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Formulation, Development, Evaluation and Solubility Enhancement of Lercanidipine Hydrochloride by Solid Dispersion Techniques

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: 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 carrier.
Aims and Objective: Evaluate the dissolution and solubility of Solid Dispersion of Lercanidipine Hydrochloride (LER).
Materials and Methods: To study the effect of polymer, dissolution and solubility studies were carried out. Solid state characterizations 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.
Results: The prepared solid dispersion exhibited 94% drug release at 30 minutes which is higher than both LER pure and LER MKT. Better dissolution characteristic of solid dispersion was confirmed by 9.86 min MDT and 63.12% DE_{30} which is higher than that of LER MKT (13.64 MDT, 46.92 % DE_{30}) Solid state characterization revealed that enhancement of dissolution is the result of conversion of crystalline form of LER to less crystalline and/or amorphous form.
Conclusion: Solid dispersion of LER can successfully be prepared with the PEG6000 in the ratio of 1:6 using solvent evaporation technique. It is a successful and easy approach for the increase in onset of action of drug after administration and facilitates treatment of cardiovascular diseases.

Keywords: Solid dispersion; dissolution; solubility; dispersion.

1. INTRODUCTION

BCS Class II drugs are the drugs having low water solubiliyity and high permeability. They suffer from poor bioavailability because of limited solubility. One of the challenging requests of drug development is to enhance the dissolution behavior of drugs that are sparingly soluble in water (BCS Class II) [1]. Dissolution of such drugs can be improved by improving solubility by preparing a formulation which allows faster drug dissolution as compared to its crystalline form [2]. Common method of improving bioavailability for the poorly soluble drugs is to prepare an amorphous formulation allowing faster drug dissolution in comparison to its corresponding crystalline form [3,4]. 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 carrier [5-7]. The solid dispersion technology adds the probability to reduce the particle size of a drug to a molecular level and increased wet ability. 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 [8]. 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 to undergo scale up and commercialization [9].

Various hydrophilic polymers have been used to successfully increase the solubility of poorly soluble drugs. Many Scientists have worked with different polymers such as Avicel 200 and Sylysia350 [10,11], TPGS1000andEudragitE100 [12], polyethylene glycol 6000 and Gelucire 44/14 [13,14], Solutol® HS15 and HPMC 2910 [15], HPMCAC [16] for successive formulation of solid dispersion of sparingly soluble drugs. The extent of improvement in solubility and dissolution depends on many factors *viz* choice of polymer, drug: polymer ratio, method of preparation etc. [17].

Lercanidipine Hydrochloride (LER) belongs to BSC class II compound [18] and has low aqueous solubility, resulting in low dissolution and poor oral bioavailability. The objective of this work was to increase the solubility and ultimately dissolution of LER by dispersing it in the polymer matrix of PEG6000 in different ratios using different techniques. To study the effect of polymer, dissolution and solubility studies were carried out. Solid state characterizations 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.

2. MATERIALS AND METHODS

2.1 Experimental Work

2.1.1 Preliminary studies

Successful solid dispersion can be prepared if the choice of hydrophilic polymer is appropriate to give best result in terms of solubility enhancement, stability and the physicochemical properties. Also the ratio of Drug to Hydrophilic polymer plays an important role in extent of solubility enhancement. To screen the hydrophilic polymers giving best result for solubility enhancement, solid dispersions of LER were prepared with different polymers *viz* PVP K30, Mannitol, PEG4000 and PEG6000. The selections of initial polymers were done on the basis of literature review. Solid dispersions were prepared by solvent evaporation and melt technique. Drug Release and Solubility in water was measured for all the solid dispersion to select the hydrophilic polymer giving best results for solubility and dissolution enhancement. Details of solid dispersion prepared with different polymers are given in Table 1.

2.1.2 Phase solubility study

Phase solubility studies were performed by Higuchi and Connors' method [19]. 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 PEG6000 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; 5mL of supernatant was withdrawn from each flask, filtered through Grade 1 What mann filter paper and evaluated by UV spectrophotometer at 236 nm. All the measurements were repeated for six times [20].

