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Enhancement of dissolution of Lercanidipine Hydrochloride using Solid Dispersion Technique

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Abstract

Lercanidipine hydrochloride (LER) is a BCS class II antihypertensive drug which results in limited oral bioavailability of 10%. The purpose of this study is to improve the dissolution and thus the bioavailability of LER by dispersing it into a hydrophilic polymer. Study involved incorporation of LER in a polymeric matrix of Polyethylene Glycol-6000 at a molecular level. Solid dispersions of LER were prepared by solvent evaporation and melt fusion techniques by varying drug to polymer ratio. The studies demonstrated that LER solid dispersions show increased solubility and dissolution rate in comparison with physical mixture and pure drug. Solid dispersion obtained by solvent evaporation and fusion techniques showed improved release i.e. 93.7% and 57% respectively as compared to pure LER and physical mixture 37.2% and 38.9% respectively in 1 hour. No interaction of LER and polymer was confirmed by DSC and IR studies. It can be confirmed from the obtained results that solid dispersion can be a method of choice for increasing the solubility, dissolution and in turn the bioavailability of Lercanidipine hydrochloride. It is also observed that out of two techniques employed for preparing solid dispersion, solvent evaporation technique shows challenging results.

Keywords: Solid dispersion, Lercanidipine hydrochloride, PEG 6000, DSC, IR.

Introduction

Lercanidipine hydrochloride chemically is 2[(3,3-diphenylpropyl) (methyl)amino]-1, 1-dimethylethyl methyl 2,6- dimethyl-4- (3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate hydrochloride. It is a novel third generation amphipathic drug belonging to the pharmacological class 1, 4-dihydropyridine calcium channel blockers[1]. Lercanidipine HCl belongs to BSC class II compound[2] and has low aqueous solubility, resulting in low dissolution and poor oral bioavailability. Thus, the improvement of solubility of lercanidipine HCl and in turn dissolution is a critical aspect for improving its bioavailability and therapeutic efficacy.

One of the challenging requests of drug development is to enhance the dissolution behavior of drugs that are sparingly soluble in water[3]. Various techniques such as complex formation with polymers, size micronization, solubilization, modification of physical form, preparing a prodrugs, derivatization of drug and others have been used to improve the dissolution and bioavailability of drugs with low water solubility[4,5]. Solid dispersions (SDs) are the dispersion of hydrophobic drugs in an inert hydrophilic carrier. SDs are prepared to improve the dissolution properties and bioavailability of slightly water-soluble drug molecules by dispersing them into an inert hydrophilic carriers[6-8]. The solid dispersion technology adds the probability to reduce the particle size of a drug to a molecular level and increased wettablility. Also conversion of the drug's crystalline state to the amorphous state can be advantageous as the dissolution of later does not need energy to break up the crystalline structure[9]. Solid dispersion (SD) is an applicable and cost effective system to elevate bioavailability of ineffectively water-soluble API. Additionally solid dispersion technique overcomes the limitations of previously used approaches[10].

The objective of this work was to increase the solubility and ultimately dissolution of lercanidipine HCl by dispersing it in the polymer matrix of PEG 6000 in different ratios using different techniques. To study the effect of polymer, dissolution and solubility studies were carried out. Solid state characterisations of prepared solid dispersions were performed by differential scanning calorimetry (DSC).Drug-carrier interactions were studied by FT-IR spectroscopy, whereas X-ray diffraction of powder was done to demonstrate the crystal structure of the dispersions.

Material and Methods

Materials: Lercanidipine hydrochrloride was received as a gift sample from Alembic Research centre, Vadodara, Gujarat, India. PEG 6000 was purchased from signet chemicals. Other materials used were of analytical grade.

Method: Saturation Solubility Measurements: A surplus Lercanidipine HCl was introduced in 25 ml limit conical flasks with 20 ml of distilled water, phosphate buffer pH 6.8 and 0.1 N HCl each. The samples were subjected to sonication for 10 min at 25 ± 2°C and closed conical flasks were agitated for 24 h at 37± 1°C in an orbital shaker. The

flasks were equilibrated at 37°C for 24 h in an incubator. The content of flasks were allowed to settle down and the supernatant liquid was filtered through a Grade 1 Whatmann filter paper .The measurement of the LER present in filtrate was done at 236 nm by UV spectrophotometer (UV-1800PC, Shimadzu, Japan). Similarly saturation solubility was measured for physical mixtures and solid dispersions in distilled water. All measurements were performed in repeatation (n=6).

Phase solubility study: Phase solubility studies were performed by Higuchi and Connors' method[11]. An excess quantity of LER was added in a 25 ml conical flask containing 0.5%, 1%, 1.5%, 2%, 2.5%, 3% and 4%w/v PEG 6000 in 20 ml distilled water. To avoid the loss of solvent, flasks were covered with cellophane membrane. Sealed flasks were then subjected to shaking at a rate of 100 agitations per minute in an orbital shaker at 37 °C for 24 h. The sealed flasks were allowed to equilibrate and settle; 5 ml of supernatant was withdrawn from each flask, filtered through Grade 1 Whatmann filter paper and evaluated by UV spectrophotometer at 236 nm. All the measurements were repeated for six times[12].

