapped density c. Carr' s index d. Angle of repose	 0.38±0.03 gm/ml 0.56±0.06 gm/ml 13.77±6.64 (flow property- poor) 38.35±0.895 (flow property –fair)
6.	**Loss of Drying**	1%
7.	**pH**	2.53±0.09
8.	**Solubility**	Methanol, ethanol, distilled water, dimethyl formide
9.	**Partition Cofficients**	2.45±0.011(lipophilic in nature)
10.	**Drug- Excipients Intrection**	No interaction

Enalapril maleate fast dissolving tablet were prepared by direct compression method was carried out by using superdisintegrants (crosscarmelose and sodium starch glycolate), excipient like lactose, sucrose, magnesium stearate, sodium lauryl sulphate. Preformulation studies such as bulk density, tapped density, angle of repose, compressibility index, hausner ratio. All the Preformulation studies were found the prescribed limits and indicated good flow properties. The FTIR also revealed there is no interaction between the pure drugs and Excipients use for the formulation. The data obtained from physicochemical parameter such as hardness, friability, weight variation, drugs content, wetting time, disintegration time, invitro dissolution studies. Out of all formulation in direct compression method, F9 direct compression was found satisfactory. The angle of repose was ranged between 25.74º±1.8071 to 35.34 º±0.4503. The compressibility index value were found to be in the range of 6.41 %to 80.34% the husner,s ratio were found to be in the range of 1.07 to 1.20. The hardness was between 3.09±0.10 to 3.83±0.61. Thickness of al nine formulation varied from 4.5±0.039mm to 5.01±0.049 mm. the loss of total weight of tablets due friability was in range of 0.19±0.18 to 0.68±0.10. The dugs content for all nine formulation was in the range of 69.97±0.38 to 99.69±0.63 %. The wetting for all nine formulation was in the range of 35.11±0.22 sec to 40.22±0.25 sec. disintegration time the value of this test range from 69.60±0.63 sec to 98.16±0.61 sec. this was one test to be considered to selects one best formulation from nine formulation according to this test F9 is best formulation as it shown lowest time for disintegration (69.60±0.63).dissolution test was carried out 50rpm using phosphate buffer P^H 6.8. Stability study was carried out for the best formulation of F9 formulation (sublimation method)at 40^0c and 75%RH for one month, 15 days interval the formulation was examined for physical appearance, hardness, friability, thickness, drugs contents, disintegration time, dissolution study, wetting time revealing excellent of the formulated formulation.

CONCLUSION

Fast dissolving tablets of enalapril maleate can be successfully prepared by direct compression technique using selected superdisintegrants for the better patient compliance for effective therapy. The fast dissolving tablets prepared by using croscarmellose and sodium starch glycolate by direct compression is more efficient by the evaluation parameter (disintegration time, wetting time, dissolution profile) and result obtained.

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