2.1.3 Gibb's Free Energy determination

The Gibbs free energy of transfer (ΔG°tr) of LER from aqueous solution of carriers was calculated using the following equation:

$$\Delta G^{\circ}_{tr} = -2.303\ RT \log \frac{S_0}{S_s}$$

Where,
S_0/S_s is the ratio of molar solubility of drug in aqueous solution of carrier to that in pure water [21].

2.1.4 Preparation of solid dispersion of LER

Solid dispersions of LER and PEG6000 in ratio of 1:3, 1:6 and 1:9 were prepared by solvent evaporation and melt fusion method.

2.1.5 Solvent evaporation method

The calculated quantities of LER and PEG6000 were accurately weighed and 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# sieves and preserved in desiccators until use [22,23]. A total of three batches (SF1 to SF3) were prepared by solvent evaporation method (Table 2).

2.2 Melt Method

Solid dispersions of LER with PEG6000 were prepared by melting the polymer at 60°C, succeeded by addition of required amount of drug. The molten 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 [24]. A total of three batches (MF1 to MF3) by melt method were prepared (Table 2).

2.2.1 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 2).

2.3 Evaluation of Solid Dispersions

2.3.1 Theoretical yield

Theoretical yield of solid dispersions prepared by various methods was calculated from the weight of final product after drying and the initial total weight of drug and polymer taken for preparation of solid dispersion. % Theoretical Yield was calculated from following equation.

$$\%\ \text{Theoretical Yield} = \frac{\text{Practical Weight}}{\text{Theoretical Weight}}\ \text{X}\ 100$$

2.3.2 Determination of LER in solid dispersion

Solid Dispersions equivalent to 10 mg of LER was accurately weighed and transfer to 100 mL volumetric flask. The solution was diluted up to the mark with methanol. Suitably diluted solution was measured Spectrophotometrically at 236 nm.

2.3.3 Saturation solubility study

A surplus LER was introduced in 25 mL capacity 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) [25]. Similarly saturation solubility was measured for physical mixtures and solid dispersions in distilled water. All measurements were performed in repetition(n=6).

2.3.4 *In vitro* dissolution study

Dissolution of LER pure, 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 [18].

The optimized solid dispersion with maximum drug release was compared with LER pure and marketed LER tablet (LER MKT)using validated dissolution method with 900 mL of 0.1 N HCl at 100 rpm using USP type I apparatus at 37±0.5°C.

2.3.5 Solid state characterization of solid dispersions

Solid state studies were carried out for LER, PEG6000, physical mixture and optimized batch of solid dispersion.

2.3.6 Fourier transform infrared (FTIR) 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 [26].

2.3.7 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 [12].

2.3.8 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 LER. 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 [15].

2.3.9 Stability study and photo stability study

To access the stability of prepared solid dispersion over storage, accelerated stability study was performed in accordance with ICH guidelines at 40º C/75% RH. Optimized solid dispersion was stored upto 6 months at the prescribed atmosphere. The samples were collected every 60days and were analysed for content and *in vitro* dissolution. The crystal structure of solid dispersion was confirmed by performing XRD studies of optimized solid dispersion after storage of 6 months. To evaluate photosensitivity of LER in the formulation, LER pure and optimized solid dispersion were subjected to sunlight and UV light both in solid state and solution state. The amount of drug remaining after periodical exposure was measured by HPLC method.

3. RESULTS AND DISCUSSION

3.1 Preliminary Studies

Preliminary studies for the selection of polymer was using four different polymers named Poly Vinyl Pyrrolidon K30 (PVP K30), Mannitol, Polly Ethylene Glycol 4000 (PEG4000) and Poly Ethylene Glycol 6000 (PEG6000). Two methods of preparation namely solvent evaporation and melt fusion were used to prepare solid dispersion in Drug: Polymer ratio of 1:1, 1:3 and 1:5. The results of solubility in water and release at 60 min in 0.1 N HCl is depicted in Table 3. All the solid dispersion showed better saturation solubility than the crystalline form of LER. However solid dispersion prepared with PEG6000 using melt technique in the ratio of 1:1 failed to increase the saturation solubility of LER. Table.3 also shows that the solubility of LER increase with increase in the polymer content of the solid dispersion. This perhaps because increase in the amount of hydrophilic polymer [27].

