



Characterization and Compatibility studies of Enalapril maleate by using various analytical techniques

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ABSTRACT

Objective: The study aimed to analyse and evaluate the physical; chemical properties of enalapril maleate by using various analytical methods.

Methods: Preliminarily, the active ingredient was admixed with Corn Starch; CMC Sodium; MCC, Crospovidone; PVP K-30; SSG; Magnesium Stearate; and DCP in a dose proportionate and carried the solubility studies; particle size (PSD); crystal characteristics (p-XRD); purity by thermogram (DSC); Assay and related substance by HPLC.

Results: The solubility of the active ingredient is 885.4mg/L in water. Further, the solubility is not affected significantly ($P \leq 0.05$) in the buffer solutions in a pH range of 1.2 to 6.8. The presence of Dv (50) 22.4 μm ; Dv (90) 95.9 μm particles in the solid powder form of the drug substance. The 2 θ values for diffraction peaks at 15.6199°, 20.4798°, 20.8780° conforms to form C of the drug substance. By the UV-Visible; FTIR; NMR and Mass spectroscopy studies characterized the drug. The endothermic peak at 152.04°C conforms to drug melting point. The % Assay content result has occurred in between 99.0%±0.8% to 99.5%±0.5 (n=3). The drug contains 0.02±0.005% to 0.08±0.004 of impurity A, 0.12±0.001 to 0.18±0.003 of impurities B, 0.09±0.003 to 0.16±0.006 C, 0.12±0.002 to 0.23±0.002 D with purity >99.95%, and all other unknown related substance has <0.01% of below detection Limit.

Conclusion: The compatibility of binary mixtures of drug and excipient were assessed, and concluded, the API does not have any incompatibility with listed excipients.

Keywords: Compatibility studies, DSC, NMR, FTIR, p-XRD, Enalapril maleate, solubility.

INTRODUCTION

All recent clinical guidelines still considered ACE inhibitors are a primary treatment for the organization of hypertension¹. Combining drug therapy at a lower dose is recommended to permit medications of different action mechanisms, complement each other, and mutually effectively lower the blood pressure than the highest doses²⁻³. The primary intention of release drug delivery is to ensure safety and improve drugs and patient compliance⁴⁻⁶. The environment for drug diffusion and absorption varies along with the gastrointestinal (G.I.) tract. Enalapril maleate, is a peptide molecule, and chemically described as (S)-1[N- [1-

(ethoxy carbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt⁷. The systemic absorption of Enalapril tablets is approximately 60%. Average peak Concentrations of drug and its active metabolite are reached in 1 hour and 3-4 hours, respectively⁸. Enalaprilat inhibits the conversion of angiotensin I to angiotensin II. It prevents the potent vasoconstrictive actions of angiotensin II. It has been decreased angiotensin-II-induced aldosterone secretion by the adrenal cortex. Which leads to an increase in sodium excretion and subsequently increases water outflow⁹. It contains one molecule of maleic acid for each molecule of enalapril. Enalapril's ethyl ester group hydrolyzed to afford the corresponding carboxylic acid, Enalaprilat, an angiotensin-converting enzyme inhibitor¹⁰. Enalapril is thus

a prodrug for Enalaprilat. Its maleate is used to treat hypertension and heart failure, reduce proteinuria and renal disease in patients with nephropathies, and prevent stroke, myocardial infarction, and cardiac death in high-risk patients¹¹. It has a role as a peptidyl-dipeptidase and inhibitor, an antihypertensive agent, and a prodrug¹²⁻¹⁵. The Enalapril maleate tablets are listed in the local index of registered pharmaceutical products¹⁶. A new formulation of Enalapril tablet has been developed by a direct compression method. All formulation tablets with 2.5-20mg strength were selected¹⁷⁻¹⁹. The absorption is not influenced by the presence of food in the gastrointestinal tract. The enalapril is

hydrolysed to Enalaprilatand (potent angiotensin-converting enzyme inhibitor)²⁰. Enalaprilat's Peak serum concentration occurs three to four hours after an oral Enalapril maleate dose²¹. It degrades to two major degradants of Enalaprilat and diketopiperazine derivative (DKP). Most of the reported analytical methods for the quantitative determination of enalapril in pharmaceutical samples, including the official method, are by liquid chromatography with U.V. detection using a high column temperature; other techniques include LC-MS analysis in biological samples²². The objectives of this research were to study the compatibility of drug and Excipients to be used for tablet formations.(Figure 1)

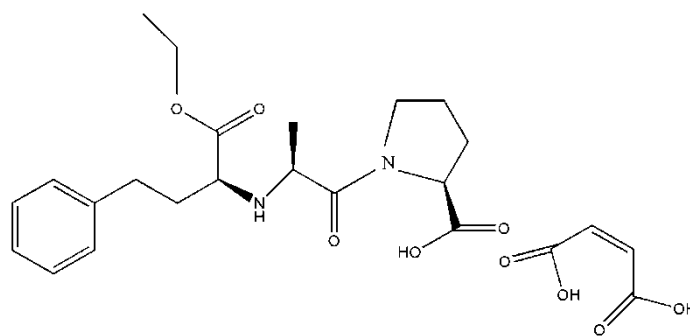


Figure 1: Typical Chemical structure of Enalapril maleate

Materials

Enalapril maleate (Sri Krishna Pharmaceuticals Ltd, Hyderabad, India); S.A. Pharma chem Pvt Ltd purchased Corn starch, Croscarmellose Sodium, Microcrystalline cellulose, Crospovidone. Polyvinylpyrrolidone K-30; Sodium starch glycolate; Magnesium Stearate, and Dibasic calcium phosphate (S.M. Pharmaceuticals SdnBhd, Malaysia). Formic acid 99%, hydrochloric acid 37%, sodium hydroxide 99%, acquired from Sigma Aldrich, Mumbai. Potassium dihydrogen phosphate, dibasic potassium phosphate, sodium dihydrogen phosphate, sodium lauryl sulphate (S.d.fine chemicals, Hyderabad). The HPLC Grade solvents methanol 99.9% and Acetonitrile 99.9% procured from Merck, Mumbai. The reference materials Enalapril maleate BPCRS, Enalapril (1R)-Isomer (impurity A), (2S)-2-[[[(1S)-1-(ethoxy carbonyl)-3-phenylpropyl] amino] propanoic acid (impurity B), Enalaprilat Dihydrate (impurity C), Enalapril Diketopiperazine (impurity D) (pharm affiliates, India).

Equipment / Instruments

The sophisticated instruments HPLC; Model: 2689; Make: Waters; UPLC; Model: H-Class; Make: Waters; UV – Visible Spectrophotometer; Model: UV 2600; Make: Shimadzu; Semi Micro Balance; Model: GR202; Make: AND Company Limited; Analytical Balance; Model: AL 204; Make: Mettler Toledo; Stability chamber; Model: TH 400 S/G; Make: Thermo lab; Differential Scanning Calorimeter; Model: Q20; Make: T.A. Instruments; Particle size analyzer; Model: Mastersizer 3000; Make: Malvern Panalytical Ltd; FTIR spectrometer; Model: Alpha; Make: Bruker; Nuclear Magnetic Resonance Spectrometer 500MHz; Model: ECZ400S/L1; Make: JEOL; X-ray diffractometer (p-XRD); Model: AERIS; Make: Malvern Panalytical Ltd; pH meter; Model: 827 pH Lab; Make:

Metrohm; Magnetic Stirrer; Model: MS7-H550-S; Make: DLab; LC-MS; Model: SQD-2; Make: Waters; UPLC-MS/MS; Model: Xevo TQ-S; Make: Waters; BurrelScientiphic wrist action laboratory shaker; Model: 75; Make: Fisher; Halogen Moisture Analyzer Model: HS153; Make: Mettler Toledo.

