

Design and Characterization of Oral Dispersible Tablets of Enalapril Maleate Using a Co-Processed Excipient

Swamy NGN^{1*}, Sachin¹ and Abbas Z²,

¹Department of Pharmaceutics, Government College of Pharmacy, Bangalore – 560 027

²Formulation development Department, Apotex Research Private Ltd, Bangalore-560 099

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ABSTRACT

In the present work, oral dispersible tablets of Enalapril maleate were prepared using three different superdisintegrants and a co-processed superdisintegrant consisting of crospovidone and sodium starch glycolate in the ratio 1:1. Oral dispersible tablets of Enalapril maleate were prepared by employing direct compression technique using the above superdisintegrants, and evaluated for precompression as well as post-compression parameters, such as determination of weight variation, thickness, hardness, friability, wetting time, disintegration time, drug content, water absorption ratio, *in vitro* dispersion time, and *in vitro* drug release study. Formulation F-VII, F-VIII and F-IX were subjected to stability Studies as per ICH guidelines at temperatures and humidity of 25±5°C/60±5%RH; 30±5°C/65±5%RH and 40±5°C/75±5%RH. Tablets didn't reveal any appreciable changes in respect to hardness, disintegration time, drug content and dissolution profiles. From the results, it could be concluded that the formulation(F-VII) made with co-processed super disintegrant (1:1) at a concentration of 5% w/w revealing a disintegrating time of 13.2 sec, and 97.84 % cumulative drug release emerged as the best formulation.

INTRODUCTION

The oral route of administration is considered to be the most widely accepted route for drug administration. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is the difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients (Masareddy *et al.*, 2008). Other categories that experience problems with conventional oral dosage forms include the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing during the common cold and bronchitis where an ultra-rapid onset of action is required (Patel *et al.*, 2010) (Shahi *et al.*, 2008). Amongst the different novel drug delivery systems, a oral fast dissolving drug delivery system (Gaur *et al.*, 2011) has been introduced to overcome these drawbacks as an alternative to oral dosage form. A oral fast dissolving drug delivery system is a novel tablet dosage form, that dissolves or disintegrates in the

oral cavity with a good taste and flavor increasing the acceptability of various bitter drugs without the need of water or chewing and hence called melt in mouth tablets or repimelts or porous tablets or oro-dispersible or quick dissolving or rapid disintegrating tablets. 'Fast Dissolve', 'Quick Dissolve', 'Rapid Melt', 'Quick Disintegrating', 'Mouth Dissolving', 'Orally Disintegrating', 'Oro Dispersible', 'Melt-in-Mouth', etc (Ratnaparkhi *et al.*, 2009) (Siddiqui *et al.*, 2010), are terms that represent the same drug delivery system. Recently orally disintegrating (OD) tablet technology has been approved by United States Pharmacopoeia (USP), Center for Drug Evaluation and Research (CDER). USFDA defined OD tablet as "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia has also adopted the term "Oro Dispersible Tablet" (ODTs) as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing (Kundu *et al.*, 2008). These dosage forms dissolve or disintegrate in the patient's mouth within 15 sec to 3 min obliterating the need of water or chewing.

* Corresponding Author

Dr. NGN Swamy Professor, Department of Pharmaceutics,
Government College of Pharmacy, No. 2, P. Kalinga Rao Road,
Bangalore – 560 027, Mob. No: + 91 9945451772

EVALUATION OF PRE-COMPRESSION PARAMETERS

Bulk density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted (Lakshmi CSR *et al.*, 2011). It is expressed in gm/cc and is given by

$$D_b = \frac{M}{V_b} \text{-----} 1$$

Where M= is the mass of powder.

V_b= is the bulk volume of the powder.

Tapped density (Dt)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to a constant volume (Indhumati D *et al.*, 2011). It is expressed in gm/cc and is given by

$$D_t = \frac{M}{V_t} \text{-----} 2$$

M = is the mass of powder.

V_t is the tapped volume of the powder.

Bulkiness (untapped density) B₀

It is the ratio of bulk volume to the mass of powder. It is expressed in ml/gm and is given by (Kamboj M *et al.*, 2011)

$$B_0 = \frac{V_b}{M} \text{-----} 3$$

Where

V_b= is the bulk volume powder.

M=mass of powder.

Bulkiness (Tapped):B_t

It is the ratio of tapped volume to the mass of powder. It is expressed in ml/gm and is given by,

$$B_t = \frac{V_t}{M} \text{-----} 4$$

V_t= is the tapped volume of powder.

M = mass of powder.

Angle of repose:(θ)

The frictional forces in a loose powder can be measured by the angle of repose. It is defined as maximum angle possible between the freely sliding surface of a pile of powder and the horizontal plane (Patel *et al.*, 2011).

$$\tan\theta = \frac{h}{r} \text{-----} 5$$

Where, θ = is the angle of repose

h = is the height

r = is the radius.