Preparation of solid dispersions: Solid dispersions of Lercanidipine HCl and PEG 6000 in ratio of 1:3, 1:6 and 1:9 were prepared by solvent evaporation and melt fusion method.

Solvent evaporation method: The calculated quantities of lercanidipine HCl and PEG 6000 were dissolved in ethanol, sonicated and stirred for 1 hour over a magnetic stirrer. The ethanol was then evaporated under vacuum in a Rotary flask evaporator at 60˚ C till the solid dispersion was completely dried. The dried mass was crushed, passed through # 100 sieve and preserved in desiccators until use[13,14]. A total of three batches (SF1 to SF3) by solvent evaporation method were prepared (table 1).

Melt method: Solid dispersions of lercanidipine HCl with PEG 6000 were prepared by melting the polymer at 60°C, succeeded by addition of required amount of drug. The melted polymer and drug were stirred and immediately cooled in an ice bath. The obtained solidified mass was crushed in mortar pestle and passed through sieve. The obtained solid dispersion was stored in the desiccator[15]. A total of three batches (MF1 to MF3) by melt method were prepared (table 1).

Physical Mixtures: Physical mixtures (PM) were obtained simply by blending the drug and polymer in required proportions using pestle in mortar. Resulting mixtures were passed through #100 sieve avoiding abrasion and stored within sealed vials in desiccator until use (table 1).

Table-1
Different formulations of Lercanidipine HCl solid dispersion

Formulation code	Composition	Method of preparation
F1	Drug: polymer (1:3) in ethanol	Solvent Evaporation
F2	Drug: polymer (1:6) in ethanol	Solvent Evaporation
F3	Drug: polymer (1:9) in ethanol	Solvent Evaporation
F4	Drug: polymer (1:3)	Melt Method
F5	Drug: polymer(1:6)	Melt Method
F6	Drug: polymer(1:9)	Melt Method
F7	Drug: polymer (1:3)	Physical Mixture
F8	Drug: polymer(1:6)	Physical Mixture
F9	Drug: polymer(1:9)	Physical Mixture

In vitro Dissolution studies: Dissolution of pure lercanidipine HCl, solid dispersions and physical mixtures equivalent to 10 mg of LER was performed in 0.1 N HCl at 50 rpm using USP basket type (ELECTROLAB, Mumbai, India) at 37±0.5 °C. At fixed time intervals for 60 min, 5 ml of dissolution medium was pipette out and filtered through Grade- 1 Whatmann filter paper. Filtered dissolution media was assayed spectrophotomerically at 236 nm to calculate the drug release. After each withdrawal, 5 ml of 0.1 N HCl was introduced to maintain the constant volume of dissolution media. Dissolution experiment was performed in triplicate.

Solid state characterization: Solid state studies were carried out for Lercanidipine HCl, PEG 6000, physical mixture and optimized batch of solid dispersion.

Fourier Transform Infrared (FT-IR) spectroscopy: FT-IR spectroscopy was carried out on an FTIR Spectrophotometer (Alpha, Bruker, Germany). The spectrum was reported between 4000–600 cm−1. The spectra obtained for drug, polymer, physical mixture and optimized solid dispersion were compared.

Differential scanning calorimetry (DSC): The thermal behaviour of the samples were studied by Differential Scanning calorimeter (DSC-PYRIS-1, perkin elmer). DSC scan was carried out in an atmosphere of dry nitrogen within the measuring range of -2 mW to 20 mW. The samples were heated at a rate of 10 °C min−1 from room temperature to the melting point using reference of an empty aluminium pan.

X-ray diffraction (XRD): The X-ray diffraction pattern of selected batches of solid dispersion was carried out using X'Pert Model, Phillips to characterise the physical form of lercanidipine HCl. The data was recorded at 2θ within 0–90° of the range inside copper target tube of X-ray at the step size of 0.0500.

Results and Discussion

Saturation Solubility Measurements: The results of solubility measurement at saturation level for lercanidipine HCl in various solvents is shown in table0-2. The lercanidipine hydrochloride solubility in water (37 °±1 °C) is 0.015±0.0023 mg/ml. The solubility values of lercanidipine HCl in phosphate buffer pH 6.8 and 0.1 N HCl were observed to be around 0.00329 ± 0.0003 mg/ml and 0.123 ±0.03 mg/ml respectively. The solubility of prepared solid dispersions and physical mixtures are shown in table 3.

Table-2
Solubility of lercanidipine HCl in selected media at 37 °C±1°C

Vehicle	Solubility of lercanidipine HCl (mg/ml)
Distilled water	0.05189±0.0023
0.01 N HCl	0.123 ±0.03
Phosphate buffer pH 6.8	0.00329 ± 0.0003

Table-3
Saturation solubility data of Lercanidipine HCl solid dispersions and physical mixtures with PEG 6000

S.N.	Formulation	Solubillity in mg/ml
1	F1	0.065125 ± 0.000625
2	F2	0.330958 ± 0.017211
3	F3	0.113458 ± 0.012189
4	F4	0.029708 ± 0.010181
5	F5	0.153667 ± 0.015339
6	F6	0.051646 ± 0.00329
7	F7	0.007833 ± 0.001443
8	F8	0.0095 ± 0.007603
9	F9	0.027 ± 0.007043

All values are expressed as mean±SD, n =6.