Methods

The Physical-chemical property of a drug candidate is an aqueous solubility for therapeutic effectiveness in the P.H. range of 1 to 8. The solubility studies conducted using U.V.-Visible Spectrophotometer; Shimadzu; U.V. 1900. The solubility of the drug had determined in distilled water; 0.1N hydrochloric acid pH - 1.2; Phosphate buffer pH 6.8 with 1% w/v sodium lauryl sulfate; acetate buffer pH 3.0 and 4.0, and phosphate buffers pH 5.0, and 6.8 phosphate buffer. The pH of all media had been verified by using pH meter; 827 pH Lab; Metrohm. The measured volume of each solvent poured into screw-capped glass vials, followed by the excess drug's addition. The glass vials were sealed and positioned on a mechanical shaker at 37 °C for 24 hours. After that, aliquots were withdrawn, centrifuged, and filtered. The diluted filtrates and absorbance recorded using U.V. Visible Spectrophotometer²³⁻²⁵. The study has been carried out by using particle size analyzer; Master sizer 3000; Malvern. The laser diffraction technique was employed to measure the powder particle size distribution in a dry dispersion apparatus²⁶. The p-XRD diffraction studies conducted on an X-ray diffractometer; Malvern Panalytical; AERIS. The goniometer uses to maintain the angle and rotate the sample²⁷. The p- XRD patterns 40 Kv of Voltage; 15 mA of Current; 2° to 50° of 2θ Angular parameter at a step size of 0.022° and the Length of 2θ is 3.02; 36seconds of Scan time; 10mm of Specimen length at 25°C temperature; 1.5418Å of CuKαα radiation with 1.392 K-β; 0.5 K-α2/K-α1 value²⁸. The drug and binary mixtures study had conducted on the

FTIR spectrometer (Make: Bruker; Model: Alpha) in a range of 4000 and 650 cm^{-1} using Attenuated total reflectance (ATR) with an average scan speed of 16 at a resolution 4cm^{-1} ²⁹. The Proton (^1H) and Carbon (^{13}C) Nuclear magnetic resonance have run by using a JEOL NMR instrument equipped with 500 MHz using tetramethylsilane (TMS) as an internal standard. About 10mg to 30mg of the sample

used for Proton (^1H NMR) resonance and Carbon resonance (^{13}C NMR). The sample preparation was taken into a clean nuclear resonance (NMR) tube. The deuterated dimethylsulfoxide (DMSO- d_6) is used as a solvent to dissolve the test substance. The spectra had scanned using the instrument parameters, as given in Table 1³⁰.

Table 1: Nuclear Magnetic Resonance (NMR) Spectroscopy Conditions

^1H - NMR instrument Parameters	^{13}C - NMR instrument Parameters
X-Domain Proton	X-Domain Carbon-13
X-Points 16384	X-Points 32768
X-Offset 7ppm	X-Offset 100 ppm
X-Sweep 18ppm	X-Sweep 250 ppm
X-Pre scans 1	X-Pre scans 4
Solvent DMSO-D6	Solvent DMSO-D6
BF or S. Exp 0.30 Hz	B.F. or S. Exp 2.0 Hz
Relaxation delay 2 sec	Relaxation delay 2 sec
Pulse 45 Degree	Pulse 30 Degree
Scans 16	

Mass analysis and detection for the pure drug were carried out using Waters LC-MS system; SQD-2; Waters equipped with electron spray ionization operated in combined mode. The mobile phase has prepared using ammonium acetate (5mM) in water and acetonitrile in a ratio of 20:80 v/v. The Chromatographic run has carried with a flow rate of 0.2ml/min. Run time was 3min. The optimized source conditions are 1000 L/hr of Desolvation gas flow; 25L/hr of cone gas flow; 3.5 kV of capillary voltages; 50V of cone voltage and 350°C of Desolvation temperature [28]. The thermal property of pure drug has been analyzing using differential scanning calorimeter Q-20 V24.11 Build 124; T.A. instruments. 2.0mg of the sample was weighed and placed on a thematically sealed pan; an empty pan has been using for blank. Then samples have heated by maintaining a temperature range of 20 to 350°C at a ramped temperature

of 10 °C / min, using nitrogen at a flow rate of 50 mL/min for maintaining the inert atmosphere³¹⁻³².

The Assay and impurities related to drug substances have been quantifying using UPLC H-Class equipped with a Photodiode array detector (PDA, Make: Waters; Model: Acquity). BEH C18; 1.7 μm ; 2.1mm I.D. x 50mm Length column previously stabilized at 40°C with 0.4mL per minute flow rate. The mobile phase has composed with 0.1%v/v formic acid in water as a buffer; Methanol and acetonitrile in a ratio of 10:90 v/v from the gradient table 2. The standard and sample solutions have prepared with a concentration of 10 $\mu\text{g}/\text{mL}$ of Enalapril maleate in methanol, followed by dilutions with an aqueous buffer containing 0.1% v/v a formic acid. The chromatography has carried with 1.0 μL injection volume; was measured at 254nm³³.(Table 2)

Table 2: Typical gradient elution program for related substance quantification

Time (min)	Flow (mL/min)	%A	%B	Curve
0	0.4	98	2	-
0.5	0.4	98	2	6
7	0.4	60	40	6
8	0.4	98	2	11
10	0.4	98	2	11

The compatibility studies used to evaluate the impact of excipients on physical and chemical stability, dissolution, and, ultimately, the formulation's bioavailability. A binary mixture of pure drug and individual excipients have been performing to assess excipients compatibility Enalapril maleate and has stored in the Stability chamber; TH 400 S/G; Thermo lab at 40°C + 2 °C / 75% R.H. for one month³⁴.