Table. 2: Flow properties and corresponding angle of repose.

Flow property	Angle of repose (Degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, Very Poor	>66

The powder mixture was allowed to flow through the funnel fixed to a stand at a definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed using the expression mentioned above. The inter relationship (Japanese Pharmacopoeia, 2007) between angle of repose and flow properties of powders is shown in table 2

Carr's index (I)

It indicates the ease with which a material can be induced to flow. It is expressed as a percentage and is given by

$$I = \frac{D_t - D_b}{D_t} \times 100 \text{-----} 6$$

Where, D_t= is the tapped density of the powder and D_b=is the bulk density of the powder (Singh H *et al.*, 2011).

The inter relationship (Bhowmik D *et al.*, 2009) between angle of repose and flow properties of powders is shown in table 3.

Table. 3: Carr's index values.

Carr's index (%)	Type of flow
5- 15	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner ratio} = \frac{D_t}{D_b} \text{-----} 7$$

Where, D_t is the tapped density, and D_b is the bulk volume. (Wells J, 2002). The inter relationship between angle of repose and flow properties of powders is shown in table 4.

Table. 4: Hausner ratio values.

Hausner ratio	Type of flow
< 1.25	Good
1.25 -1.5	Moderate
> 1.5	Poor

POST COMPRESSION PARAMETERS

General appearance

By visual method

Hardness

The hardness of the tablet was measured using a Pfizer hardness tester. It is expressed in Kg/cm² (Jadhav SB, *et al.*, 2011).

Thickness

The thickness of the tablets was measured by using a micrometer screw gauge and expressed in millimeters (Gandhi GS *et al.*, 2011).

Friability (F)

The friability of the tablet was measured using Roche friabilator (European Pharmacopoeia, 2005). It is expressed in percentage (%). 10 tablets were weighed (W_{initial}) and transferred

to the Friabilator. The friabilator was operated at 25 rpm for 4 min. The tablets were weighed again (W_{final}). The % friability was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100 \quad \text{-----} \quad 8$$

Tablet porosity

If the tablet doesn't have the intra and interparticle voids then, the bulk volume equals to the true volume ($v_b = v_t$), such a situation can be created by compression pressure of 1422.47 psi so that a tablet without any intra and interparticle voids is produced (Tanabe H *et al.*, 2007). Then the bulk volume is calculated from the formula (Wood GC *et al.*, 2005),

$$v_b = \frac{(W_2 - W_1)}{\rho} - \frac{(W_4 - W_3)}{\rho} \quad \text{-----} \quad 9$$

Where W_2 = Weight of benzene with bottle, W_1 = weight of empty bottle, W_3 = Weight of tablet with bottle, and W_4 = weight of bottle, benzene and tablet.

Then true density of the tablet is calculated by using the formula,

$$\text{True density of the tablet} = \frac{\text{mass of the tablet}}{\text{true volume of the tablet}} \quad \text{-----} \quad 10$$

True volume of the tablet is calculated from the formula (Lachman L, 1991),

$$v_t = \frac{\left(\frac{\text{Weight of the tablet}}{1000}\right)}{\text{True density of the tablet}} \quad \text{-----} \quad 11$$

And the porosity of the tablet is calculated by using the formula,

$$\varepsilon = 100 \left[1 - \frac{v_t}{v_b} \right] \quad \text{-----} \quad 12$$

Where ε = Porosity of the tablet.

Disintegration time

The disintegration time of tablet was determined using disintegration apparatus in pH 6.8 buffer (simulated salivary fluid) as disintegration medium maintained at 37°C. When all the six tablets are completely disintegrated, the time was noted (Malik K *et al.*, 2011).

Weight variation

Weight variation was carried out for the tablets. 20 tablets were weighed and the average weight was arrived. Then the tablets were weighed individually. The percentage weight deviation of each tablet from average weight was calculated using the following formula

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Individual weight}} \times 100 \quad \text{-----} \quad 13$$

Table. 5: BP limits for Weight variation.

Average weight of the tablet (mg)	Percentage deviation
80 or less	± 10
80-250	± 7.5
More than 250	± 5.0

The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet deviated beyond the

percentage limit given in table 5 (British Pharmacopoeia, 2005).

In vitro dispersion time

In vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5°C and the time required for complete dispersion was recorded (Shirsand SB *et al.*, 2010).

Water absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water.

A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$$R = 100[(W_a - W_b)/W_b] \quad \text{-----} \quad 14$$

where, W_b is weight of tablet before water absorption & W_a is weight of tablet after water absorption (Shukla d *et al.*, 2009).

Assay

Twenty tablets were powdered, and 10 mg equivalent weight of Enalapril maleate tablet powder was accurately weighed and transferred into a 100 ml volumetric flask.

Initially, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with same phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 206.6 nm (Paul Y *et al.*, 2011).