Fig. 4 shows the dissolution profiles comparison of LER pure and solid dispersion prepared form each of the four polymers. From the Fig. 1 (a), (b), (c) and (d) it can be concluded that PVP K30, Mannitol and PEG4000 showed better drug release at 30 minutes than the LER pure. It was seen that solid dispersion with PEG6000 showed not much release of LER from the formulation at 60 minutes with ratio less than 1:5. However SDP6S3 showed highest drug release amongst all the solid dispersion.

Comparison of the solid dispersions prepared with different polymer at same weight ratio is shown in Fig. 2B to select the amount of polymers that can be used for the preparation of solid dispersion. Fig. 2B (a) shows that the release obtained with the solid dispersion prepared with different polymers at the Drug: Polymer ratio 1:1 is almost same as that of the obtained with LER pure. Fig. 2 (b) and (c) shows increase in the dissolution of LER from the solid

dispersion obtained with Drug: Polymer ration of 1:3 and1:5. Release of LER from PVPK30, Mannitol and PEG4000 was high with increase in the polymer amount. PEG6000 in solid dispersion resulted into low release of LER from the solid dispersion when the ratio was 1:1 and 1:3. However with ratio 1:5 drastic initial increase in drug release was obtained. The result obtained suggests that PEG4000 and PEG6000 can give better results for solubility and in turn dissolution enhancement of the LER. Hence, further studies were targeted for the preparation of solid dispersion with PEG4000 and PEG6000.

For final selection of hydrophilic polymer, solid dispersions were prepared with PEG4000 and PEG6000 in different ratio. But the solid dispersion prepared by PEG4000 showed processing difficulties forming lumps and resulting in poor flow properties (Fig. 8). As a result final studies for solubility and dissolution enhancement of LER were done using PEG6000 as a hydrophilic polymer.

3.2 Preparation and Evaluation of Solid Dispersions of LER

Before actual preparation of solid dispersions, phase solubility study was performed to analyse the probability of solubility enhancement of LER in PEG6000.

3.3 Phase Solubility Study

Based on the results obtained from the preliminary studies, it was postulated that increase in the amount of PEG6000 in a solid dispersion can lead to further increase in the dissolution of LER. The effect of PEG6000 concentration on the solubility of LER in water at 37°C is depicted in Fig. 4. Increase in the release of LER from polymer mixture is attributed to the surface activity whereby wetting effect lead to decrease in agglomeration and increase in surface area [28]. When polymer molecules come in contact with water, they get hydrated rapidly to form polymer solution and the hydration leads to increase in wett ability of solid drug added to the polymer solution resulting in the local enhancement of solubility of LER at the diffusion layer. Increase in diffusion of drug to the medium shows increase in solubility of LER in presence of PEG6000 [29].The obtained phase solubility diagram shows the formation of a soluble complex. At concentrations of 4% w/v PEG6000, the solubility of LER was increased by 8.4 fold. The enhancement in solubility is the result of presence of soluble complexes.

3.4 Gibbs-free Energy ($\Delta G°_{tr}$) Determination

Gibbs-free energy is the indication of transfer of LER to aqueous solution of PEG6000. The obtained value of Gibb's free energy and stability constant is shown in Fig 4. Gibb's free energy is found to be negative for all the concentrations of PEG6000. Moreover, decrease in Gibb's free energy is observed as the concentration of PEG6000 is increased. All the observations collectively suggest that the reaction with PEG6000 is favourable for solubilisation of LER and reaction becomes more favourable as the concentration of PEG6000 was increased [21].

3.5 Saturation Solubility Measurements

The result of solubility measurement at saturation level for LER in various solvents is shown in Table 5. The LER solubility in water (37°±1°C) is 0.051±0.0023 mg/mL. The solubility values of LER 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 5. Solubility results depicts that solubility of LER was increased with the Drug: polymer ratio of 1:6. Below and above this ratio, solubility of LER did not show any appreciable increase.