RESULTS AND DISCUSSION

Solubility studies for saturated solutions have carried out over the pH range of 1.2-6.8. The data of the solubility studies have shown in table 3. The solubility in the water at 37°C is 885.4mg/L. The drug shows significantly high

solubility in pH 6.8 buffer solution with 1% w/w SLS 911.2 \pm 0.12mg/L, 0.1N Sodium hydroxide 922.1 \pm 0.04mg/L, Water 882.9 \pm 0.19mg/L, 0.1N HCl (pH 1.2) 841.3 \pm 0.12mg/L from table 5. The drug substance has limited solubility >800mg/L in all pH range 3.0-6.8. The representing solubility graph has shown in Fig. 2. The range of single dose 5-40mg of drug substance from prescriber's information and the Dose / Solvent ratio has \leq 250mL³⁵. According to drug substance literature reveals, the salt form of Enalapril has poor solubility in water³⁶⁻³⁷. The literature provides the solubility profile at 37°C in pH range 1.2-6. In this established work, the solubility studies carried for 24hrs at different periodic intervals in pH range of 1.2-12 with maximum saturation in the dissolution media to set the

dissolution of drug product in the scope of tablet formulation. (Table 3)

Table 3: Solubility data of Enalapril maleate

Sr. No	Name of Solvent / Media	Mean solubility (mg/L) ± SEM
1	Water	882.9±0.19
2	0.1N HCl, pH 1.2	841.3±0.12
3	Phosphate buffer, pH 6.8 + 1% SLS	911.2±0.12
3	Acetate buffer, pH 3.0	585.8±0.06
4	Acetate buffer, pH 4.0	572.2±0.04
5	Phosphate buffer, pH 5.0	581.2±0.16
6	Phosphate buffer, pH 6.8	780.8±0.05
7	0.1N Sodium hydroxide	922.1±0.04

SEM=Standard Error Mean (n=3)

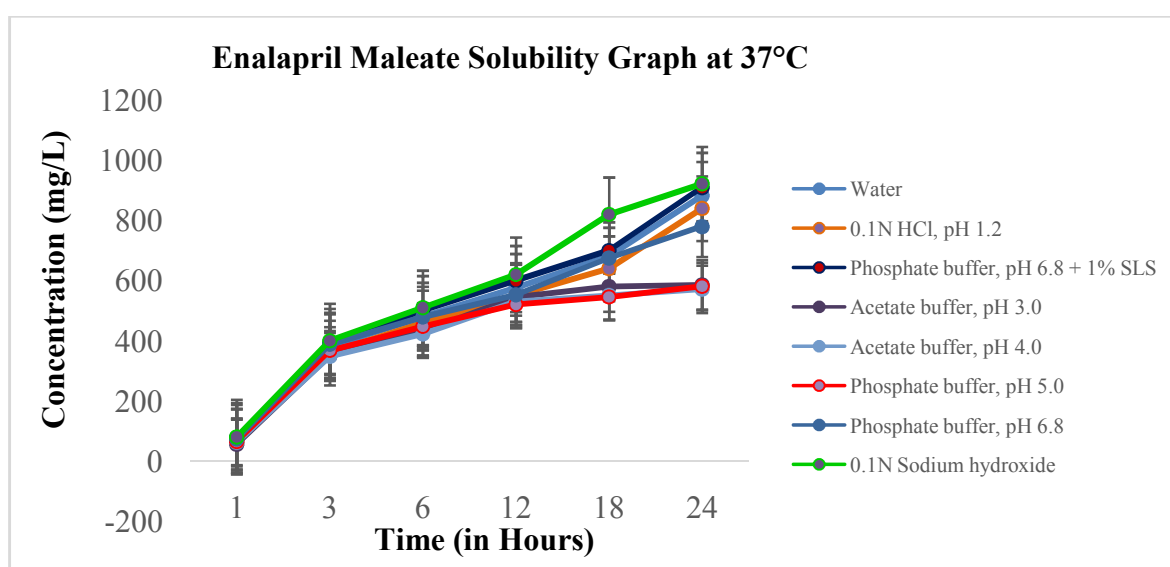


Fig. 2: Typical Solubility graph for Enalapril maleate

Particle size distribution study

The study has carried out by using on Master sizer 3000 particle size analyzer. The Enalapril maleate PSD histogram represented in Figure 3 conforms, the presence of D_v (10) 4.01 μm; D_v (50) 22.4 μm; D_v (90) 95.9 μm and D_v (95) 137 μm particles in the crystalline material by dry dispersion

technique. The current regulatory guideline ICH (Q6A) provide guidance particle size has critical attribute of drug from formulation development of solid oral dosage forms³⁸. The literature reveals the extremely limited research works has been conducted on microencapsulation particles³⁹. (Figure 3)

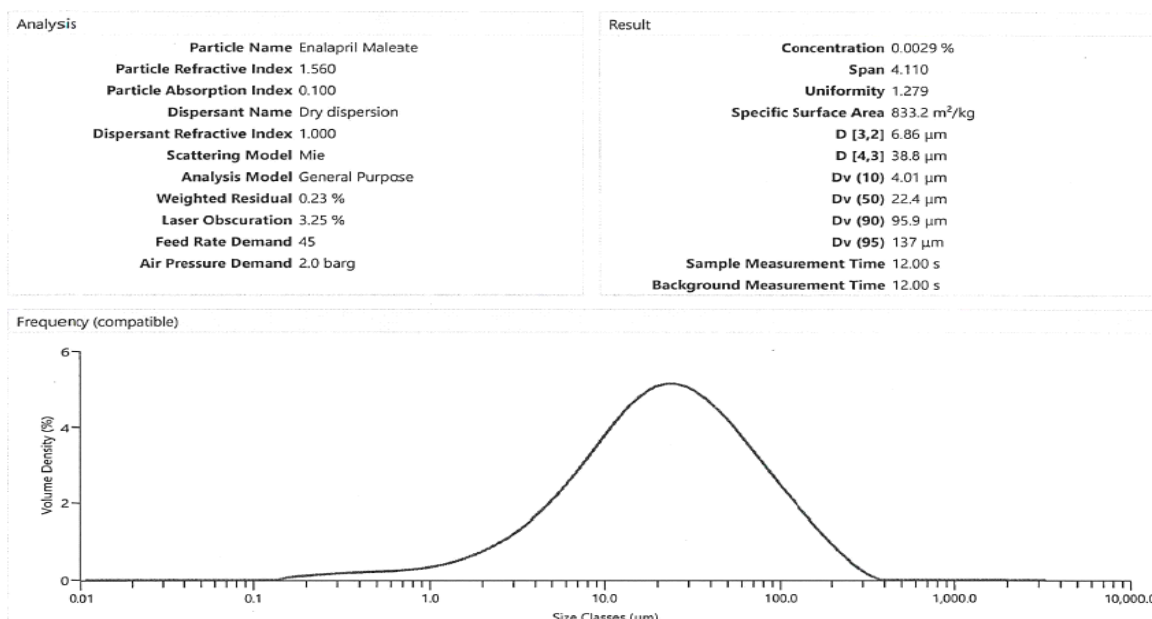


Fig. 3: Typical PSD Histogram of Enalapril maleate

X-ray diffraction studies

The main characteristics of diffraction line profiles are 2θ position, peak height, peak area, and shape (characterized by, e.g., peak width, or asymmetry, analytical function, and empirical representation). From figure 4, the diffraction line

profiles 2θ values are at 5.1848°, 10.3887°, 15.6199°, 20.4798°, 20.8780° conforms to form C solid phase. Several literatures on crystal structure of Enalapril maleate reveals to the polymorphic form II⁴⁰. From the present research work has conformed to the polymorphic form C and this form is a novelty from the current research. (Figure 4)