In vitro Dissolution Studies

Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for ENM tablet was carried out as per USP method for dissolution test for tablets and capsules using apparatus II (paddle type). Dissolution medium used was 900 mL of 6.8 pH phosphate buffer, agitation speed at 50 rpm at 37±0.5°C.

An aliquot sample of 5 mL was withdrawn at different time periods and replaced with fresh medium. These samples were filtered and diluted suitably. Absorbance of the resulting solution was measured at 206.4 nm (experimental λ_{max} for ENM in pH 6.8 phosphate buffer). Percentage cumulative drug release was calculated (Senthil A *et al.*, 2011).

Stability Studies

The selected formulations were subjected for stability studies by keeping sample in stability chamber. The formulations were stored at different storage conditions like 5°C/Ambient, 25°C/ 60 % RH, and 40°C/ 75 % RH for 90 days.

The formulations were subjected to different tests such as determination of hardness, drug content and *in-vitro* drug release study (ICH tripartite guidelines 2003).

RESULTS AND DISCUSSION

Compatibility Studies

Fourier Transform Infra Red Spectroscopy (FTIR)

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish or rule out any possible interaction of Enalapril maleate with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results are shown in fig 1-4, indicating that the characteristic absorption peaks due to pure Enalapril maleate have appeared in the formulated tablets, without any significant change in their position after successful formulation, indicating the absence of any chemical interaction between Enalapril maleate and Polymers.

Differential Scanning Calorimetry (DSC)

DSC is useful in the investigation of solid-state interactions. The DSC analysis of pure ENM showed a sharp endothermic peak at 152.55°C corresponding to its melting point. The thermograms were generated for pure drug and drug excipient mixtures. The DSC analysis of physical mixture of the drug and excipients revealed negligible change in the melting point of ENM in the presence of other excipients. Thermograms are shown in fig 5-8.

Pre-compression Parameters of Powder Blend

Precompression parameter for the formulations prepared by direct compression technique is shown in Table 6. Tapped bulk density was found to be in the range of 0.458±0.02 to 0.518±0.06g/cc and untapped bulk density ranged from 0.396±0.00 to 0.454±0.01 g/cc, tapped bulkness was between 1.930±0.06 to

2.183±0.02, and untapped bulkness varied from 2.202±0.01 to 2.525±0.00. Angle of repose was found to be between 28°29'±0.14 to 34°09'±0.51, indicating fair flow properties; Carr's index ranged from 12.27 to 13.68 %, and Hausner ratio ranged from 1.13 to 1.19.

Evaluation of Post Compression Parameters of Enalapril Maleate Tablets

The tablets of different formulations (F-1 to F-IX) were evaluated for various parameters viz; thickness, hardness, friability, percentage weight variation and percentage drug content, water absorption ratio, *in vitro* dispersion time, disintegration time, wetting time, percentage porosity (data is given in Table 7, 8 and 9) and *in vitro* drug release studies. All the formulations showed uniform thickness and diameter. The average percentage deviation of all tablet formulations was found to be within the limit of ±5% and hence all formulations passed the test for uniformity of weight as per official requirements. Drug content was found to be uniform among different batches of the tablets and the percentage of the drug content was found to be in the range of 95.73±0.87 to 98.67±0.25. The tablets displayed a hardness ranging between 3.1±0.04 to 3.3±0.17 kg/cm². The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. The percentage of water absorption was between 84.26±1.67 to 98.86±0.17. The disintegration time of the tablets varied from 13.2 to 23.22 sec. The first step in the disintegration process is the penetration of water into the tablet. Porosity depends on the pressure at which tablets are compressed as well as the nature of material being tableted. At low compression force levels many cavities remain in the tablet, on the other hand, a high compression force leads to tablet with a lower porosity.

Table-6 Precompression parameters for the different enalapril maleate tablet formulations.

Formulations	BD (gm/cc)		Bulkness (cc/gm)		Carr's index (%)	Hausner's ratio	Angle of repose
	TBD	UBD	TBD	UTD			
F-I	0.458±0.02	0.396±0.00	2.183±0.02	2.525±0.00	13.53	1.15	29°45'±0.25
F-II	0.470±0.03	0.409±0.00	2.127±0.03	2.444±0.00	12.9	1.14	30°25'±0.12
F-III	0.497±0.04	0.429±0.01	2.012±0.04	2.331±0.01	13.68	1.15	31°58'±0.62
F-IV	0.518±0.06	0.454±0.01	1.930±0.06	2.202±0.01	12.35	1.14	29°48'±0.77
F-V	0.509±0.02	0.441±0.02	1.964±0.02	2.267±0.02	13.35	1.15	33°69'±0.42
F-VI	0.512±0.05	0.429±0.01	1.953±0.05	2.331±0.01	16.2	1.19	34°09'±0.51
F-VII	0.494±0.03	0.430±0.01	2.024±0.03	2.325±0.01	12.9	1.14	28°29'±0.14
F-VIII	0.497±0.04	0.436±0.01	2.012±0.04	2.293±0.01	12.27	1.13	32°41'±0.24
F-IX	0.516±0.05	0.450±0.01	1.937±0.05	2.222±0.01	12.79	1.14	33°15'±0.59

Table. 7: Post compression parameters for the different enalapril maleate tablet formulations.