3.6 *In vitro* Dissolution Study of Solid Dispersions Prepared with PEG6000

Dissolution profiles of LER, physical mixtures and solid dispersions with PEG6000 over a period of 60 min at 50 rpm in 0.1 N HCl are depicted in Fig. 5. The values of dissolution release of the same formulations are shown in Table 6 It is clearly observed that the rate of dissolution of LER pure is only 37.40% in 60 min. whereas; solid dispersions of LER with PEG6000 significantly enhanced the dissolution rate of LER (43- 96%) within 60 min as compared to LER pure and physical mixtures (30.05%). Effect of concentration of polymer played a vital role in the increase in dissolution of LER. As seen from the Fig. 5, increase in the amount of PEG6000 lead to increase in the release. For both type of solid dispersion prepared by solvent evaporation and melt fusion, higher drug release was achieved at 30 min compared to LER pure. However, the solid dispersion prepared by solvent evaporation method showed decline in the drug release when drug to polymer ration was changed from 1:6 to

1:9. This may be because of the firm adsorption of the drug on PEG6000, which hinders the dissolution of the drug [10]. In melt fusion technique, dissolution was increased in all the solid dispersions but the extent of release was not as high as F2 formulation. This concludes that the method of preparation of solid dispersion also played a major role in increasing the dissolution of the LER from polymer matrix. Solid dispersion with better properties can be obtained with the solvent evaporation technique. This can be due to many reasons such as incomplete miscibility of drug in highly viscous molten state of the PEG 6000 [30] and /or degradation of LER at melting temperature of PEG6000 [31]. Highest improvement was seen in solvent evaporated solid dispersion in the drug to polymer ratio of1:6.

The dissolution increase of LER and PEG6000 solid dispersion is attributed to several factors. The factors playing major role are decrease in crystallinity (or increase in amorphous structure), solubilisation property of PEG6000, absence of aggregation of drug crystallite, increased wettability and dispersibility of LER in PEG6000,reduction of interfacial tension, particle size reduction and improved polymer surface adsorption by drug molecules [13]. This in turn confirms the formation of surface solid dispersion. Final comparison of optimized solid dispersion was carried out with LER pure and LER marketed tablet using validated dissolution test procedure. The result of comparison is shown in Fig. 6. Corresponding data for the same is depicted in Table 6. The table also shows mean dissolution time (MDT) and dissolution efficiency (DE).

MDT obtained for optimized solid dispersion F_2 is lowest indicating that rapid release of LER is obtained from solid dispersion as compared to LER marketed tablet (MDT-13.64 min) and LER pure (MDT – 13.74 min). Also the Dissolution Efficiency of Solid dispersion was found to be 63.12 % which is higher than LER pure (28.52 %) and LER marketed tablet (46.92 %). Dissolution Efficiency thus obtained indicates that all the three dissolution profiles are different and the same is supported by calculation of similarity factor (f2) in model independent method which is not within 50-100 (Table 8).

3.7 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 (PEG6000 SD). Further solid state characterization was performed on the optimized solid dispersion in comparison with physical mixture of drug with PEG6000 (PEG6000 PM) in same ratio.

3.8 Fourier Transform Infrared Spectroscopy

LER has both proton donor and acceptor site which contributes in formation of H-bond. Similarly PEG6000 has capacity to donate or accept a proton via hydroxyl group and oxygen of ether groups [32]. In physical mixture of LER and PEG6000, presence of drug was confirmed by the appearance of peaks of corresponding to N–H at 3202.68 cm^{-1}, 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 LER at 1695 cm^{-1}. The FTIR studies prove that change in vibrational stretching takes place within the solid dispersions. FTIR spectrum of Solid Dispersion showed absence of characteristic peaks of LER which is attributed to the formation of solid solutions of the drug within PEG6000matrix. The FTIR studies exhibit compelling evidences of change in the vibrational stretching within the different dispersions. The missing distinctive peaks, for instance, between pure LER and LER in dispersions are attributed to the dispersion of the drug in the polymer Cavity [33].

3.9 Differential Scanning Calorimetry

The Differential Scanning Calorimetric (DSC) thermogram of LER, Physical mixture and optimized solid dispersion are shown in Fig. 8 The thermal behaviour of all the components in terms of peak point, peak height, peak area and heat of fusion is given in Table 9 In DSC thermo gram of LER, 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 peak corresponding to LER is absent. This suggests that a complete solution of LER has formed within the PEG6000 and conversion of physicals state of LER form crystalline to amorphous [13,32].