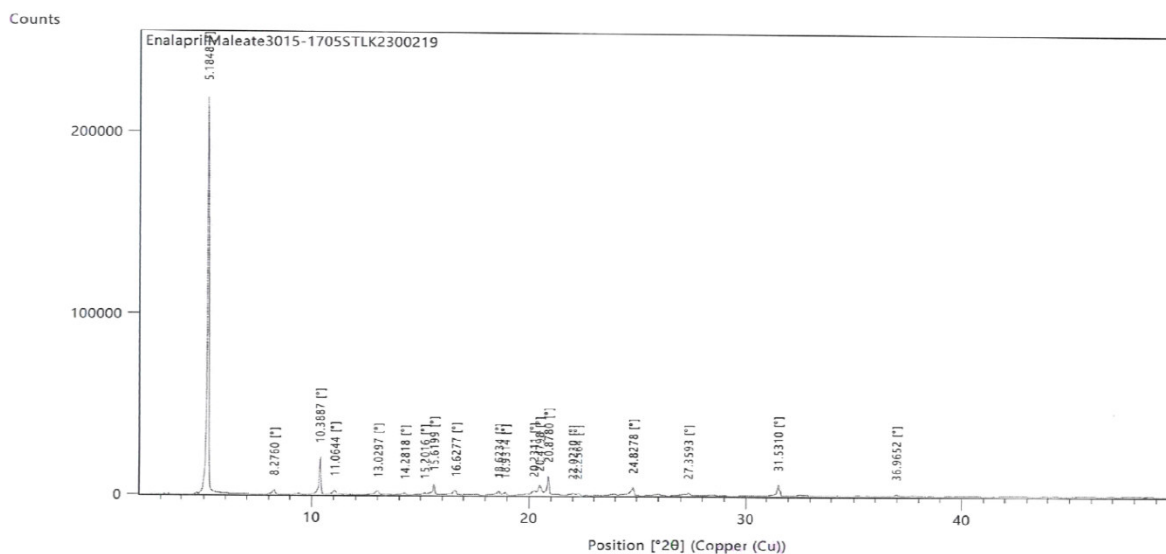


Fig. 4: Typical diffract graph of Enalapril maleate

Characterization studies

The chemical Portrayal of Enalapril maleate has been revealed by many literatures by various analytical techniques. The U.V. spectrum of Enalapril maleate represented in Figure 5 was scanned using the Shimadzu

Model: UV-2600 instrument in a range of 200nm to 400nm. The standard solution of Enalapril Maleate 20ppm in methanol exhibits the characteristic maximum absorbance at 203nm. (Figure 5)

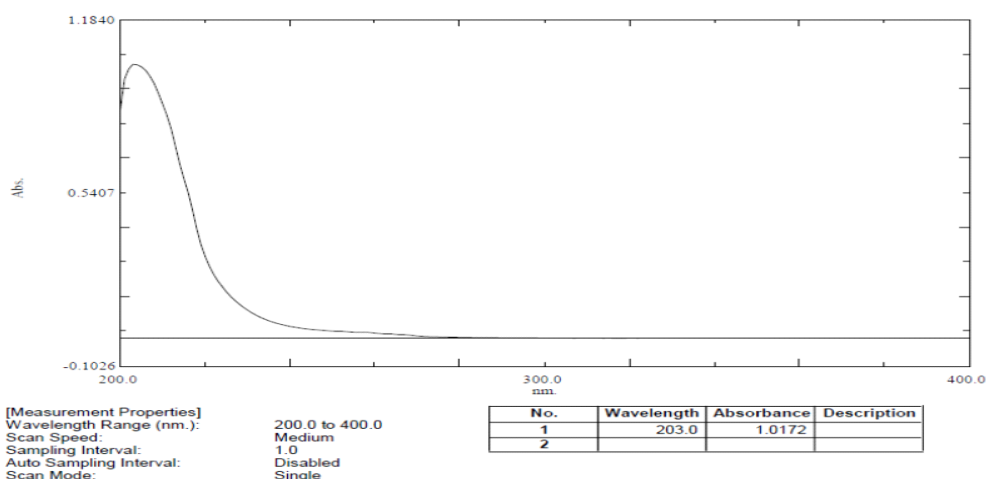


Fig. 5: Typical U.V. Spectrum of Enalapril maleate

The FT-IR spectrum of the drug from Figure 6 discloses the characteristic peaks, which comprises of absorption bands at 1751cm⁻¹ due to C=O stretching (ester), 1647cm⁻¹ due to N-H bending (secondary amine), at 1452cm⁻¹ due to C-H bending (methyl), and 1378 cm⁻¹ due to C-H bending

(methyl, and methylene) vibrations. The absorption peaks at 3211cm⁻¹ due to O-H stretching (carboxylic acid), 2981 cm⁻¹ due to CH stretching, 1299 cm⁻¹, 1268 cm⁻¹ due to C-N stretching (L-proline) vibrations. (Figure 6)

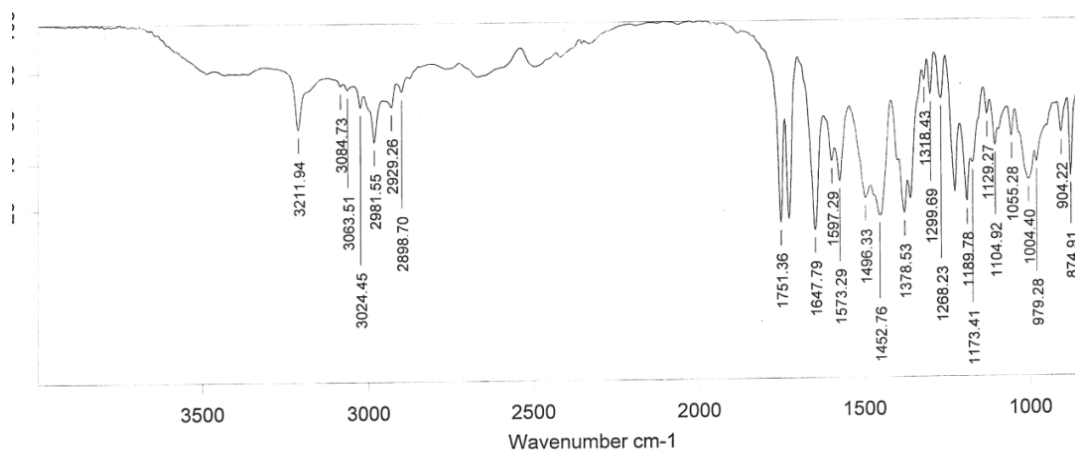


Fig. 6: Typical FTIR Spectrum of Enalapril maleate

Chemical shift values are reported on the δ scale in ppm relative to TMS (δ 0.00) as an internal standard. The ¹H NMR spectrum from Fig. 7 shows the multiplet at 7.31ppm was assigned to proton at Ortho and quartet at 7.21(J=6.9Hz) attributed to protons at Meta and Para indicating the presence of the aromatic ring. A singlet at 10.00 ppm for the hydroxyl protons of a carboxyl group at C-2. The quartet at 4.30(J=4.6Hz) has ascribed to the proton of C-2. Assigned multiplet at 1.89ppm and one doublet at 2.01ppm has been assigning to methylene protons of C-3 and C-4, and C-5 of L-proline. The spectrum shows multiplet at 4.18ppm and doublet of a doublet at 1.35ppm (J₁ = 25.5Hz, J₂ = 6.2Hz) has been assigned to methylene methyl protons of the ethoxy carbonyl group. The spectrum also reveals two multiplets at 2.19 and 2.57ppm each of one proton intensity, assigned to methylene protons of C-2, two multiplets at 2.72 and 3.36 ppm each of one proton integrity, assigned to methylene protons of C-3, and multiplet at 3.59