Table-4
Interpretations of DSC Thermo gram

System	Peak point °C	Peak height (mW)	Peak area (mJ)	Heat of fusion (J/g)
Lercanidipine HCl	178.35	4.1373	189.493	73.56
PEG 6000 PM (1:6)	62.39	21.91	388.439	152.5683
PEG 6000 SD (1:6)	62.25	11.53	86.278	33.62

Phase solubility study: The effect of PEG 6000 concentration on the solubility of lercanidipine HCl in water at 37 °C is depicted in Figure-1. The obtained phase solubility diagram shows the formation of a soluble complex. At concentrations of 4% w/v PEG6000, the solubility of lercanidipine HCl was increased by 8.4 fold. The enhancement in solubility is the result of presence of soluble complexes.

In vitro dissolution study of solid dispersiosn prepared with PEG6000: Dissolution profiles of lercanidipine HCl, physical mixtures and solid dispersions with PEG 6000 over a period of 60 min are depicted in figure 2. It is clearly observed that the rate of dissolution of pure drug is only 37.40% in 60 min. whereas; solid dispersions of lercanidipine HCl with PEG6000 significantly enhanced the dissolution rate of lercanidipine HCl (43-96%) within 60 min as compared to pure drug (36.05%) and physical mixtures (30.05%). Highest improvement was seen in solvent evaporates solid dispersion in the drug to polymer ratio of 1:6.

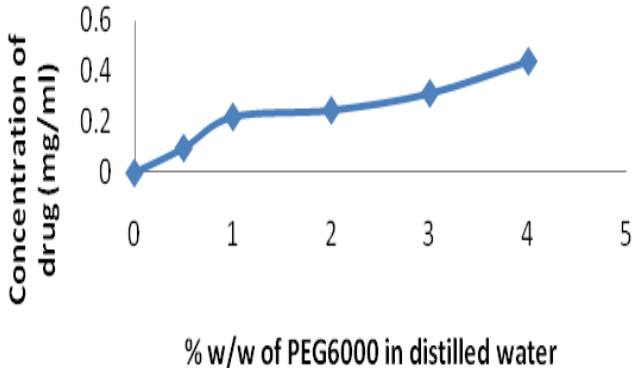


Figure-1
Phase solubility study diagram

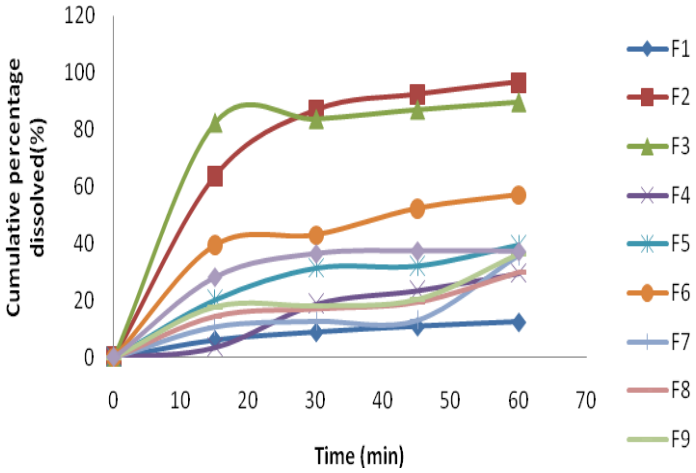


Figure-2
in vitro dissolution of lercanidipine HCl ,its physical mixtures and solid dispersions with PEG6000

The dissolution increase of lercanidipine HCl and PEG 6000 solid dispersion is attributed to several factors. The factors playing major role are decrease in crystallinity (or increase in amorphous structure), reduction interfacial tension, particle size reduction and improved polymer surface adsorption by drug molecules. This in turn confirms the formation of surface solid dispersion.

Solid state characterization study: From solubility and in vitro dissolution studies, solvent evaporated solid dispersion of drug and polymer in ratio 1:6 was selected as an optimized solid dispersion (PEG 6000 SD). Further solid state characterization was performed on the optimized solid dispersion in comparison with physical mixture of drug with PEG 6000 (PEG6000 PM) in same ratio.