Solid dispersions showed almost the same thermal behaviour as their physical mixtures of the same composition except the slight change in PEG6000 melting. This change involved the small shoulder appearing before the melting

point of PEG6000. Also the onset of peak is shifted from 59.74°C to 58.21°C which might be the result of dispersion of drug into PEG6000 or residual moisture effect. Also as the literature suggests, PEG6000 exists in extended or folded form, the folded form of which gives rise to shoulder effect before the melting of extended form [34].

3.10 X Ray Diffraction

The XRD scan of LER pure, PEG6000, solid dispersions and physical mixtures are shown in Fig. 6A.9. The XRD behaviour of LER pure illustrated strong and sharp peaks at diffraction angle (2θ) of 7.0, 18.9, 23.1 and 24.9 outlining well defined crystal structure; Similarly PEG6000 showed two sharp peaks with the highest intensity at 2θ of 19.15 and 23.35. Solid dispersionin XRD pattern shows various speak but not at the diffraction angle of LER pure. The complete disappearance of the melting peak in DSC supports this finding suggesting that no crystal form of LER exists in the Solid dispersion prepared by solvent evaporation technique and with the Drug: Polymer ratio of 1:6. Decrease in the drug release in the solid dispersion prepared with the Drug:Polymer ratio of 1:9 might be due to altered crystalline behaviour of LER in solid dispersion with higher amount of PEG6000. The XRD studies confirm that upon preparation solid dispersion crystal behaviour or LER is lost and it is present in amorphous form which increased its solubility and dissolution [2,13,35].

3.11 Stability and Photostability Study

Based on the result obtained for solubility and *in vitro* dissolution, solid dispersion prepared with PEG 6000 in the ratio of 1:6 by freeze drying technique was selected a optimized and subjected to stability study. The % drug content and % cumulative drug release obtained after storage at 40º C /75% RH is shown in Table 10 and profile for the same is depicted in Fig.10

Drug content of solid dispersion was found to be in range of 97.10 to 98.4 after storage. Drug release after storage is also unaltered after storage. Similarity factor for all the duration studied for stability was in the range 50-100 indicating that the drug release pattern after stability is similar to the initial release. The results obtained for stability study indicates that the solid dispersion produced is stable for six months.

Table 1. Solid dispersion formulation of LER for screening of polymers

Batch Code	Polymer	Drug : Polymer Ratio	Preparation Technique
SDPS1		1:1	
SDPS2	PVP K30	1:3	
SDPS3		1:5	Solvent Evaporation
SDMS1		1:1	
SDMS2		1:3	
SDMS3		1:5	Solvent Evaporation
SDMM1		1:1	
SDMM2	Mannitol	1:3	
SDMM3		1:5	Melt Fusion
SDP4S1		1:1	
SDP4S2		1: 3	
SDP4S3		1:5	Solvent Evaporation
SDP4M1		1:1	
SDP4M2	PEG4000	1:3	
SDP4M3		1:5	Melt Fusion
SDP6S1		1:1	
SDP6S2		1:3	
SDP6S3		1:5	Solvent Evaporation
SDP6M1		1:1	
SDP6M2	PEG6000	1:3	
SDP6M3		1:5	Melt Fusion