ppm has attributed to one proton at C-1 of propyl group. Moreover, the ¹H NMR spectrum displays multiplet at 3.48ppm and quartet at 1.24ppm (J₁ = 7.2Hz) corresponding to alanine protons. The olefinic protons resonated as a singlet at 6.09ppm, indicating >C=C< of butenedioate in the structure. The ¹³C NMR spectrum from Fig. 8 indicated 18 signals. Three signals at 30.3, 30.4, and 61.8 ppm are corresponding to C-3', C-2' and C-1' of propyl. Three signals at 126.1, 128.3, and 128.4ppm h attributed to C-4 (Para), C-2, C-6 (Ortho) as and C-3, C-5 (Meta) of phenyl. Two signals at 16.5 and 61.8 ppm have been acquiring to C-2 and C-3 of ethoxy. Three signals at 21.7, 57.6 and 172.7 ppm, are represented to C-3, C-2, and C-1 of alanyl; four signals at 24.6, 28.5, 46.4, and 174.3ppm has assigned to C-4, C-3, C-5, and C-1 of proline, two signals at 134.6 and 167.1 ppm each signal corresponding to C-2, C-3, and C-1, C-4 of butenedioate from the compound. Finally, ¹H/¹³C-NMR spectra confirm the structure. (Figure 7, 8)

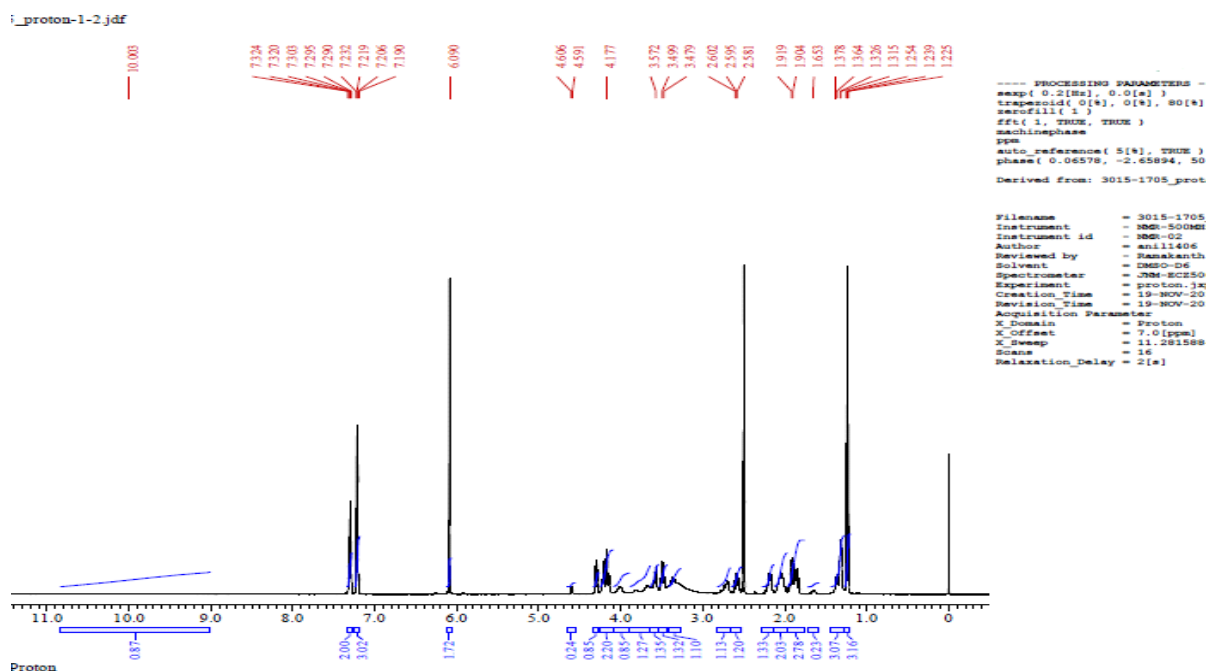


Fig. 7: ¹H NMR Spectrum of Enalapril maleate

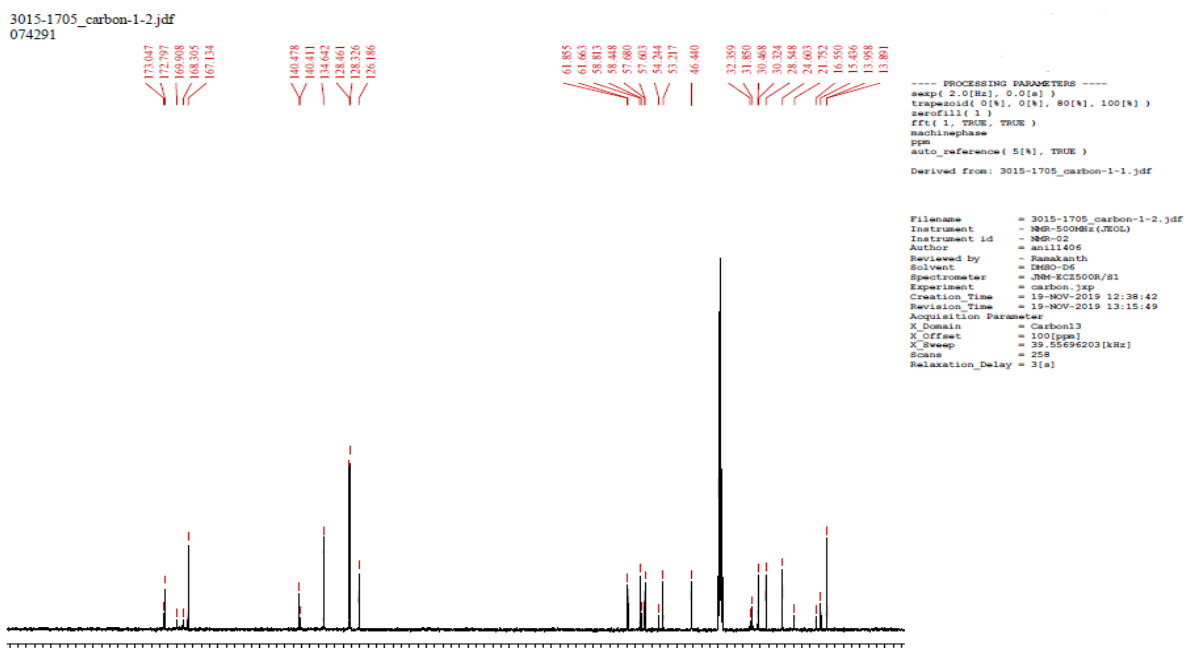


Fig. 8: Typical ¹³C NMR Spectrum of Enalapril maleate

The molecular ion provides the molecular mass of the analyte. The molecular ion masses for the Enalapril maleate has been predicting in E.S. combined mode. Two molecular ion peaks (M+1) +and (M-1)-were observed at m/z 377.3

and 375.3, respectively, in positive and negative ionization mode. Based on these molecular ion masses, we confirmed that the molecular weight is 376.4, as in the spectrum shown in Fig. 9.