Formulations	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation (%)	Drug content (%)
F-I	2.98±0.07	3.1±0.10	0.32	-1.86 to 2.64	95.73±0.87
F-II	2.99±0.04	3.2±0.02	0.34	-2.76 to 3.81	97.23±1.15
F-III	3.19±0.06	3.1±0.04	0.49	-2.99 to 2.88	96.67±1.15
F-IV	2.98±0.11	3.3±0.04	0.39	-3.18 to 3.19	97.43±0.87
F-V	3.11±0.06	3.3±0.03	0.39	-2.25 to 2.77	95.73±0.87
F-VI	3.23±0.08	3.2±0.10	0.32	-2.98 to 2.78	96.27±0.86
F-VII	3.27±0.05	3.2±0.12	0.36	-1.69 to 2.01	98.67±0.25
F-VIII	3.21±0.10	3.3±0.12	0.33	-2.03 to 3.57	96.30±1.15
F-IX	2.99±0.09	3.3±0.17	0.32	-1.8 to 3.32	96.67±1.15

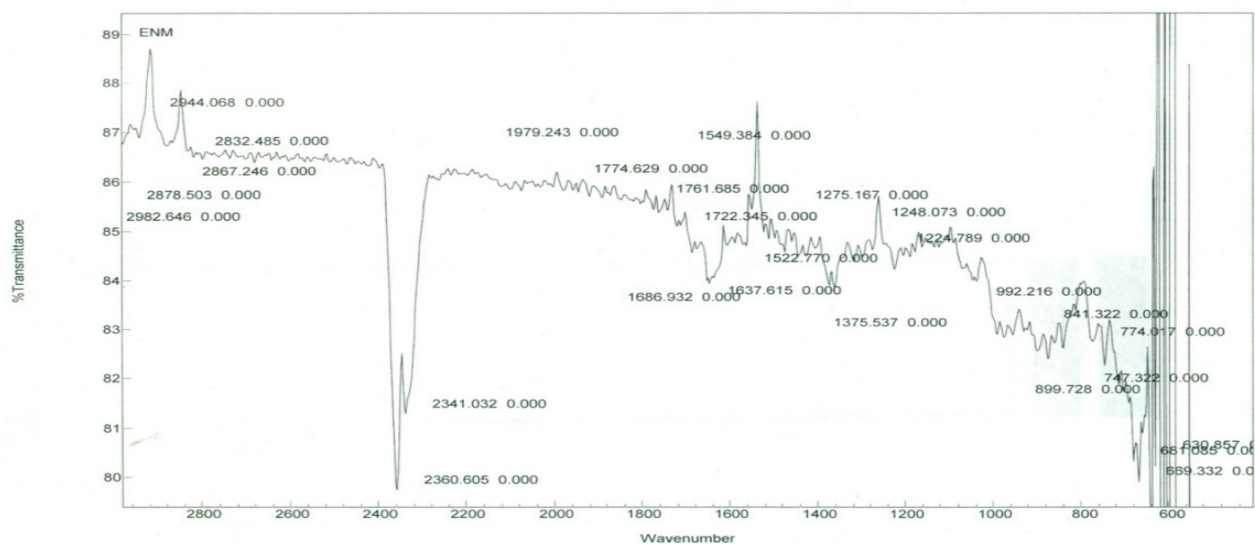
Table 8: Post-compression parameters of different enalapril maleate tablet formulations.

Formulations	Water absorption ratio (%)	<i>In vitro</i> dispersion time (sec)	Disintegration time (sec)	Wetting time (sec)
F-I	84.26±1.67	120.57±1.96	19.05	7.96±0.61
F-II	94.66±2.60	128.90±2.77	22.32	9.37±0.08
F-III	96.13±0.83	130.98±1.96	23.22	10.46±0.09
F-IV	94.26±0.61	151.76±1.67	22.01	11.76±0.31
F-V	94.13±1.01	146.83±2.35	21.31	10.06±0.25
F-VI	92.8±1.06	138.61±3.69	18.5	8.8±0.17
F-VII	96.93±0.41	87.90±3.63	13.2	7.76±0.06
F-VIII	95.26±0.80	95.85±3.08	14.8	8.63±0.31
F-IX	98.86±0.17	103.93±2.30	14.99	9.20±0.36

Table 9: Post compression parameter of the selected formulations.