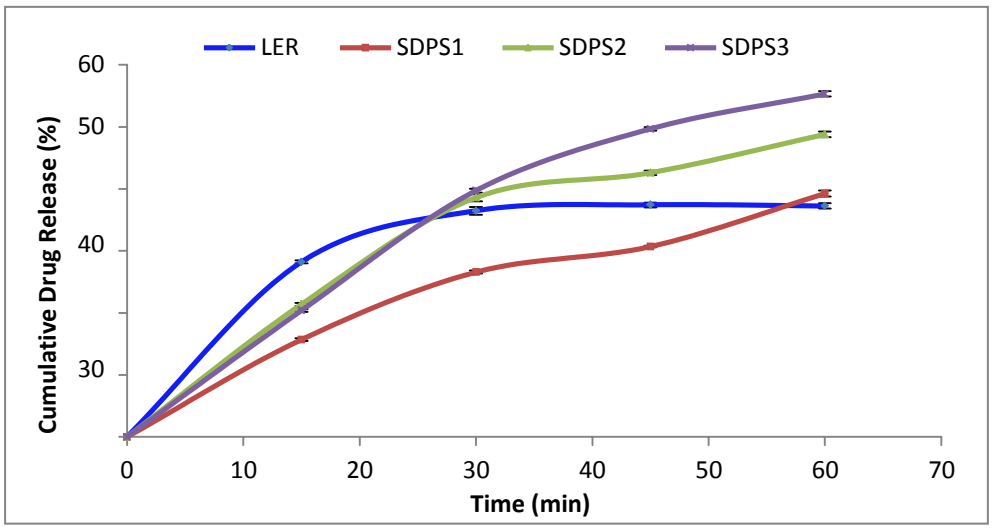


Fig. 1 (a). Dissolution profile of Solid Dispersions prepared withPVPK30

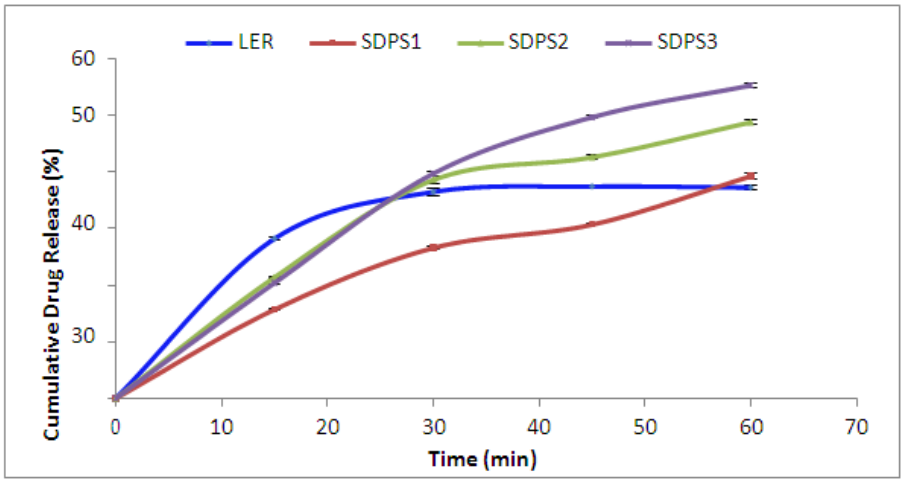


Fig. 1 (b). Dissolution profile of Solid Dispersions prepared with Mannitol

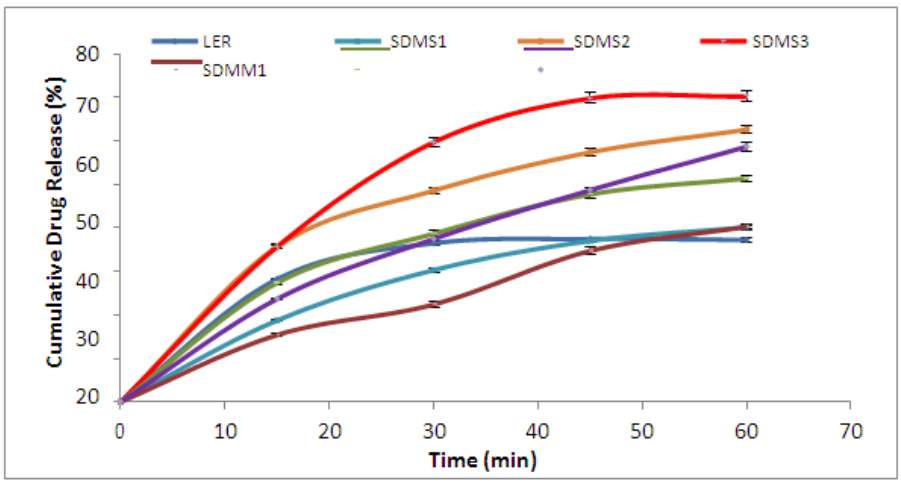


Fig. 1 (c). Dissolution profile of Solid Dispersions prepared withPEG4000

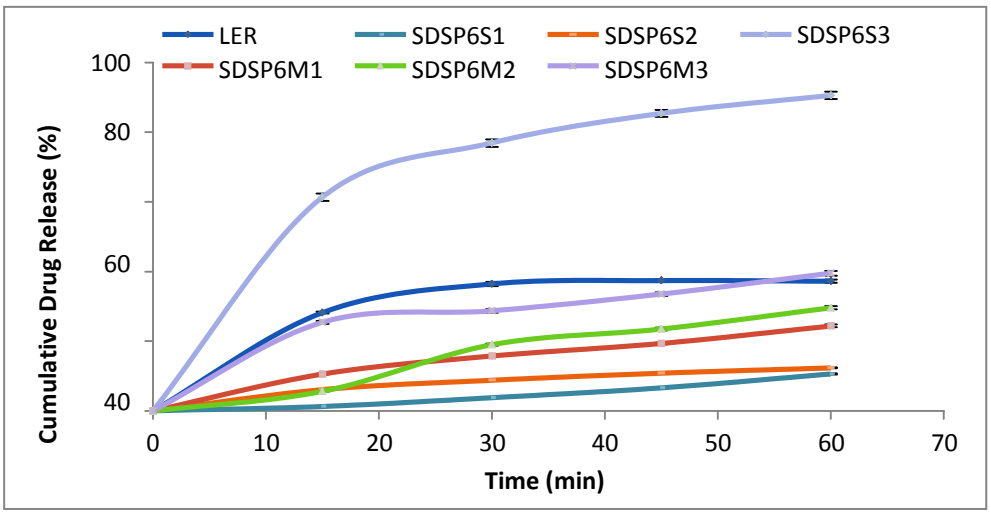