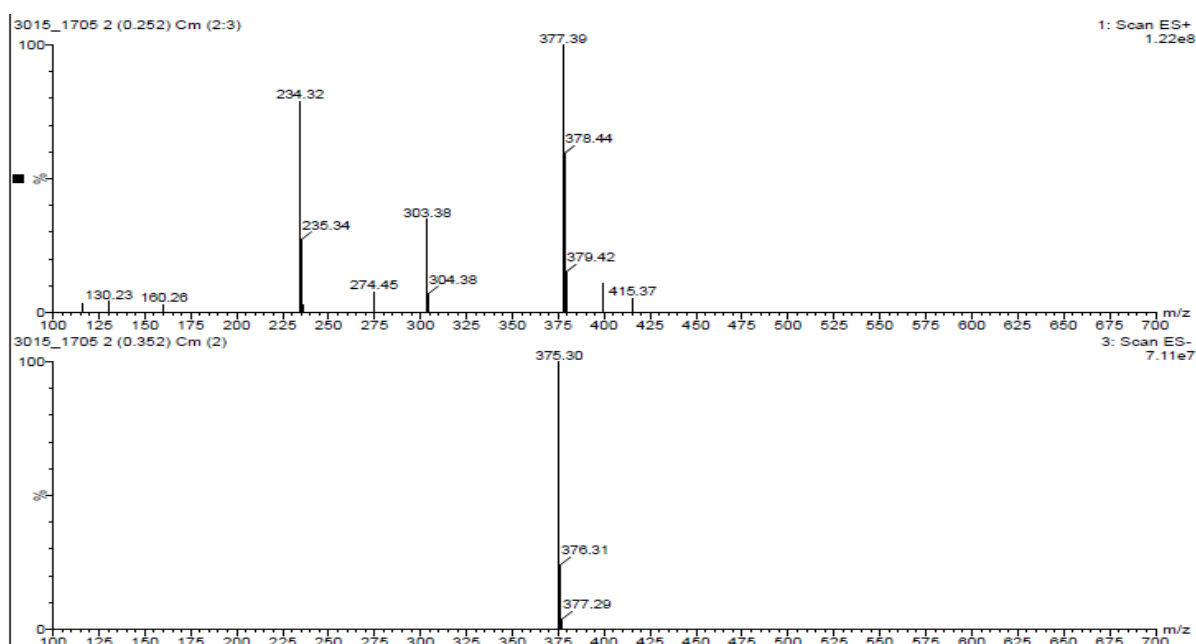


Fig. 9: Typical Mass spectrum of enalapril

The differential scanning calorimeter (DSC) is a fundamental tool in thermal analysis. Melting is an endothermic process, requiring the absorption of heat. The temperature remains constant during melting despite continued heating from 20 to 350°C with a rate of 10°C/min.

The representing figure 10, the peak has observed at 152.04°C, and the onset value is 150.26°C represents the characteristic endothermic peak of Enalapril maleate and the energy required for melting is 118.8J/g. (Figure 10)

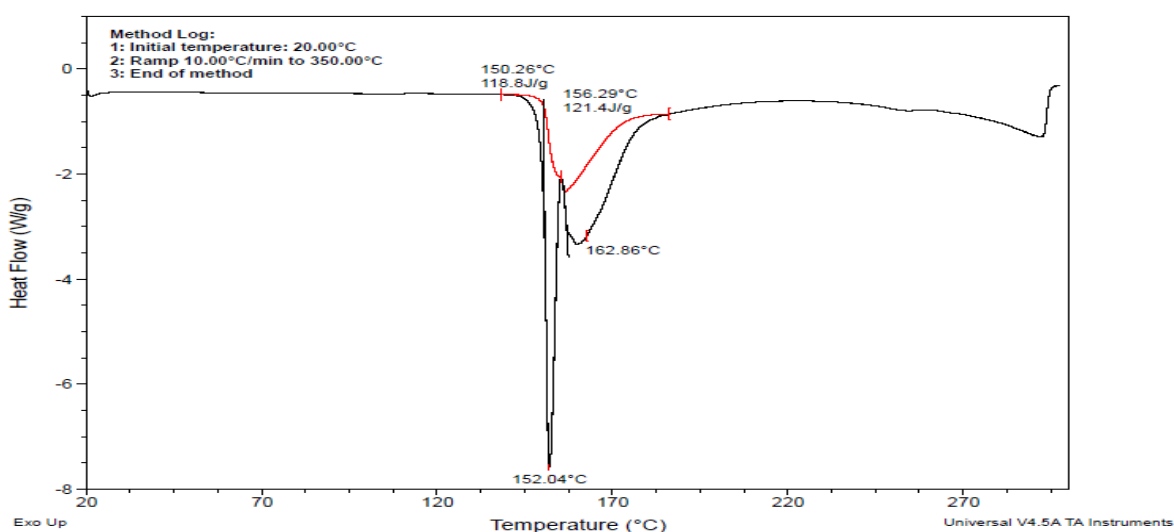


Fig. 10: Typical DSC graph of Enalapril maleate

Assay Content and Related Substances

The purity of enalapril maleate by UPLC is 99.5%. The % of impurity A is 0.02%, impurity B is 0.11%, impurity C is 0.09%, and impurity D is 0.12%, and other impurities are <0.01% respectively by UPLC-MS/MS, and results have shown in Table 8.

Drug-Excipients Compatibility studies

The drug and binary mixture of drug and selected excipients were Corn starch, MCC, Crospovidone, PVP K-30, Sodium

starch glycolate, Magnesium stearate, Croscarmellose sodium, and dibasic calcium phosphate. The FT-IR spectra of the drug and excipients have overlaid to identify probable chemical interaction between them. The Corn starch produces broadband around at 3300cm⁻¹ is due to the stretching vibration of the O.H. group; the stretching vibration at 1082cm⁻¹ have attributed to the C-O bond of the C-O-C group in the anhydrous glucose ring of the starch structure. In magnesium stearate, the spectrum shows a robust stretching vibration of CH₂-CH₃ in the region of 2917cm⁻¹ to 2850cm⁻¹, asymmetric stretching vibrations at 1577cm⁻¹, 1466cm⁻¹ is corresponding to COO- group. In the I.R. spectrum of microcrystalline cellulose, robust

broadband at 3383cm^{-1} and band at 1635cm^{-1} are due to stretching. Bending vibrations of a surface hydroxyl group, asymmetric stretching vibration of C-H in the paranooid ring have appeared at 2900cm^{-1} . The C-H bending vibration at 1338cm^{-1} and the broad absorption peak at 1059cm^{-1} belongs to C-O stretching. The C-O-C (glycoside linkage) of glucose cellulose. The FT-IR spectrum of PVP K30 and Crospovidone showed similar characteristic absorption bands as follows. Absorption peaks at 1654cm^{-1} and 1645cm^{-1} are due to stretching vibration of the carbonyl group and a very broadband at 3426cm^{-1} , and 3443cm^{-1} is due to

O.H. stretching vibrations of absorbed water indicating hygroscopic nature. The Characteristic peaks at 2958cm^{-1} and 2957cm^{-1} are attributable to C-H stretching, and $1,424\text{cm}^{-1}$ ascribable to the N-H band. Sodium starch glycollate, Croscarmellose sodium have been showing identical characteristic bands at C=O stretching at 1598 and 1634cm^{-1} and O-H stretching vibration at 3441 and 3443cm^{-1} . Finally, the I.R. spectra of excipients do not cause significant intermolecular interactions at the Drug substance's absorption peaks from Fig. 11.

