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COMPATIBILITY STUDIES OF LISINOPRIL WITH SELECTED EXCIPIENTS FOR AN ORAL DISINTEGRATING FILM FORMULATION

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ABSTRACT

The compatibility studies are an important phase that should be performed at the preformulation stage. The physical and chemical interaction between the drug and excipients can affect the chemical nature, stability, bioavailability, the therapeutic efficacy and safety of a drug and its dosage form. The compatibility studies of drug Lisinopril with different excipients were performed using the analytical techniques like Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Isothermal Stress Testing (IST) and High-Performance Liquid Chromatography (HPLC). The compatibility study of Lisinopril was performed with PVPk30 polymer, Polyplasdone XL, Indacol allurared, 1:1% mixture the drug, each excipient was prepared and stored at 40°C real humidity for one month. The studies were compared to find out the drug interaction between drug and excipients mixture was examined, no interaction with the results of Lisinopril and selected excipients, it indicates no concrete evidence of interaction between drug and the excipients. The finding results have shown that the selected excipients were found to be compatible with the drug, it can be used for the oral disintegrating film formulation.

Keywords: Lisinopril, compatibility, DSC, FTIR, IST, HPLC, Oral disintegrating films

1.INTRODUCTION

The compatibility studies are an important part of preformulation studies. It should be performed to check the physical and chemical interaction between the drug and excipients incompatibility between them may affect the stability, bioavailability, subsequently the safety and therapeutic efficacy of drug formulation **(Lira *et al*., 2007, Neto *et al*., 2009)**. The excipient facilitates to the administration and modulates the release of the active component **(Tiţa *et al*., 2011)**.

The analytical technique like Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) and Isothermal Stress Testing (IST) were adopted in the present study to check the compatibility between the physical mixtures of anti-hypertensive drug Lisinopril and excipients. PVPk30, Polyplasdone XL, Indacol allurared incompatibility studies reduce the cost and time in the formulation development **(Dave *et al*., 2015, Carlson *et al*., 2005)**.

DSC is a rapid analytical technique for the evaluation of the formulation components. Possible interaction between drug and excipients according to appearance **(Aulton, 2016)** shift or dis-appearance of endothermic or exothermic peaks **(Roumeli *et al*., 2013)**. It must be emphasized that the interactions observed at temperature may not always be relevant under ambient conditions **(Marini *et al*., 2003, Pereira *et al*., 2014)**. Isothermal Stress Testing is a commonly used method for evaluation of compatibility and it involves the storage of drug and excipients mixture with or without moisture at an elevated temperature for a specific period and drug content is determined by a suitable method **(Bharate *et al*., 2010, Pereira *et al*., 2014)**. Despite an important issue and there is no universally accepted protocol for drug excipients incompatibility testing **(Abhinandana, 2019, Shrivastava *et al*., 2013)**.

2. MATERIALS AND METHODS:

2.1. MATERIALS

Lisinopril and excipients (PVPk30, Polyplasdone XL, Indacol allurared) purchased from PAR formulation Pvt Ltd, Chennai. All other chemicals and reagents were purchased from NICE laboratories which are analytical grade.

2.2. METHODS

2.2.1. Preparation of samples

The samples for Differential Scanning Calorimetry and Fourier Transform Infra-Red Spectroscopy studies were prepared by mixing equal amounts of Lisinopril and individual adjuvants (1:1 ratio). The mixtures were transferred to glass vials and sealed with Teflon lined screw cap. The vials were then stored at 40°C in a Hot Air Oven for one month. The

samples for Isothermal Stress Testing were prepared as described above and mixed with distilled water in a mortar for 3 mins and transferred to vials and sealed with Teflon lined screw cap. The vials were then stored at 50°C in Oven for two weeks

2.2.2. Fourier transform infrared spectroscopy

FT-IR spectra were recorded on an FTIR spectrometer (Shimadzu instrument FTIR 8400S) in the frequency range of 400 - 4000cm^{-1} with the resolution of 4cm^{-1} using Potassium bromide disc method **(Zuberi and Ahmed, 2013)**. Individual samples, as well as the mixture of drug with excipients, were ground and mixed thoroughly with Potassium bromide for 3-5 minutes in a mortar and compressed into the disc by applying a pressure of 5 tons for 5 mins in the hydraulic press. The concentration of the sample in Potassium bromide disc should be in the range of 0.2% to 1% **(Mallik *et al*., 2011)**. The pellets were placed in the light path. The spectra were obtained and reviewed for evidence of any interactions **(Hasanuzzaman *et al*., 2011)**.

2.2.3. Differential Scanning Calorimetry

The DSC studies were performed using DSC-60, Shimadzu. Individual samples (drug and excipients) were weighed to about 10mg in DSC aluminium Pan **(Manikandan, 2013)**.

The pan was then crimped for effective heat conduction and scanned in the temperature range of 50-300°C **(Kunasekaran and Krishnamoorthy, 2015)**. The heating rate of 20°C min^{-1} were used and the thermogram obtained were reviewed for evidence of any interaction **(Pani *et al*., 2011, Bozdag-Pehlivan *et al*., 2011)**.

2.2.4. Isothermal Stress Testing

The IST studies mixtures of drug and selected excipients were weighed in a glass vial and mixed on a vortex mixer for 3 mins. Each glass vial sealed by Teflon lined screw cap and stored at 50°C in hot air oven (Technico India). The samples were examined regularly for any unusual colour change. These samples were analysed after two weeks of storage at the above condition the samples were quantitatively analysed by using HPLC **(Choudhury, 2012; Bipul *et al*., 2016)**.

2.2.5. HPLC analysis

The mixture is vortexed by adding 2ml of diluent (methanol-water) and transferred to 100ml volumetric flask as well as the vials were rinsed with diluent to make up the volume in a volumetric flask. After dilution, the samples were analysed by using HPLC and the drug content is determined by the calibration curve **(Choudhury, 2012; Arayne and Sultana 2013)**.