Fig. 1 (d). Dissolution profile of Solid Dispersions prepared withPEG6000

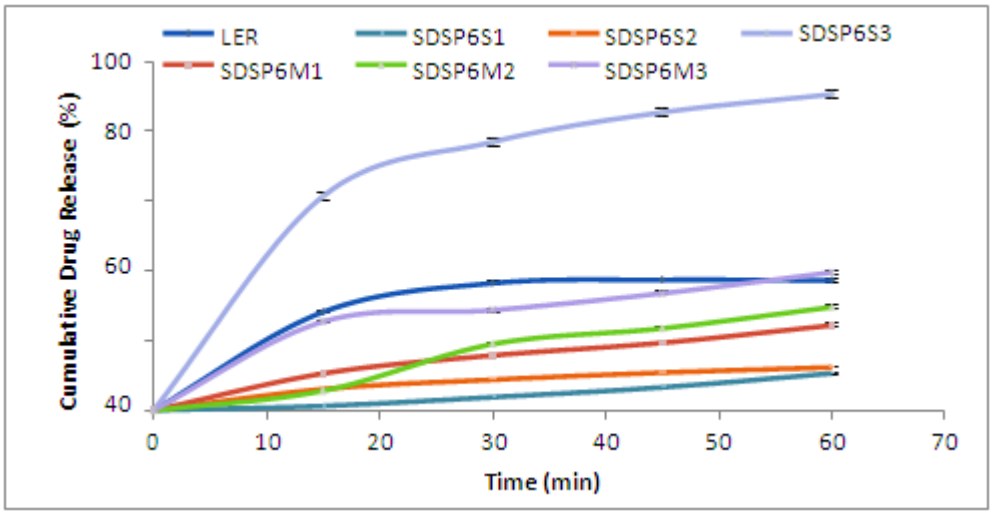


Fig. 2(a). Dissolution profiles of LER in 0.1 N HCl from solid dispersions prepared with different kinds of polymers in 1:1ratio

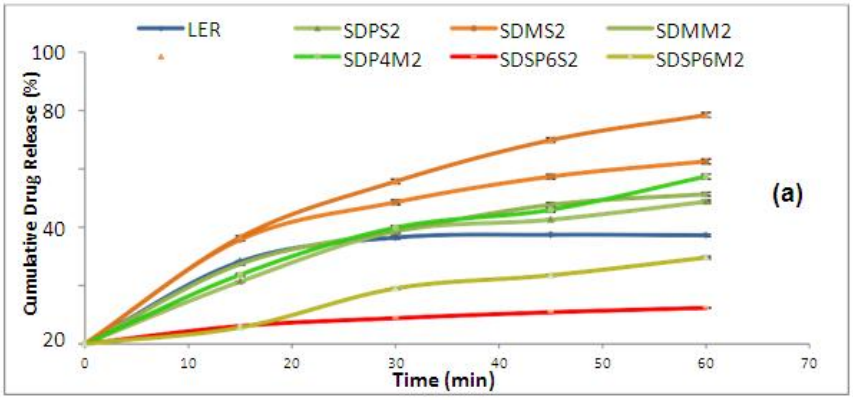


Fig. 2 (b). Dissolution profiles of LER in 0.1 N HCl from solid dispersionsprepared with different kinds of polymers in 1:3ratio