Formulation	True density (gm/ml)	Bulk volume(ml)	True volume (ml)	Porosity (%)
F-VII	1.25	0.26	0.2	23.1
F-VIII	1.21	0.25	0.2	18
F-IX	1.21	0.23	0.2	11

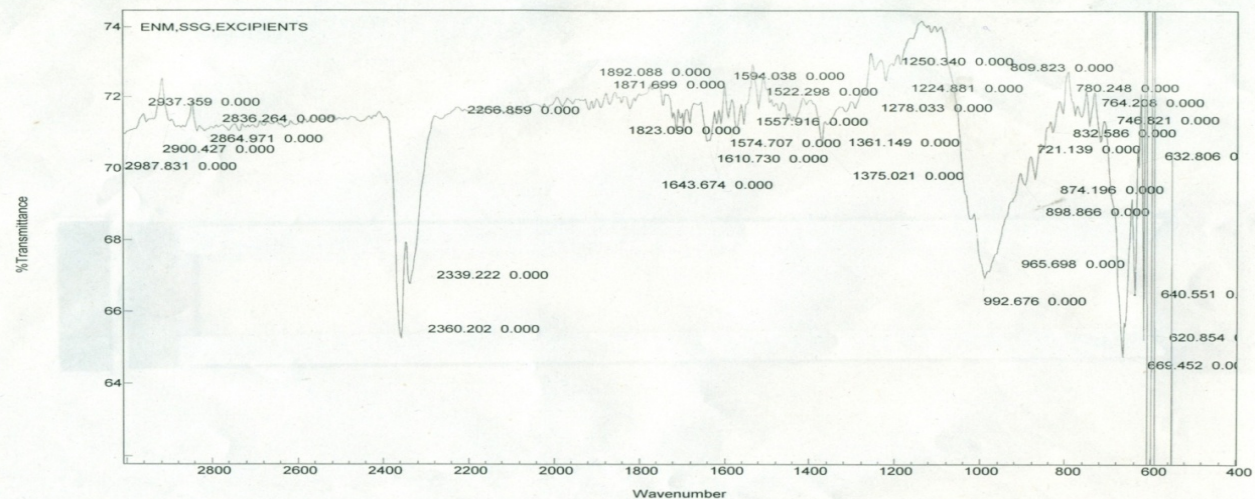
Varian Resolutions Pro



Name
ENM

Fig.1: FT-IR Spectra of Enalapril maleate.

Varian Resolutions Pro



Name
ENM,SSG,EXCIPIENTS

Fig. 2: FT-IR Spectra of Enalapril maleate+Sodium starch glycolate+Excipients.

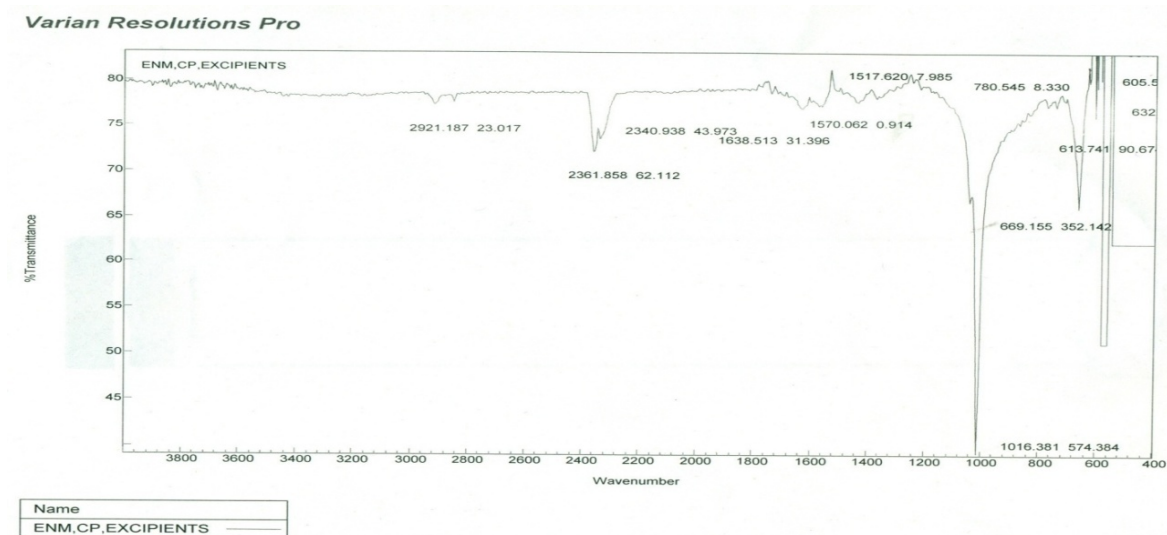


Fig.3: FT-IR Spectra of Enalapril maleate+Crospovidone+Excipients.