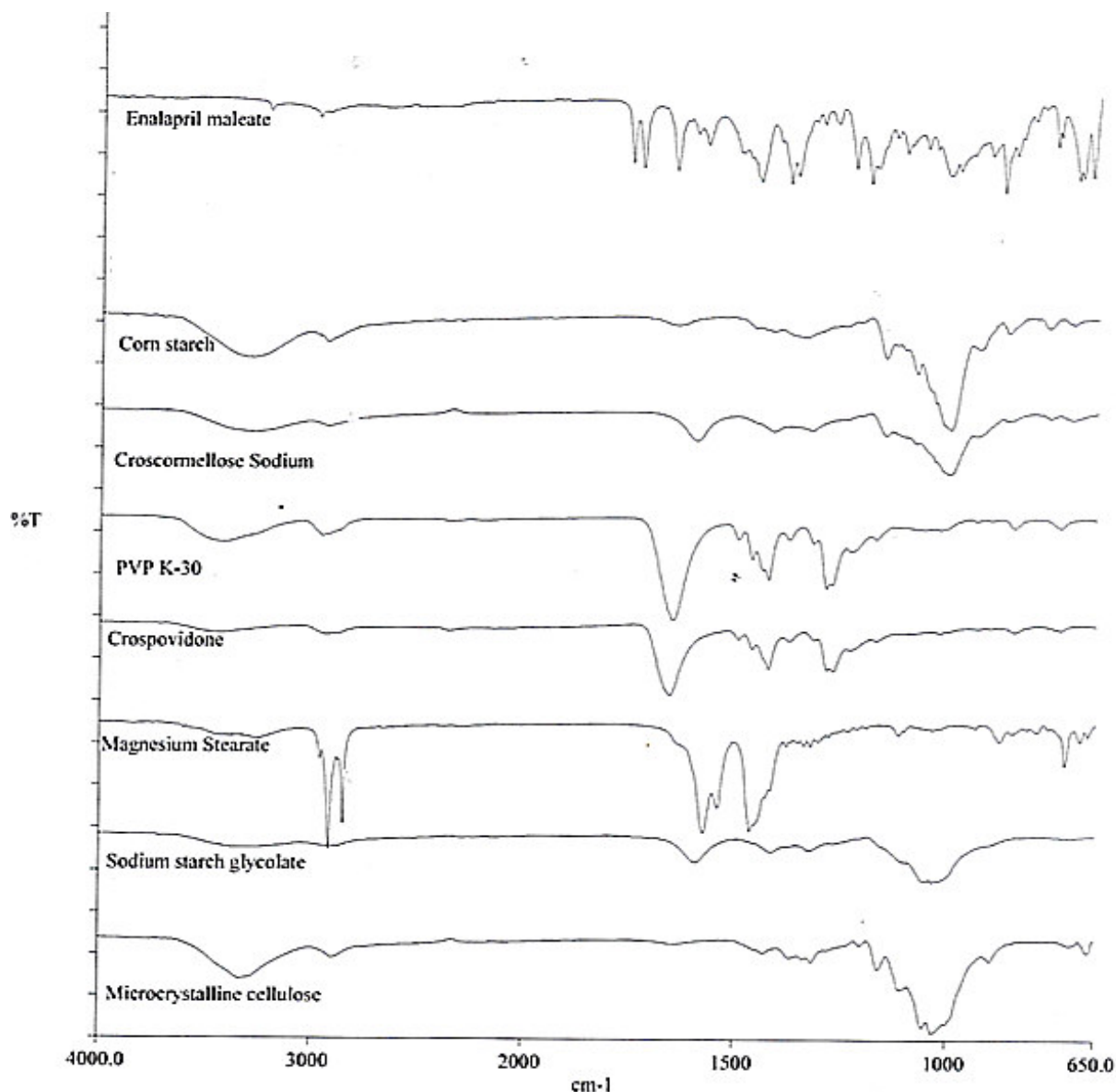


Fig.11: Overlay FT-IR spectra for Enalapril Maleate, and Excipients

DSC thermogram of drug substance has been showing a distinct endothermic peak at 152.04°C . The correspondent endothermic peak appeared in the thermogram of immediate

release granules. The DSC graph of drug and immediate-release layer granules has shown in Fig. 12.

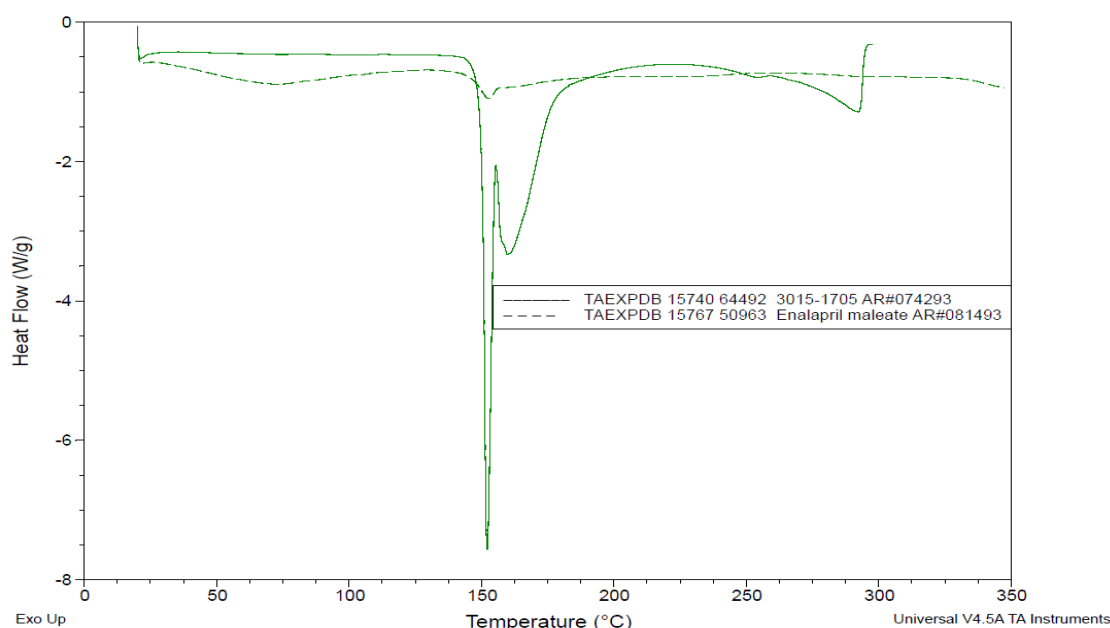


Fig. 12: DSC graph for Enalapril Maleate and Proposed Bilayer tablets immediate release layer granules

The Assay of Enalapril Maleate is greater than 99%, and the relative standard deviation is <1.0% from the initial results to 30th-day results. The calculated confidence interval at 95% level from descriptive statistics is 0.3, represents no significant change in the assay results from the initial. The content of related impurities of Enalapril (1R)-Isomer (impurity A) was varies from 0.02% to 0.08%; (2S)-2-[[[(1S)-1-(ethoxy carbonyl)-3-phenylpropyl] amino]

propanoic Acid (impurity B) was varies from 0.11% to 0.23%; Enalaprilat Dihydrate (impurity C) was varies from 0.09% to 0.26%; Enalapril Diketopiperazine (impurity D) was varies from 0.12% to 0.23% of entire study intervals for API and Excipients binary mixture. The compatibility results of binary mixtures of API and individual excipient has given in table 4-5.