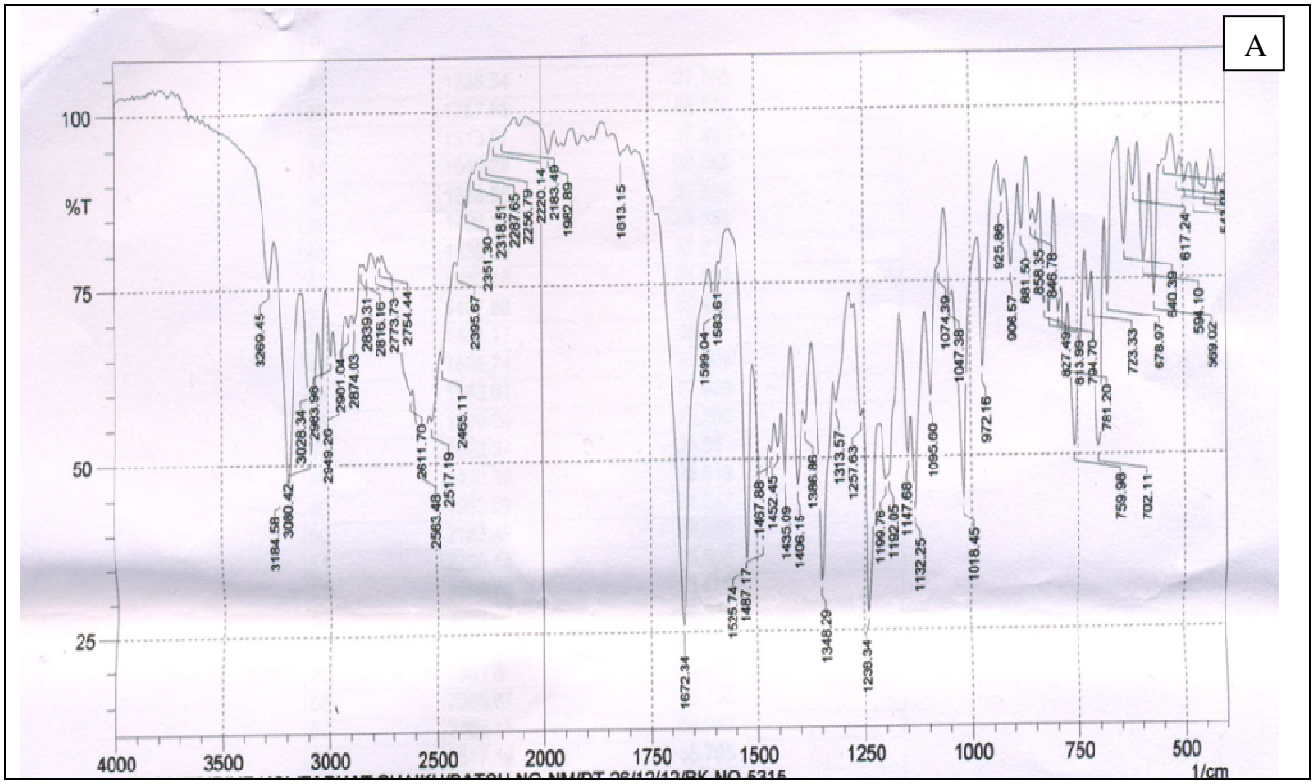
FTIR: The FTIR scan of lercanidipine HCl, the physical mixtures and optimized SDs are depicted in figures. 3. The FTIR scan of lercanidipine HCl shows distinct and sharp peaks at 3184 cm^{-1} (N-H stretching vibration), 3080-2800 cm^{-1} (alkyl and phenyl stretching), 2754 cm^{-1} N-H stretching, 1672 cm^{-1} c=o stretching, 1525 cm^{-1}; 1348 cm^{-1} (asymmetric and symmetric stretching of NO2 group), 1406 cm^{-1}; 1386 cm^{-1} (bending of germinal methyl groups); 813 cm^{-1}-640 cm^{-1} (out of place bending of 5 and 3 adjacent hydrogen on aromatic rings). FTIR spectra of PEG6000 shows stretching of C-H at 2878cm^{-1} and that of C-O (ether) at 1145 cm^{-1}.