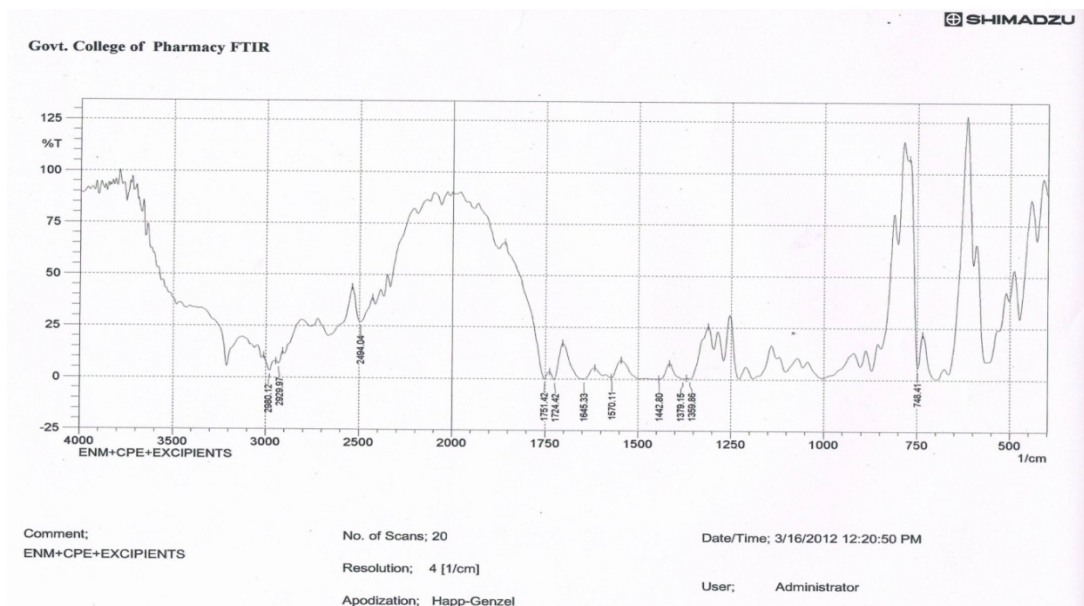


Fig.4: FT-IR Spectra of Enalapril maleate+CPE+Excipients.

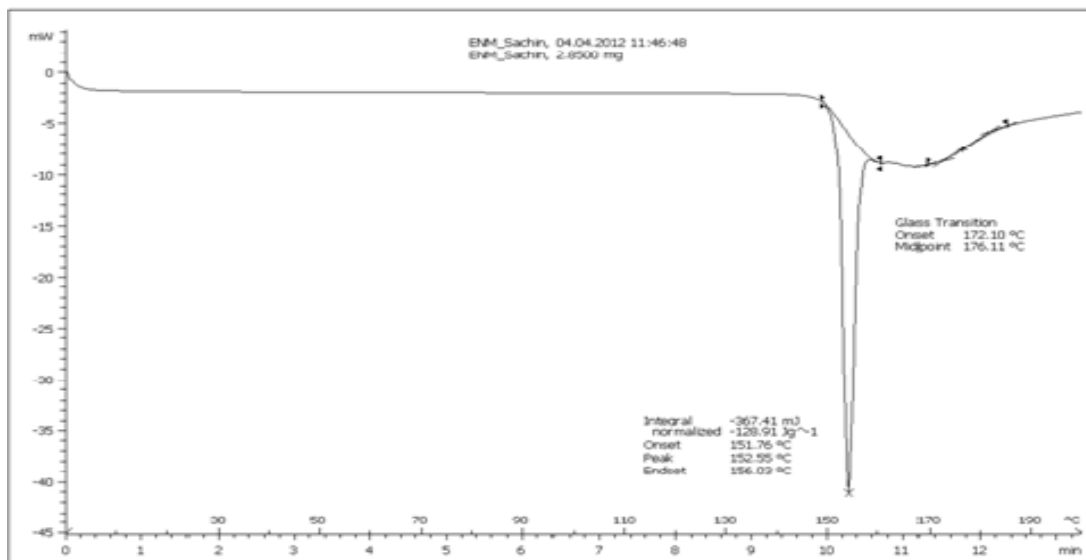


Fig.5: DSC thermogram of ENM.