3. RESULTS AND DISCUSSION

3.1. Fourier Transform Infrared Spectroscopy

The characteristic spectra of Lisinopril have shown a band of 2919cm^{-1} and 7438cm^{-1} owing to Alkane C-H stretching and Aromatic C-H bending groups. The bands peak at 1386cm^{-1} (phenols C=O stretching), 1650cm^{-1} (Amide C=O stretching) and 1586cm^{-1} Aromatic stretching C=C respectively.

FTIR spectra of Lisinopril, Polyplasdone XL and mixture of Lisinopril with Polyplasdone XL shown in **Figure 1**. Polyplasdone exhibits a band at 2931cm^{-1} corresponds to the combined peaks of the Alkane stretching, the vibration of C-H characteristic broadband at 2926cm^{-1}, and associated with the Aromatic stretching of C=C band at 1649cm^{-1} the other band peak at phenols stretching C=O **(Table 1)**.

The binary mixtures of Lisinopril and Polyplasdone XL showed no significant changes in the peaks of Alkane stretching C-H, Aromatic bending C-H, phenols stretching C=O and Aromatic stretching C=C about the observed value of Lisinopril and Polyplasdone XL.

The FTIR spectra of Lisinopril, Indacol allurared, and the mixture of Lisinopril with Indacol allurared. The characteristic band peaks at around 2960cm^{-1} and 722cm^{-1} are assigned to the Alkane stretching C-H and C-H Aromatic bending respectively. The peaks present at 1376cm^{-1}, 1617cm^{-1} and 1545cm^{-1} owing to phenols stretching C=O, Amide stretching C=O and C=C Aromatic stretching mixture of Lisinopril and Indacol allurared showed no change in positions of the bands at 2932cm^{-1} (Alkane stretching C-H), 723cm^{-1} (Aromatic bending C-H) bands at 1650cm^{-1} (Amide stretching C=O) and 1544cm^{-1} (Aromatic stretching C=C) in Lisinopril and Indacol Allura red **(Table. 2)**.

The FTIR spectrum of PVPk30 is characterized by principal absorption band peaks at 2946cm^{-1} (Alkane stretching C-C) 731cm^{-1} (Aromatic bending C-H) bands at 1372cm^{-1} (phenols stretching C=O) 1647cm^{-1} (Amide stretching C=O) and 1491cm^{-1} **(Table. 3)**. The Lisinopril PVPk30 mixtures showed the respective characteristic bands peaks at 2922cm^{-1}, 742cm^{-1}, 1386cm^{-1}, 1649cm^{-1} and 1568cm^{-1} were shown in **Figure. 3**. The results confirm there is no change in positions of the bands' peaks in the mixtures Lisinopril and PVPk30 spectra.

The **(Table. 1, 2, 3)** peaks are considered as characteristic peaks of Lisinopril. These peaks were not affected and prominently observed in the IR spectra of the drug and excipients, this indicates there is no interaction between drug and excipients.

3.2. DIFFERENTIAL SCANNING CALORIMETRY

The DSC thermogram of Lisinopril showed an endothermic peak at 158.22°C

(It represents the dehydration of bound water) and 190.20℃ (melting point) Lisinopril and Indacol allura red mixture showed the endothermic peak at 156.52℃ and 190.20℃ **(Figure 4)** the melting endothermic peak at 158.22℃ in Lisinopril and Indacol allurared mixture confirm there is no interaction between Lisinopril and Indacol allurared.

The DSC Thermogram of Lisinopril and Polyplasdone XL showed an endothermic peak at 150.05℃ and 190.20℃ showed in **Figure 5**. In this Lisinopril melting peak appears at the same value of temperature 190.20℃ the Binary mixture of thermogram Indicate no Interaction between these substances.

The DSC thermogram of Lisinopril and binary mixture of Lisinopril and PVPk30 showed an endothermic peak at 148.10℃ and 190.20℃ showed in **Figure 6**. In this Lisinopril, melting peak appears at the same value of Temperature. The binary mixture of thermogram indicates no Interaction between the substance.

3.3. ISOTHERMAL STRESS TESTING

In the isothermal stress testing the drug and mixture of drugs, excipients were physically observed. There is no change in physical appearance at ambient temperature. The assay value was observed using HPLC from the samples of the drug and excipient mixture was stored at 50℃ for 2 weeks. The assay of the drug and excipient mixtures found good within the acceptable range. This indicates the stable nature of the Lisinopril with PVPk30, Polyplasdone XL, Indacol allurared.

3.4. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

The proposed LC method for the drug and mixture of drug excipient compatibility studies. The most simple and precise among other methods. This system is quite robust. The analysis was performed with the best chromatographic condition equipped with the C18 column (ODS-250mm×4.6mm with 5-micron pore size, Phenomenex) column is recommended because it demonstrated ruggedness and reproducibility in this assay. Atypical reference chromatogram drug and the mixture of drug excipient (Lisinopril, Polyplasdone XL, PVPk30, Indacol allurared).

The column flow rate is 1.0ml min^{1} the optimum wavelength selected was 218.0nm at which much better detector response for each sample and sample mixture was obtained the typical chromatogram shown in **(Figures 7, 8, 9.)**.

The Lisinopril- Polyplasdone XL mixtures are subjected to chromatogram studies and its compared with the Lisinopril pure drug and Polyplasdone with Lisinopril. Their bands' peaks are shown in **Figure 7**.

The characteristic bands of Lisinopril were observed in the retention time of 1.841 area of the peak is 703088 height of the peak is 84924 area % is 98.975 height % is 98.484 and tailing factor is 0.987. The characteristic peak of Lisinopril with Polyplasdone XL was observed in the retention time of Lisinopril is 1.610 area of the peak is 1572083 height of the peak is 195894 area % is 0.216 height % is 98.900 tailing factor is 0.906 is obtained there is not much difference in the retention time of pure drug and along with the mixture.

The Lisinopril-indacol allurared mixtures are subjected to chromatograms studies, its compared with the Lisinopril and mixture of Lisinopril with indacol allurared bands peak are shown in **Figure 8**. The characteristic bands of Lisinopril were observed in the retention time of 1.841 area of the peak is 703088 height of the peak is 84924 area % is 98.975 height % is 98.484 and tailing factor is 0.987. The characteristic peak of Lisinopril with indacol allurared was observed in the retention time of 1.305 area of the peak is 4557914 height of the peak is 640345 area % is 78.824 height % is 77.942 tailing factor is 0.842 is obtained there is not much difference in the retention time of pure drug along with the mixture.