Table 4: % Assay results from Compatibility mixture of API and Excipients

Mixture Name	% Assay ± SEM @ 40°C/75% R.H.			
	Initial	7th Day	15th Day	30th Day
Enalapril maleate (API)	99.5±0.5	99.4±0.4	99.2±0.7	99.1±1.2
API+ Corn starch	99.2±1.0	99.1±0.5	99.0±0.8	99.3±0.7
API+ Avicel PH 101	99.4±0.9	99.3±1.1	99.6±0.7	99.5±0.8
API+ Crospovidone	99.6±0.9	99.4±0.1	99.2±0.3	99.0±0.3
API+ PVP K-30	99.5±0.7	99.4±0.9	99.3±1.2	99.1±1.1
API+ Sodium starch glycolate	99.2±0.3	99.3±0.3	99.1±0.7	99.0±0.8
API+ Mg. stearate	99.6±0.4	99.2±0.6	99.1±1.1	99.0±1.2
API+ Croscormellose sodium	99.4±1.1	99.3±1.2	99.2±1.1	99.1±0.5
API+ Dibasic calcium phosphate	99.6±0.6	99.4±1.1	99.3±1.1	99.1±0.9

SEM=Standard Error Mean (n=3)

Table 5: % Impurities results from Compatibility mixture of API and Excipients

Mixture Name	Time period	% Impurities ± SEM @ 40°C/75%RH				Unknown impurity (%)
		A (%)	B (%)	C (%)	D (%)	
Enalapril maleate (API)	Initial	0.02±0.005	0.12±0.001	0.09±0.003	0.12±0.002	<0.01%
	7 th Day	0.04±0.006	0.14±0.001	0.12±0.003	0.14±0.004	<0.01%
	15 th Day	0.08±0.004	0.18±0.003	0.14±0.003	0.21±0.005	<0.01%
	30 th Day	0.06±0.002	0.22±0.002	0.16±0.006	0.23±0.002	<0.01%
API + Corn starch	Initial	0.04±0.002	0.12±0.006	0.11±0.002	0.13±0.001	<0.01%

	7 th Day	0.05±0.003	0.15±0.008	0.14±0.001	0.19±0.007	<0.01%
	15 th Day	0.06±0.001	0.18±0.003	0.16±0.002	0.22±0.002	<0.01%
	30 th Day	0.07±0.004	0.23±0.001	0.22±0.003	0.24±0.004	<0.01%
API + Avicel PH 101	Initial	0.05±0.004	0.08±0.001	0.07±0.002	0.05±0.004	<0.01%
	7 th Day	0.07±0.007	0.14±0.002	0.12±0.003	0.09±0.005	<0.01%
	15 th Day	0.06±0.005	0.16±0.002	0.18±0.001	0.17±0.002	<0.01%
	30 th Day	0.06±0.003	0.21±0.004	0.21±0.003	0.22±0.002	<0.01%
API + Crospovidone	Initial	0.03±0.003	0.11±0.003	0.08±0.002	0.07±0.005	<0.01%
	7 th Day	0.05±0.004	0.14±0.006	0.16±0.002	0.11±0.004	<0.01%
	15 th Day	0.08±0.003	0.19±0.007	0.19±0.001	0.16±0.006	<0.01%
	30 th Day	0.07±0.003	0.24±0.007	0.23±0.003	0.21±0.007	<0.01%
API +PVP K-30	Initial	0.03±0.001	0.12±0.003	0.07±0.005	0.09±0.008	<0.01%
	7 th Day	0.05±0.003	0.15±0.003	0.17±0.004	0.15±0.006	<0.01%
	15 th Day	0.06±0.003	0.22±0.001	0.22±0.004	0.18±0.006	<0.01%
	30 th Day	0.07±0.005	0.26±0.003	0.27±0.001	0.23±0.006	<0.01%
API + Sodium starch glycolate	Initial	0.05±0.006	0.08±0.009	0.06±0.005	0.07±0.007	<0.01%
	7 th Day	0.07±0.007	0.13±0.003	0.14±0.002	0.13±0.005	<0.01%
	15 th Day	0.08±0.004	0.16±0.003	0.19±0.001	0.16±0.003	<0.01%
	30 th Day	0.04±0.003	0.22±0.003	0.24±0.004	0.24±0.001	<0.01%
API +Mg. stearate	Initial	0.06±0.005	0.11±0.004	0.12±0.003	0.09±0.004	<0.01%
	7 th Day	0.07±0.005	0.15±0.004	0.16±0.003	0.14±0.003	<0.01%
	15 th Day	0.08±0.002	0.18±0.006	0.21±0.002	0.19±0.005	<0.01%
	30 th Day	0.07±0.001	0.23±0.005	0.23±0.002	0.26±0.003	<0.01%
API + Croscormellose sodium	Initial	0.03±0.003	0.13±0.006	0.11±0.003	0.12±0.005	<0.01%
	7 th Day	0.04±0.003	0.14±0.006	0.13±0.004	0.16±0.005	<0.01%
	15 th Day	0.06±0.009	0.16±0.008	0.22±0.004	0.18±0.004	<0.01%
	30 th Day	0.07±0.003	0.21±0.007	0.26±0.004	0.24±0.004	<0.01%
API +Dibasic calcium phosphate	Initial	0.04±0.002	0.11±0.002	0.08±0.005	0.11±0.004	<0.01%
	7 th Day	0.06±0.007	0.16±0.002	0.11±0.006	0.14±0.002	<0.01%
	15 th Day	0.07±0.007	0.17±0.002	0.19±0.004	0.16±0.004	<0.01%
	30 th Day	0.07±0.006	0.23±0.005	0.24±0.006	0.23±0.005	<0.01%

±SEM=Standard Error Mean (n=3)

CONCLUSION

The drug solubility conforms to its low solubility in an all pH 1.2 - 8 buffer solution at 37°C. The particle size of the drug is suitable flow property and the compressibility. In this study, the drug's chemical structure has confirmed by UV-Visible, FT-IR, LC-MS, and NMR Spectroscopy. The FT-IR overlay spectral studies indicated no intermolecular interactions between the drug and Excipients binary mixture. In the DSC thermograms of drug and immediate release granules, the drug melting peak was quite visible at the same melting point, confirming the no physical and chemical incompatibility between drugs and excipients.

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All the author has contributed equally.

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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