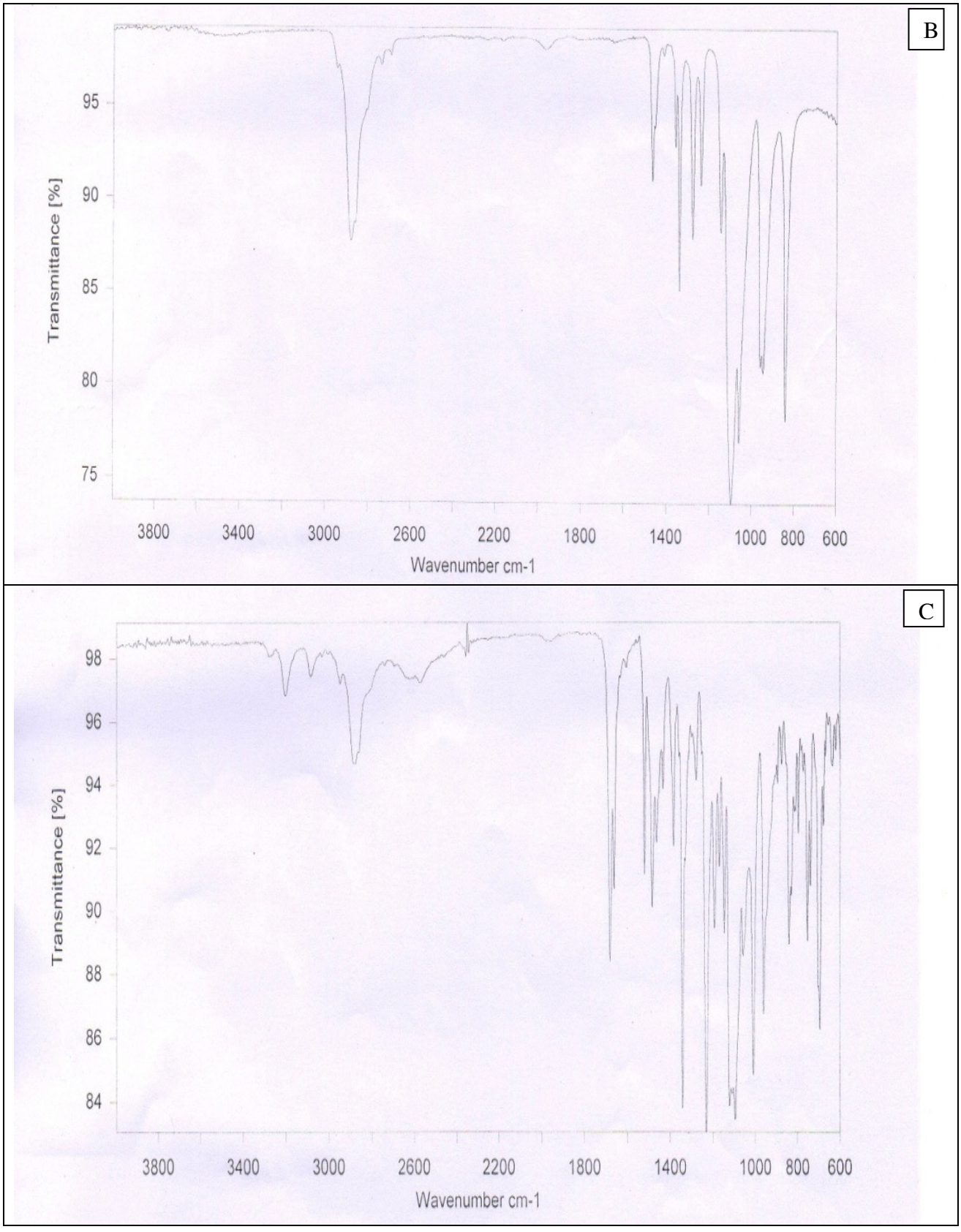
In physical mixture of lercanidipine HCl and PEG6000, presence of drug was confirmed by the appearance of peaks of corresponding to N–H at 3202.68 cm^{-1},N–H stretching at 3085.20 cm^{-1} and c=o stretching at 1680.69 cm^{-1} . While the FTIR spectra of solid dispersion with the same ratio showed a single peak due to c=o stretching of lercanidipine HCl at 1695 cm^{-1} , which suggests the possible entrapment of lercanidipine HCl inside PEG6000 matrix.

DSC Interpretation: The various Differential Scanning Calorimetric curves are shown in figure-4. In DSC thermo gram of Lercanidipine HCl, a sharp endothermic peak is observed at 178.35 °C analogues to its melting point. Whereas in thermo graph of solid dispersion and physical mixture, a significant reduction in height of an endothermic peak and heat of fusion was observed, which suggest transformation of physical state from crystalline to amorphous. This physical state transformation results in higher water solubility and better dissolution behaviour.

X Ray Diffraction: The XRD scan of pure lercanidipine HCl, PEG 6000, solid dispersions and physical mixtures are shown in Figures. 5. The XRD behaviour of pure lercanidipine HCl illustrated strong and sharp peaks outlining well defined crystal structure; however the XRD pattern of SD depicted an observable decrease in number as well as magnitude of peaks compared to pure lercanidipine HCl confirming the reduction in crystal behaviour or noticeable amorphization of dispersed drug [17].

The XRD sweep of immaculate lercanidipine HCl, PEG 6000, strong scatterings and physical mixtures are indicated in Figures. 5. The XRD conduct of unadulterated lercanidipine HCl outlined solid and sharp tops outlining very much characterized precious stone structure; however the XRD example of strong scatterings portrayed an observable lessening in number and also force of crests contrasted with the immaculate lercanidipine HCl affirming the diminishment in crystallinity or discernible amorphization of the medication in its scattered structure