The Lisinopril-PVPk30 mixtures are subjected to chromatogram studies and its compared with the Lisinopril and mixture of Lisinopril with PVPk30 bands peaks are shown in **Figure 9**. The characteristic bands of Lisinopril observed at the retention time of 1.841 area of the peak is 703088 height of the peak is 84924 area % is 98.975 height % is 98.484 tailing factor is 0.987. The characteristic peak of Lisinopril with PVPk30 was observed in the retention time of Lisinopril is 1.597 area of the peak is 1289142 height of the peak is 172908 area % is 99.264 height % is 99.052 tailing factor is 0.924 obtained there is not much differ from the retention time of pure drugs.

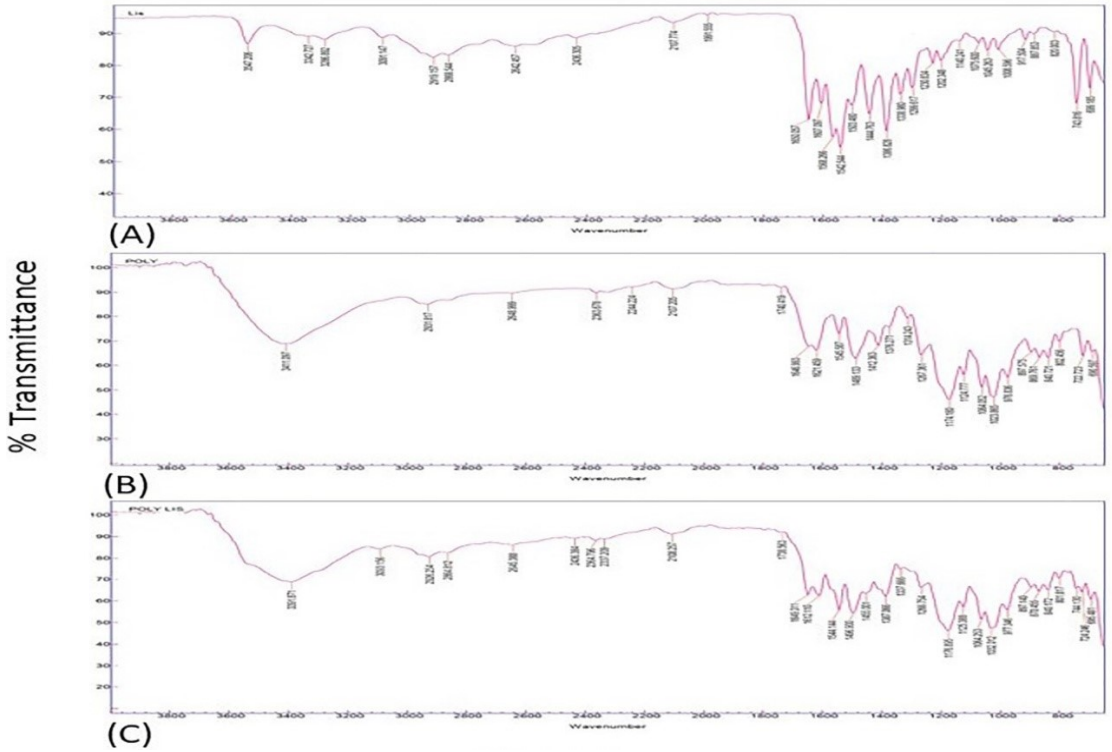


Figure 1: FTIR spectrum of pure Lisinopril (A), pure Polyplasdone XL (B) and a mixture of Lisinopril with Polyplasdone XL (C)

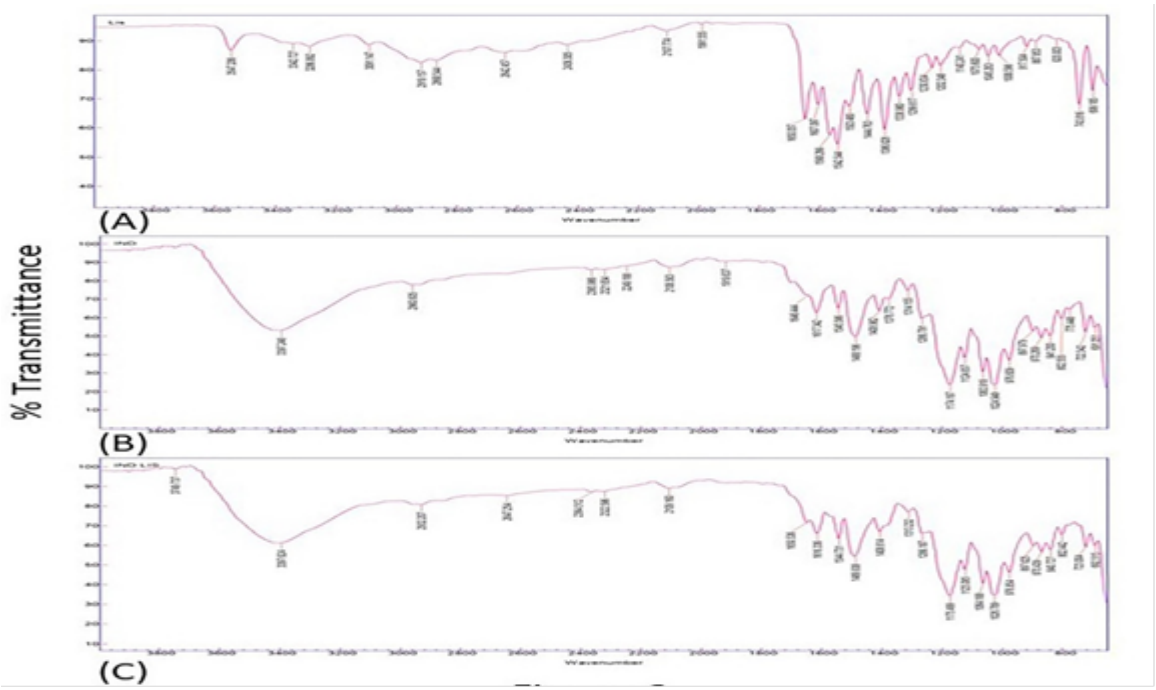


Figure 2: FTIR spectrum of pure Lisinopril (A), pure Indacol allurared (B) and a mixture of Lisinopril with Indacol allurared (C)