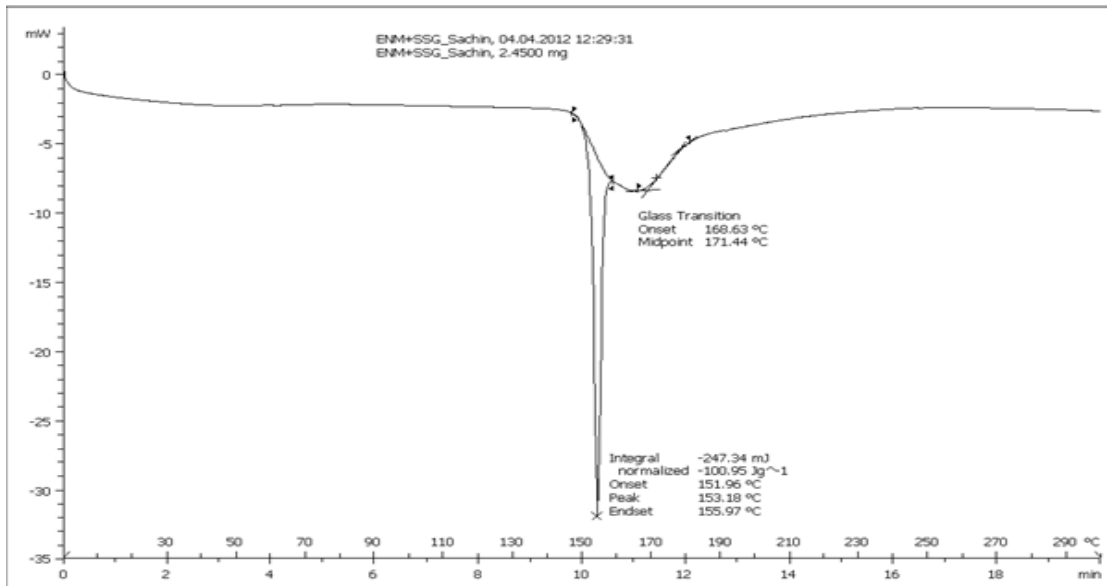


Fig.6: DSC thermogram of ENM with SSG.

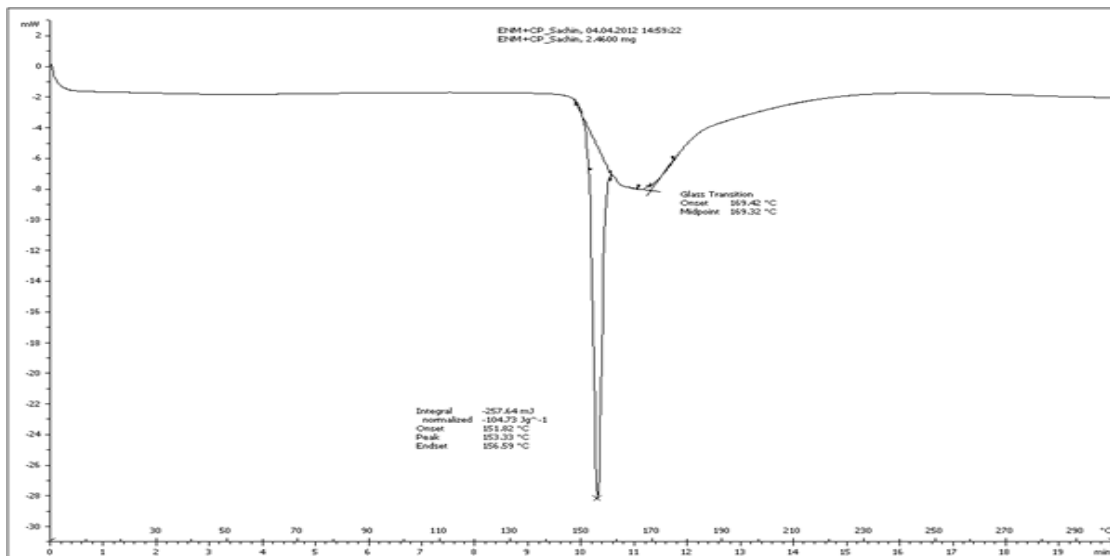


Fig.7: DSC thermogram of ENM with CP.

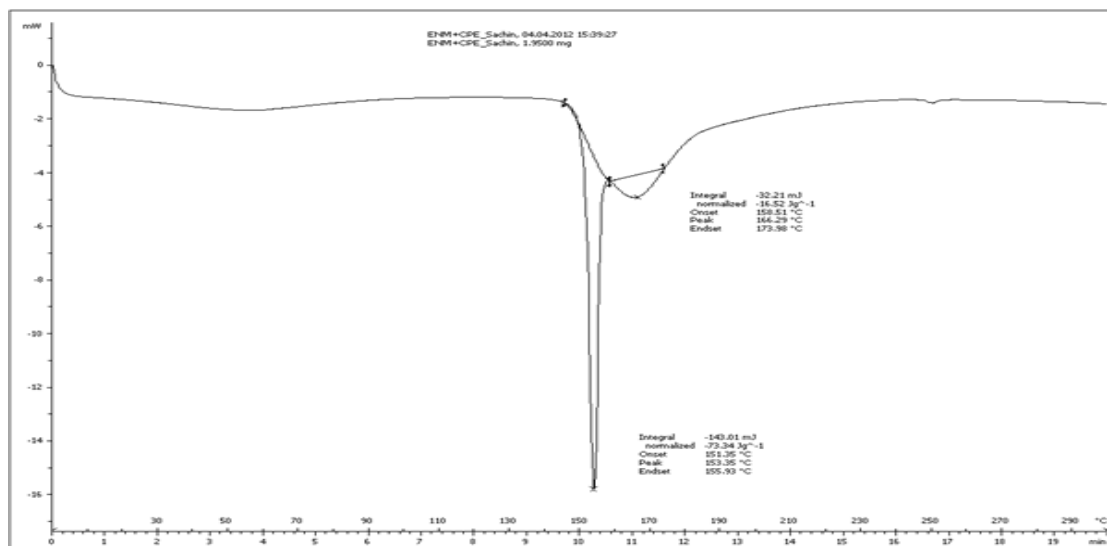


Fig.8: DSC thermogram of ENM with coprocessed superdisintegrating agent.