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Transmittance [%]
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Wavenumber cm-1
C
Transmittance [%]
98
96
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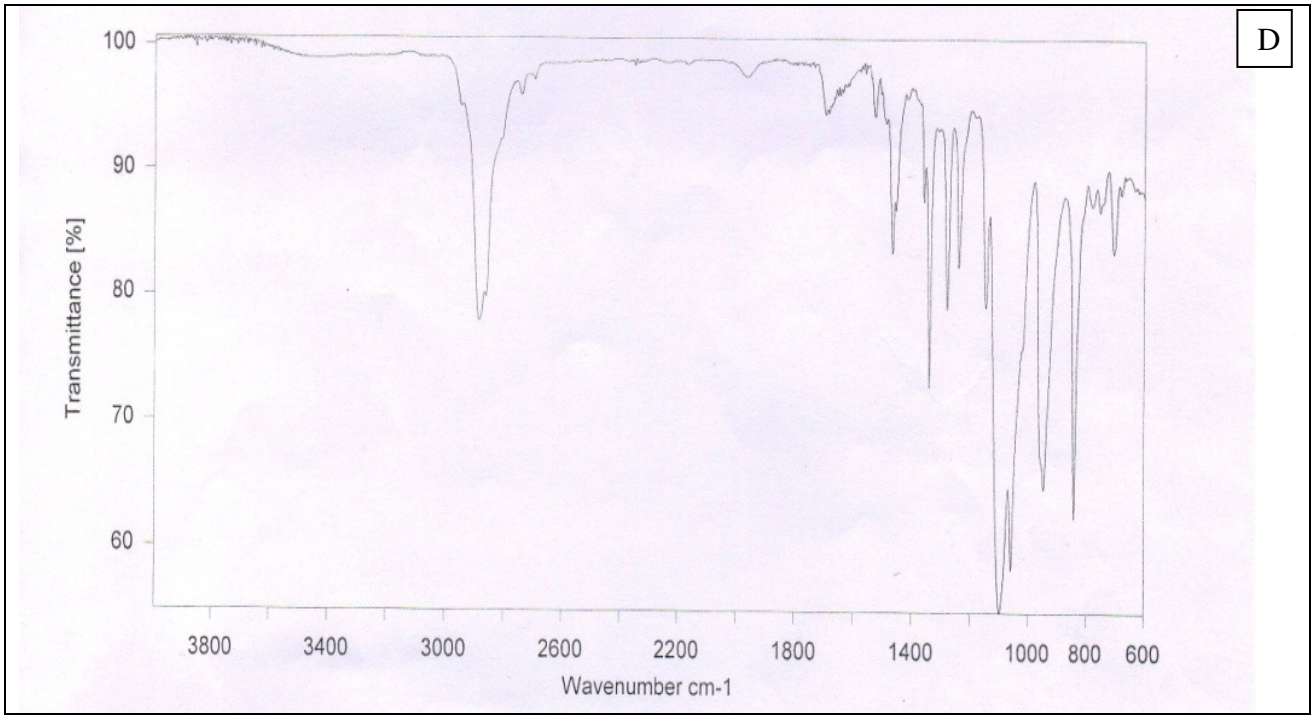
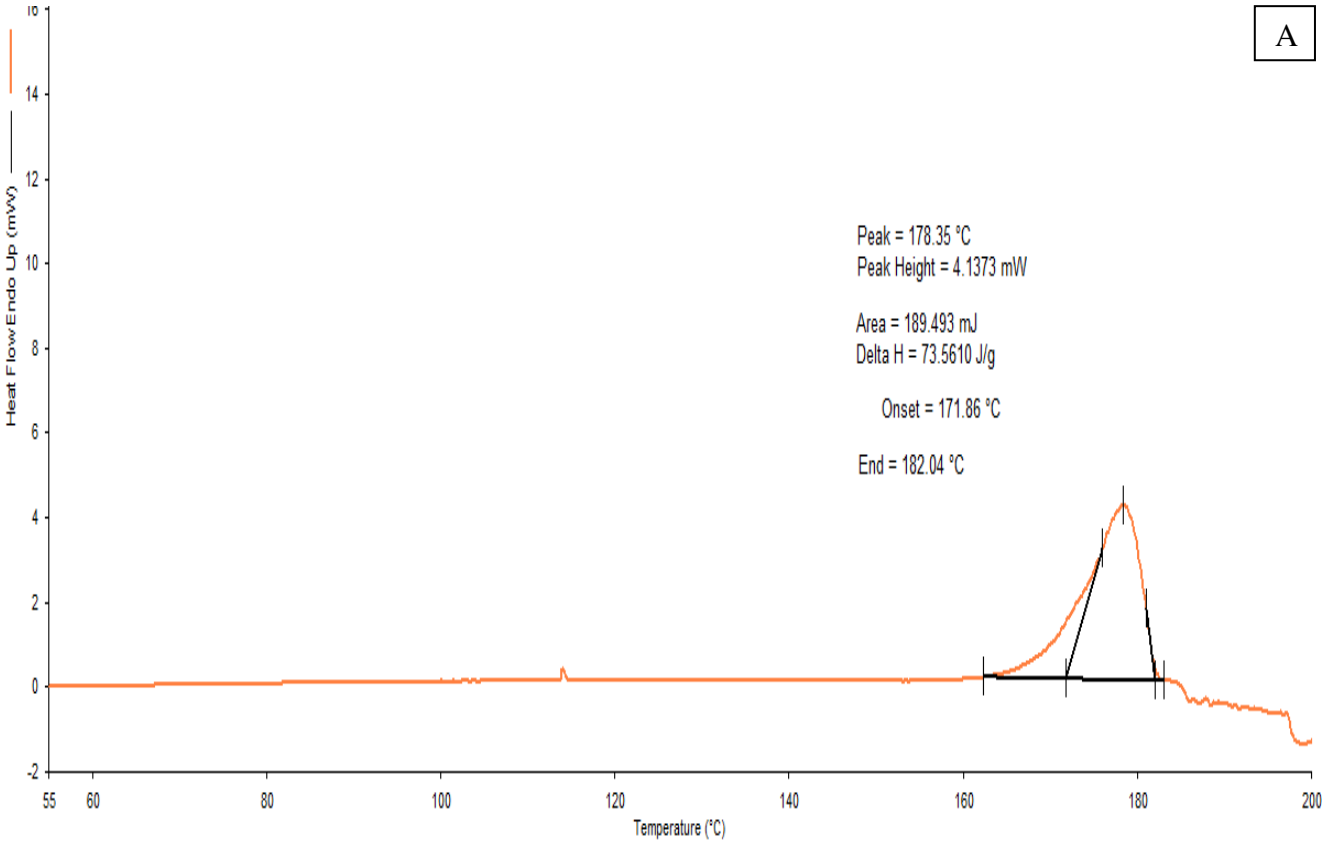