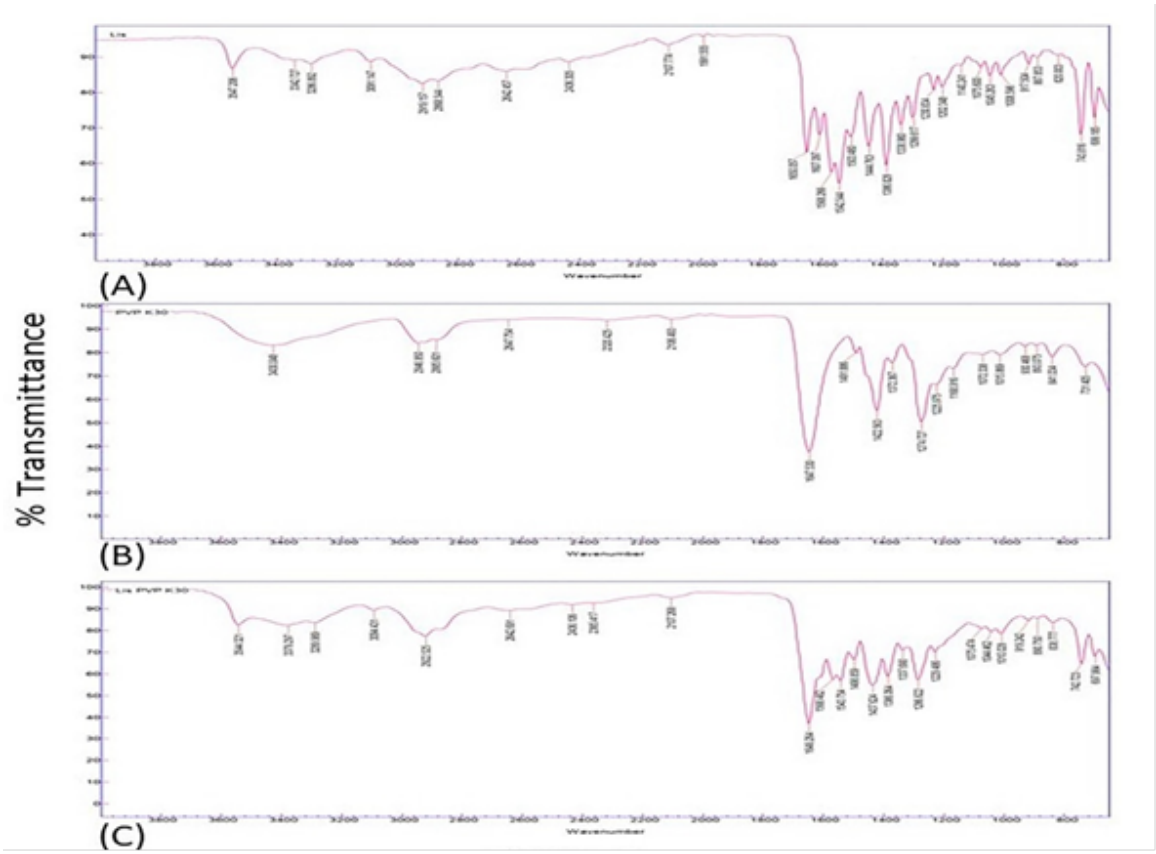


Figure 3: FTIR spectrum of pure Lisinopril (A), pure PVPk30 (B) and a mixture of Lisinopril with PVPk30 (C)

Table 1: FTIR spectroscopy data of Lisinopril, PolyplasdoneXL, and mixture of Lisinopril with PolyplasdoneXL

S.NO	Functional group	Standard cm^{-1}	Lisinopril cm^{-1}	PolyplasdoneXL cm^{-1}	Lisinopril + PolyplasdoneXL cm^{-1}
1	StretchingAlkane (C-H)	2840-3000	2919	2931	2926
2	BendingAromatic (C-H)	700-900	743	722	744
3	StretchingPhenols (C=O)	1310-1390	1386	1376	1387
4	StretchingAmide (C=O)	1650-2000	1650	1646	1649
5	StretchingAromatic (C=C)	1300-1600	1568	1545	1544

Table 2: FTIR spectroscopy data of Lisinopril, Indacol allurared, and Mixture of Lisinopril with lndacol allurared

S.NO	Functional group	Standard cm^{-1}	Lisinopril cm^{-1}	Allura red cm^{-1}	Lisinopril + Indacol allurared cm^{-1}
1	Stretching Alkane (C-H)	2840-3000	2919	2960	2932
2	Bending Aromatic (C-H)	700-900	743	722	723
3	Stretching Phenols (C=O)	1310-1390	1386	1376	1408
4	Stretching Amide (C=O)	1650-2000	1650	1617	1650
5	Stretching Aromatic (C=C)	1300-1600	1568	1545	1544

Table 3: It shows FTIR spectroscopy data of Lisinopril, PVPk30, and Mixture of Lisinopril with PVPk30

S.NO	Functional group	Standard cm^{-1}	Lisinopril cm^{-1}	PVPk30 cm^{-1}	Lisinopril+PVPk30 cm^{-1}
1	Stretching Alkane C-H	2840-3000	2919	2946	2922
2	Bending Aromatic C-H	700-900	743	731	742
3	Stretching Phenols C=O	1310-1390	1386	1372	1386
4	Stretching Amide C=O	1650-2000	1650	1647	1649
5	Stretching Aromatic C=C	1300-1600	1568	1491	1568