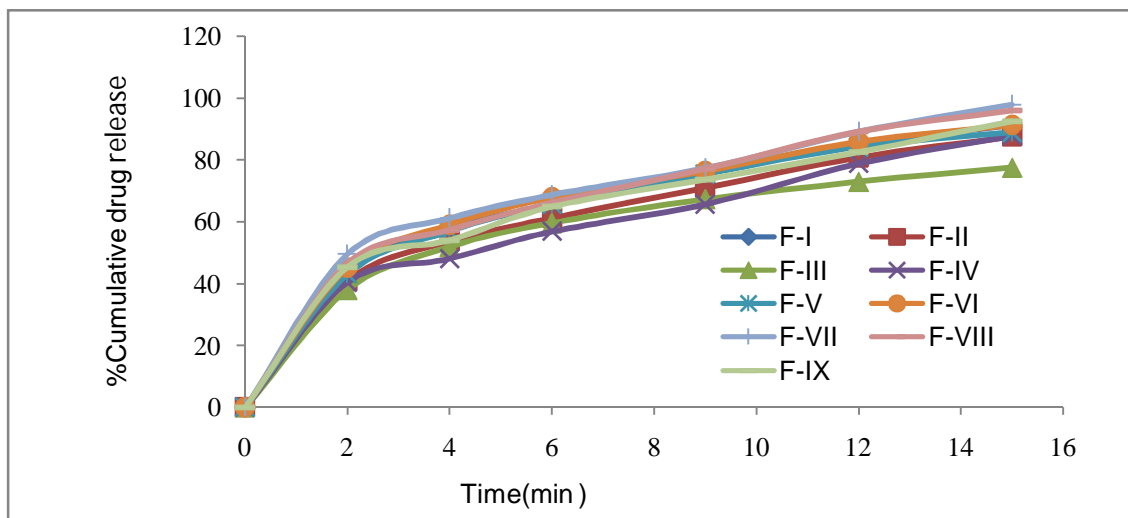


Fig. 9: Dissolution profile of different ENM oral dispersible tablet formulations.

Effect Of Disintegrating Agents

Three different super disintegrants namely sodium starch glycolate, Crospovidone, and a co-processed excipient made with crospovidone and sodium starch glycolate have been used in making tablets. The most important parameter that needs to be optimized in the development of ODTs is the disintegration time of tablets. From the data it is observed that the disintegration time and wetting time of the ENM tablets made with crospovidone is decreased with increase in the concentration of crospovidone. In case of tablets made with sodium starch glycolate the disintegration time and wetting time is increased with increase in the level of super disintegrant. In case of tablets made with co-processed super disintegrant, the disintegration time and wetting time is increased with increase in the level of co-processed super disintegrant. In respect to the drug release, with increase in the disintegrant amount there is an increase in the amount of drug release in case of crospovidone, whereas, in case of sodium starch glycolate and co-processed super disintegrant, there is an decrease in drug release with increase in disintegrant amount. Highest drug release of 97.84% was observed in formulation containing 5% w/w of co-processed excipient in 6.8 pH buffer. The percentage cumulative drug release for the formulations is depicted in fig 9.

Stability Studies

The stability studies revealed that there was no change in the physical appearance of the tablets indicating that the formulations were stable at all the conditions to which they were exposed. It was observed that there was slight reduction in the drug content of the tablets which were stored at $40^{\circ}\pm 2^{\circ}\text{C} / 75\pm 5\%$ RH at the end of 90 days and no significant change in drug content were observed for formulations stored at room temperature and at 5°C . *In-vitro* drug release studies for all the three formulations were carried out at the end of 90 days and no significant in drug release was observed from different formulations. Thus, we may conclude that, the drug does not undergo degradation on storage.

CONCLUSION

From the FT-IR spectroscopic study it was observed that there is no significant shift in the IR values. Hence it may be concluded that there is no chemical interaction between the drug and the polymers. All the preformulation parameters viz, Carr's index, Hausner's ratio and Angle of repose values are within the acceptable range and hence the tablets comply with requirement. Post-compression parameters such as hardness, friability, weight variation, thickness measurement, disintegration time and drug content determination have indicated that the values are within the acceptable range. Overall, the results suggest that ODTs of enalapril maleate containing co-processed superdisintegrating agent could be successfully formulated. Thus the present study has demonstrated the potential of ODTs of ENM for rapid absorption, leading to enhanced bioavailability, resulting in efficacious therapy and improved patient compliance.

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