Figure-3
FTIR spectra of (A) Lercanidipine HCl (B) PEG 6000 (C) PEG6000 PM (D) PEG6000 SD



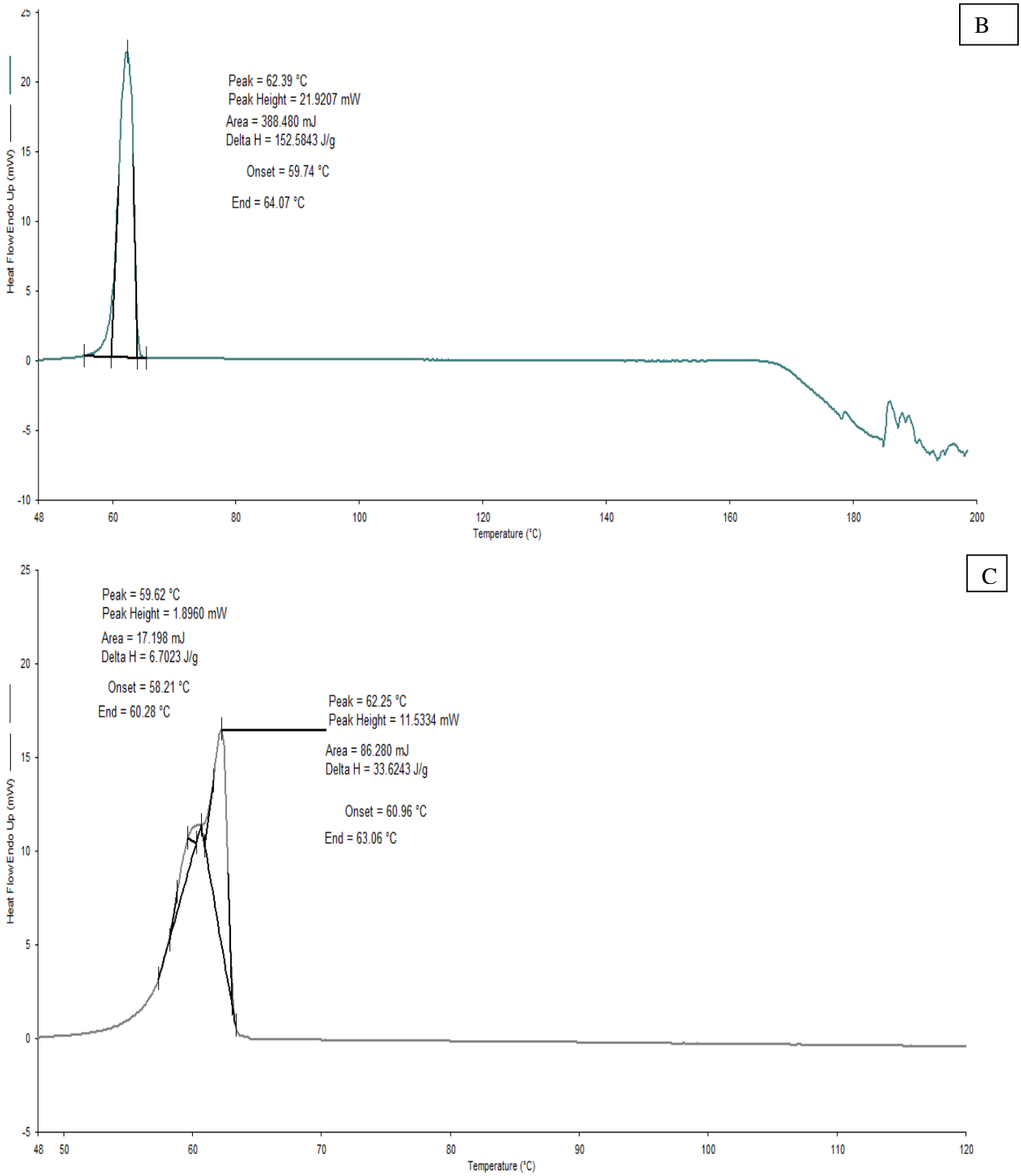


Figure-4
DSC Thermogram of A= pure lercanidipine HCl B= PEG6000 PM (1:6) C= PEG6000 SD (1:6)