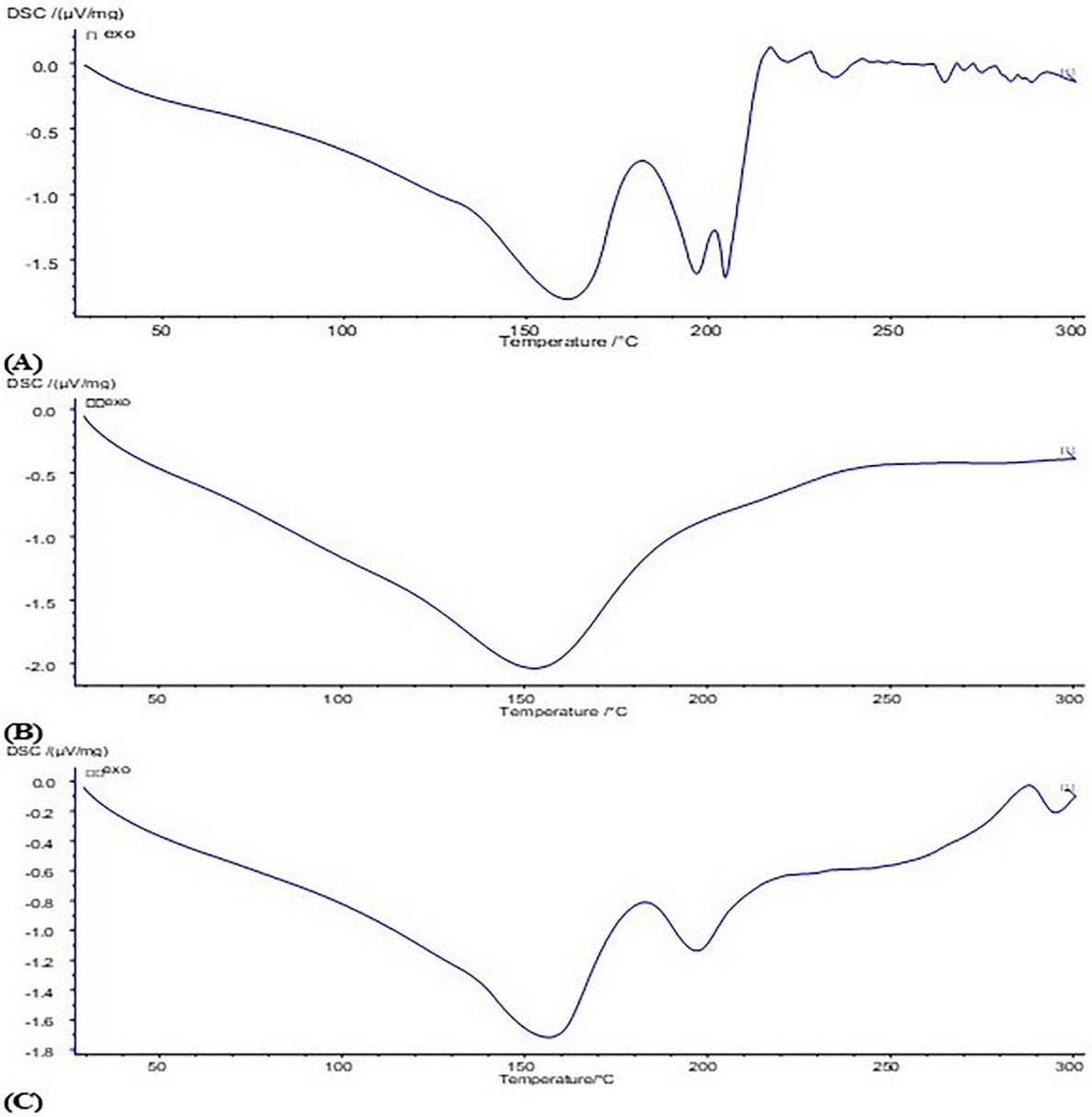


Figure 4: DSC thermogram of pure Lisinopril (A), pure Indacol allurared (B) and physical mixture of Lisinopril with Indacol allurared (C)

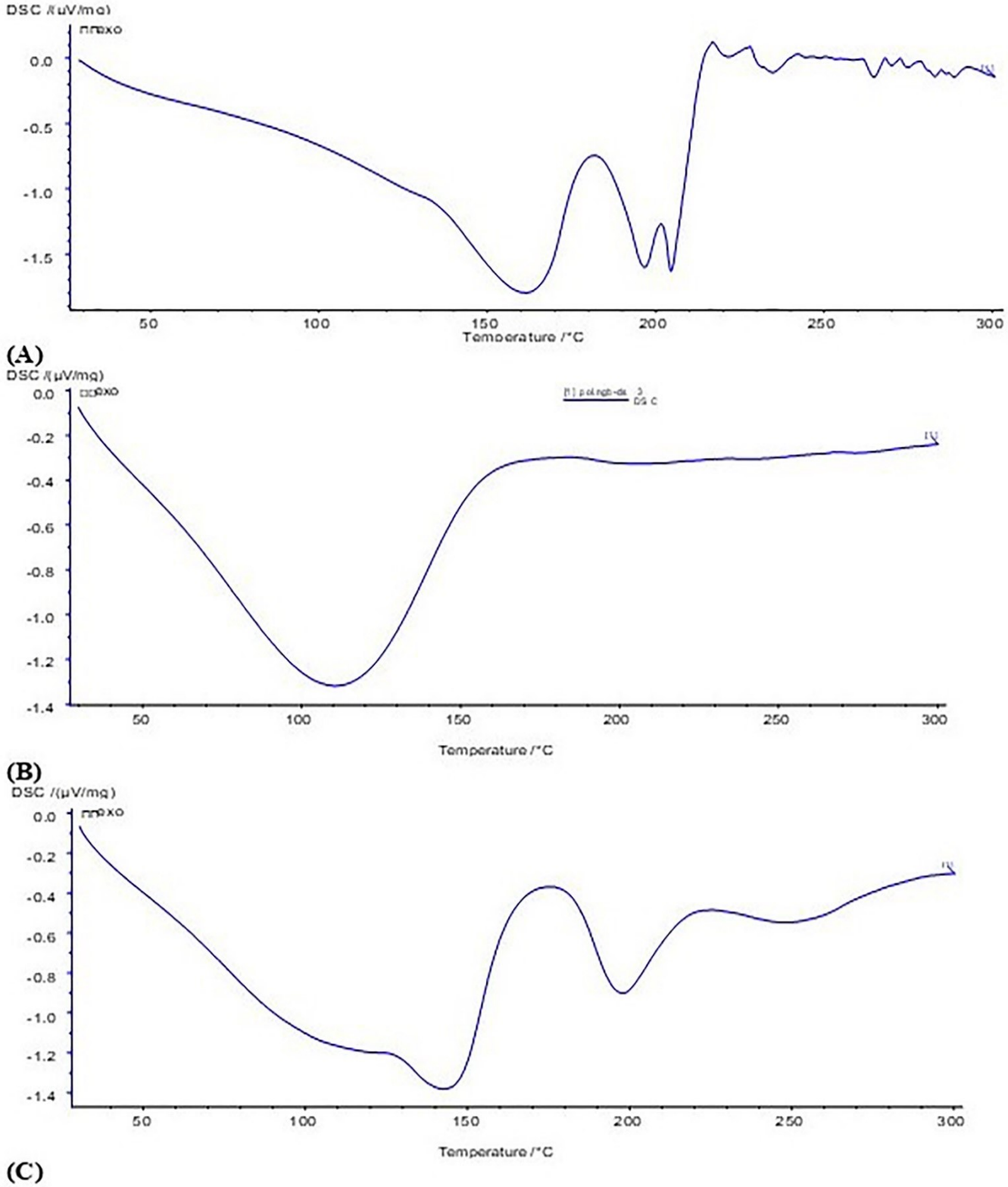
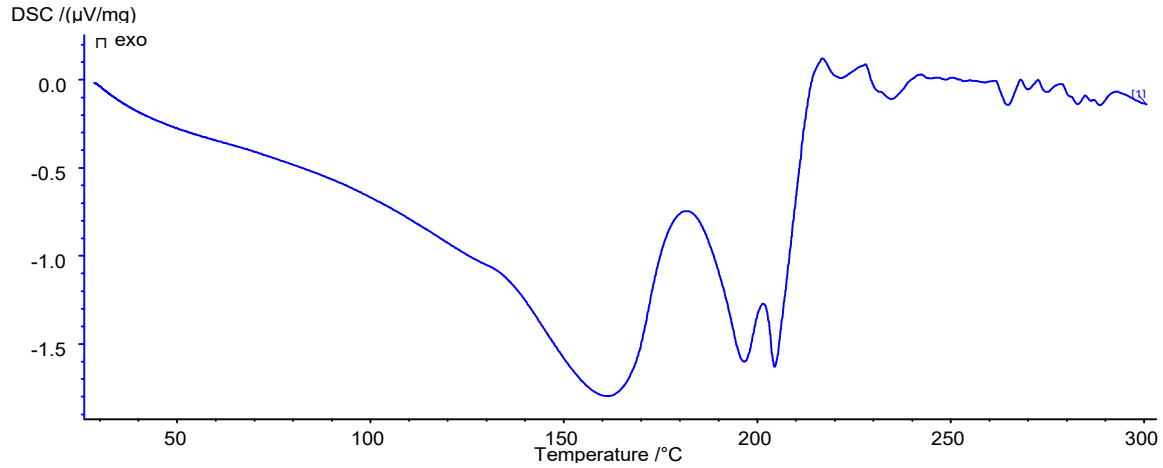
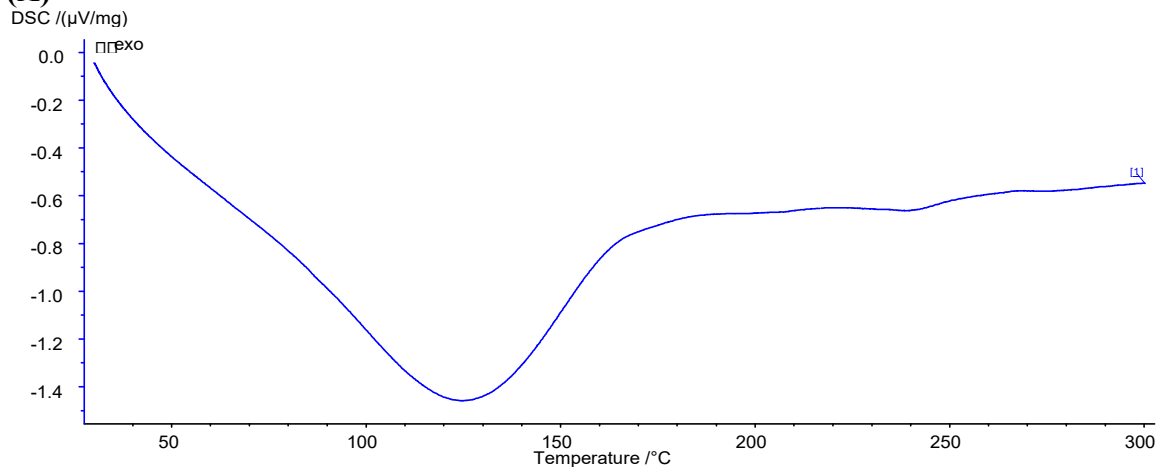