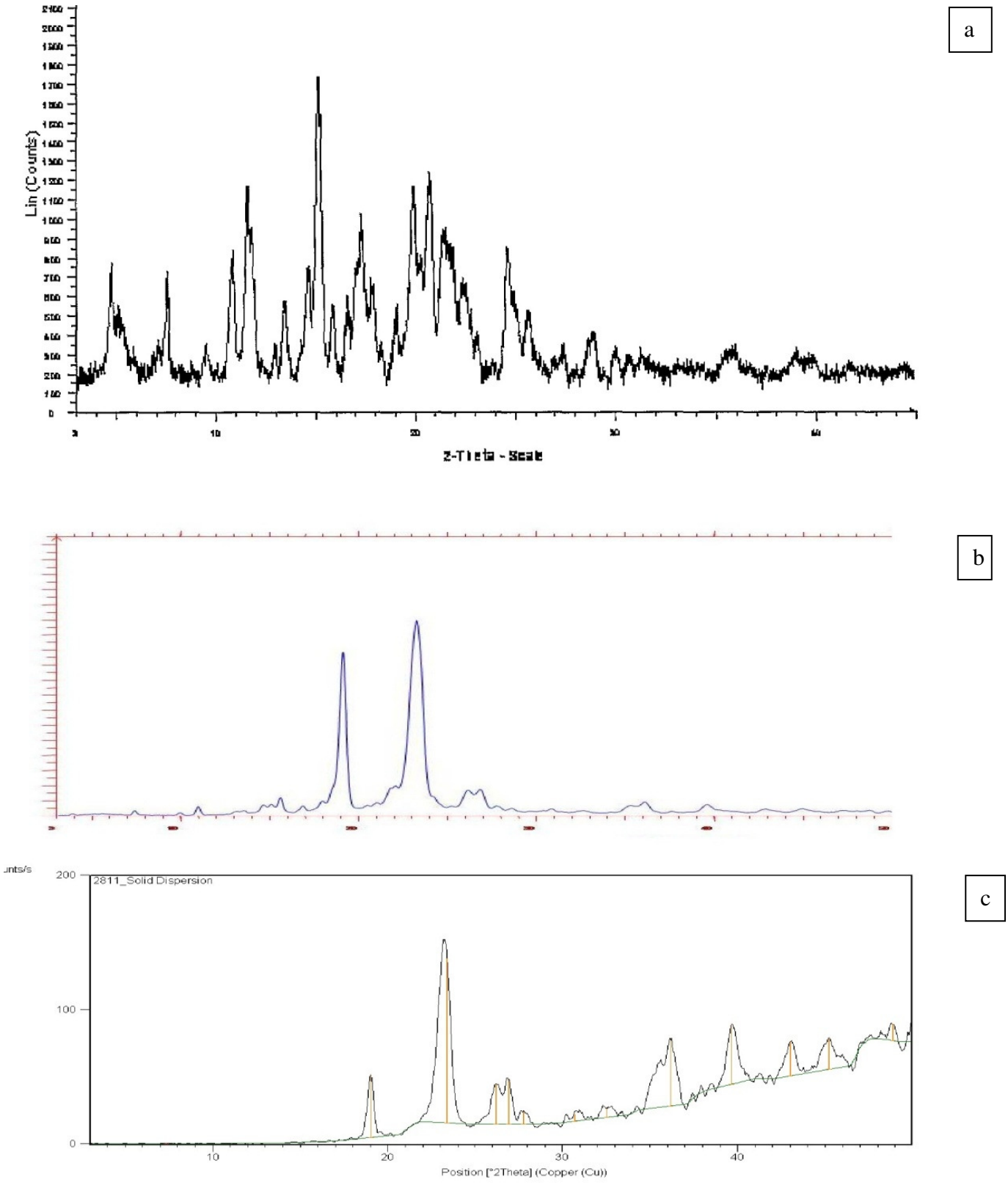


Figure-5
XRD spectra of (a) lercanidipine HCl (b) PEG 6000 (c) PEG6000 SD (1:6)

Conclusion

The current investigation established an effective and easy method to formulate lercanidipine HCl solid dispersion with PEG6000 to increase its water solubility and also its dissolution. Solid dispersions were prepared by solvent evaporation and melt fusion technique using different Drug: Polymer ratio. Out of all the solid dispersions, the one with drug to polymer ratio of 1:6 and prepared by solvent evaporation technique was proved to have the best results in terms of solubility and dissolution. Optimized solid dispersion showed increased dissolution of lercanidipine HCl up to 98% w/w after 60 min. FTIR spectral data of solid dispersion shows interaction between lercanidipine HCl and PEG6000, which confirms that the drug is dispersed at molecular level into polymer matrix. DSC measurement and XRD showed decrease in the crystallinity of drug when it is in solid dispersion. The results obtained confirm that solid dispersion in drug to polymer ratio of 1:6 and prepared by solvent evaporation method would improve the oral bioavailability of lercanidipine HCl. The rise in dissolution efficiency could give quick onset of action after oral administration of the lercanidipine HCl. In addition of improving bioavailability it would also facilitate quick onset of action hence improving patient compliance. This can serve as a novel approach for the treatment of cardiovascular diseases. Moreover, the scale-up of this formulation would be easy and can be extrapolated to commercialization.

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