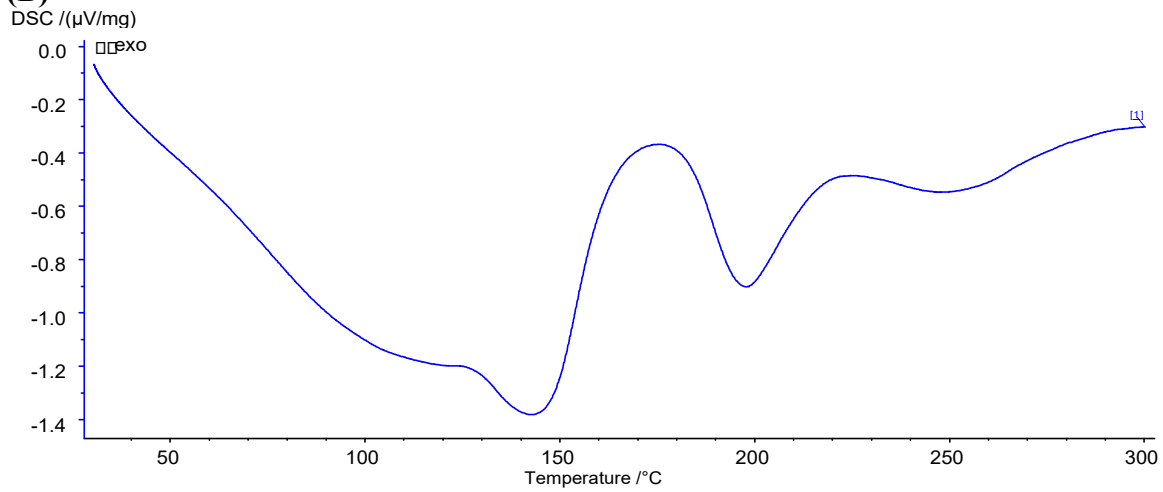
Figure 5: DSC thermogram of pure Lisinopril (A) pure PolyplasdoneXL (B) and physical mixture of Lisinopril with PolyplasdoneXL (C)



(A)



(B)



(C)

Figure 6: DSC thermogram of pure Lisinopril (A) pure PVPk30 (B) and physical mixture Lisinopril with PVPk30 (C)

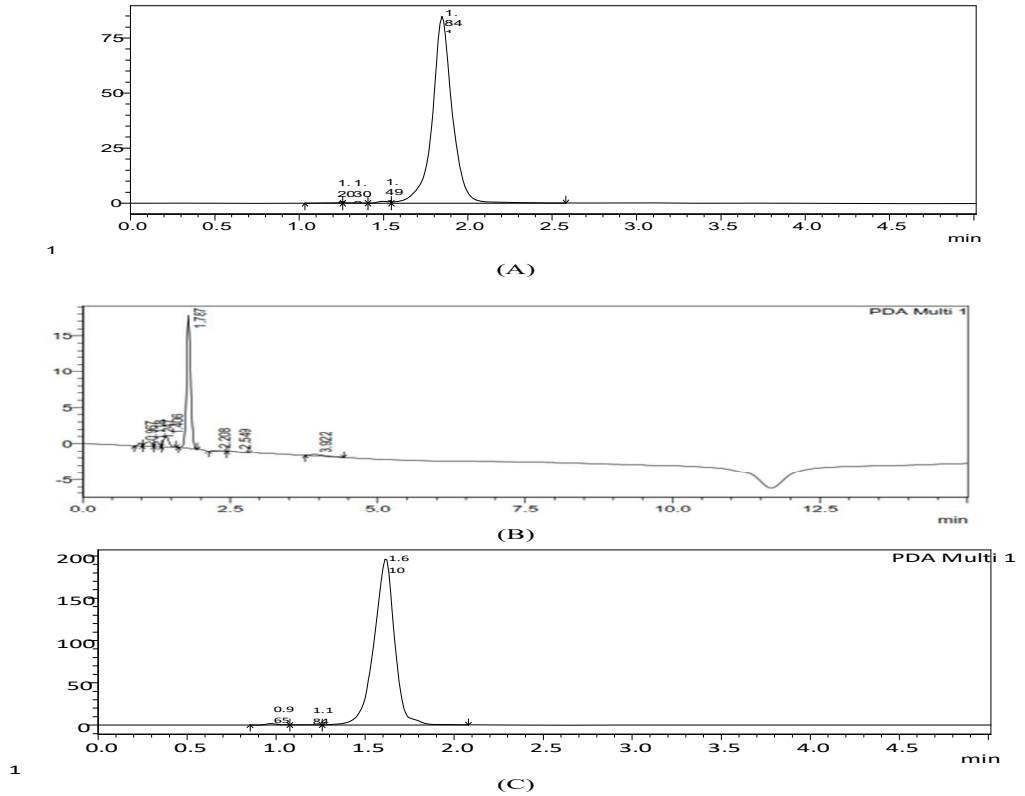


Figure 7: Atypical chromatogram of pure Lisinopril (A) pure Polyplasdone XL (B) and physical mixture of Lisinopril with Polyplasdone XL (C)

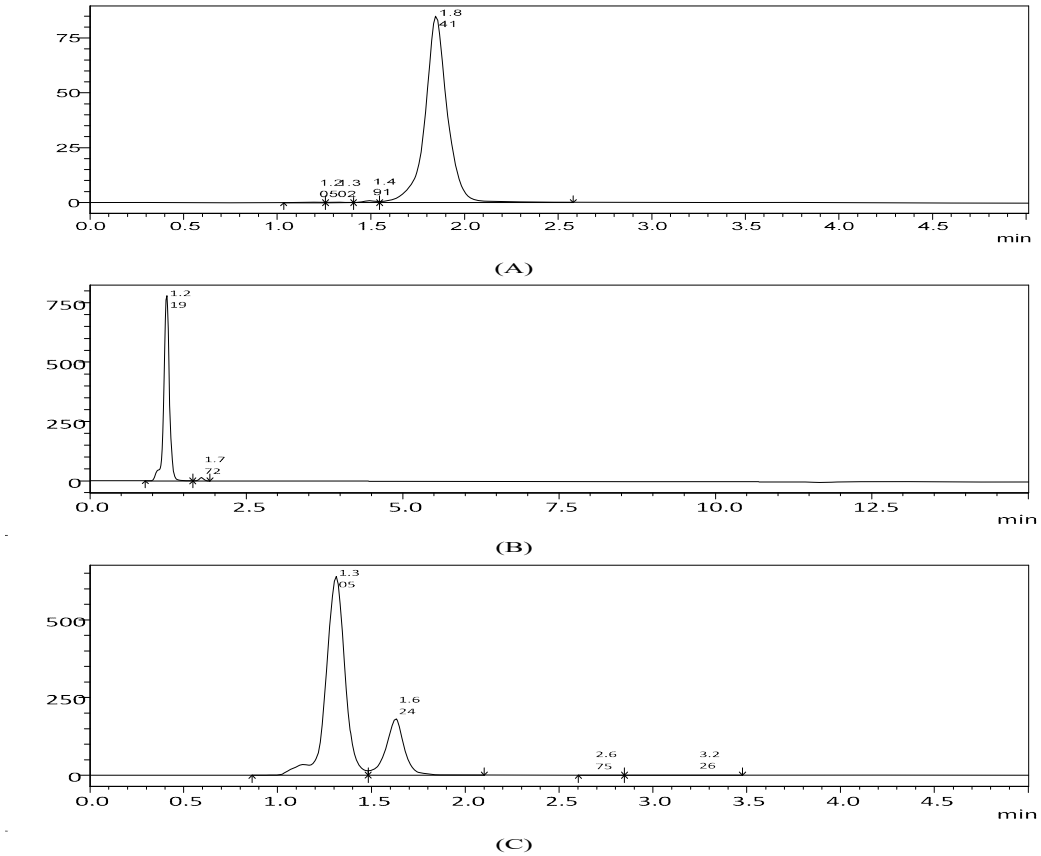


Figure 8: Atypical chromatogram of pure Lisinopril (A), pure Indacol allurared (B) and physical mixture of Lisinopril with Indacol allurared (C)

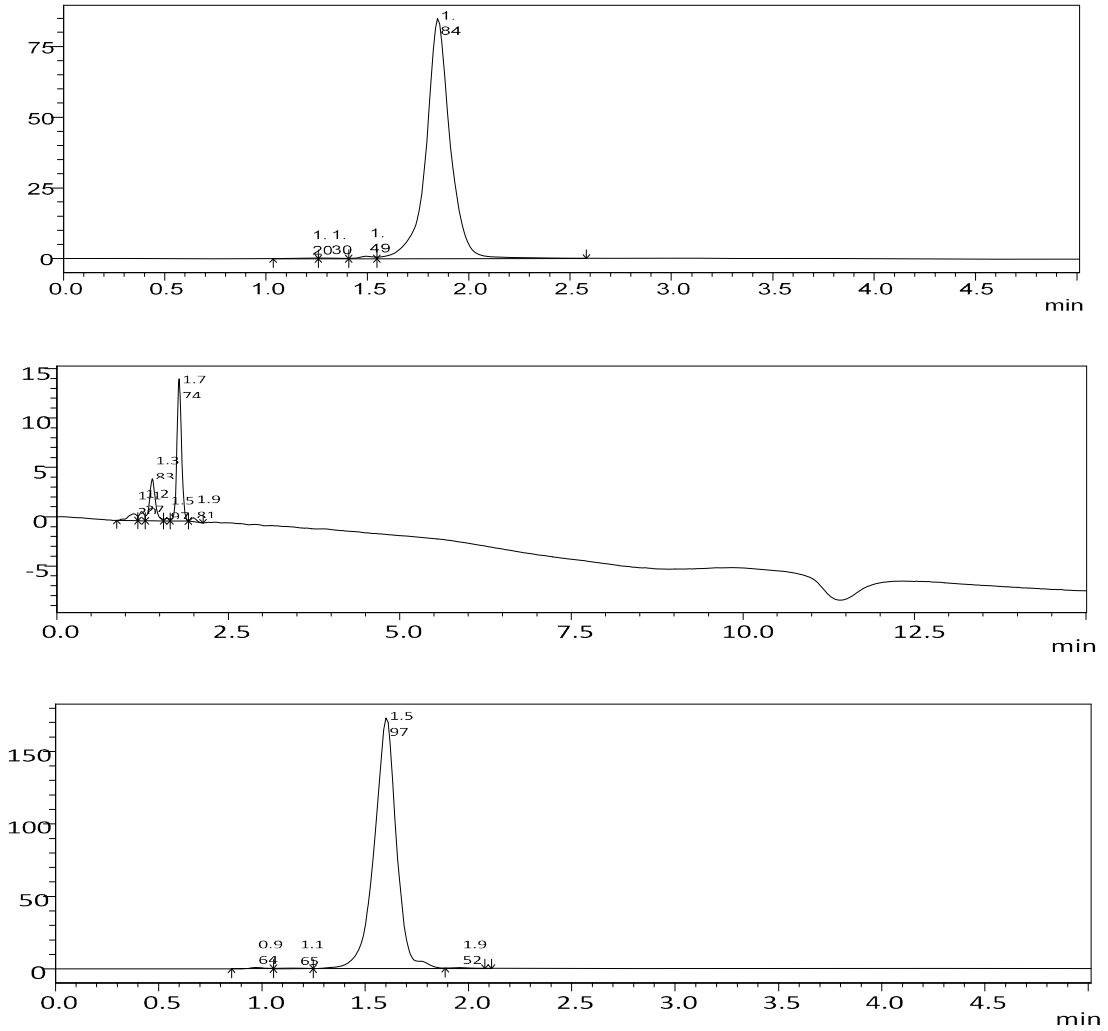


Figure 9: A typical chromatogram of pure Lisinopril (A), pure PVPk30 (B) and physical mixture Lisinopril with PVPk30 (C)

4. CONCLUSION

The compatibility studies of Lisinopril with selected excipients and polymers were investigated using FTIR, DSC and IST. These techniques to evaluate possible incompatibilities of drugs and excipients. FTIR spectra show the absence of physical and chemical interaction between Lisinopril and selected excipients. In DSC studies, there was no significant change in the thermogram of Lisinopril and selected excipients. The results of the IST study showed there was no colour change after 2 weeks of storage under stress conditions and it indicates the stable nature of Lisinopril with other excipients.

The compatibility studies conclude that Lisinopril is compatible with the excipients like Polyplasdone XL, Indacol allurared, PVPk30. The Lisinopril and selected excipients used to be the formulation of orally disintegrating films.

5. ACKNOWLEDGEMENT

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