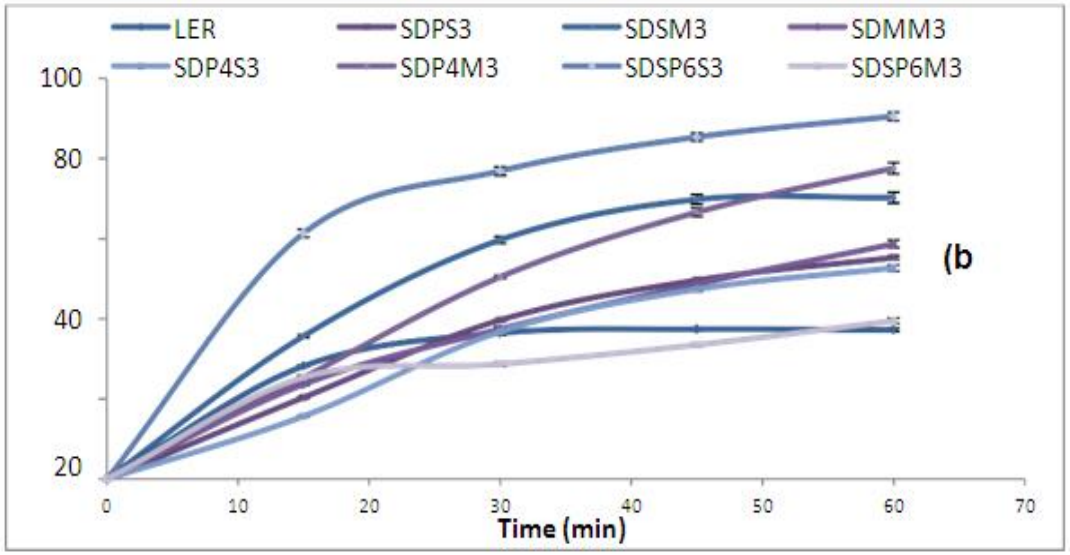


Fig. 2 (c). Dissolution profiles of LER in 0.1 N HCl from solid dispersions prepared with different kinds of polymers in 1:5

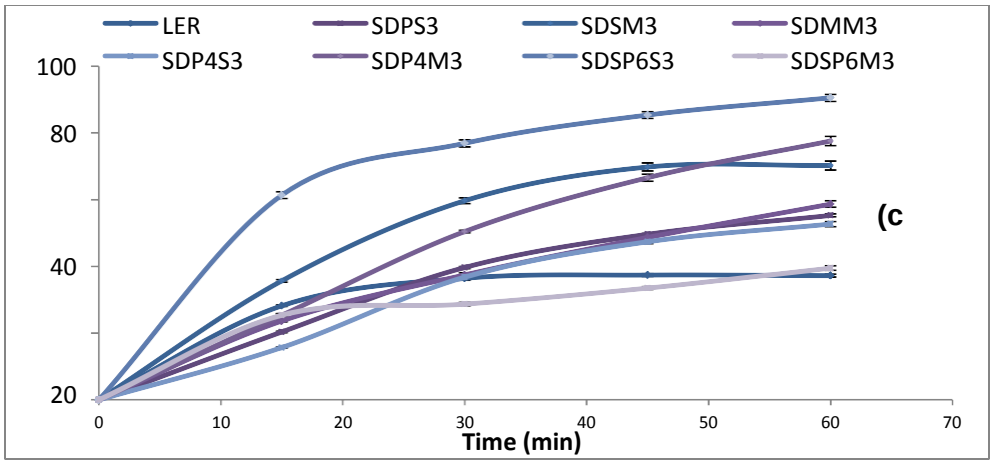


Fig. 3. Processing difficulties of Solid dispersion prepared with PEG4000

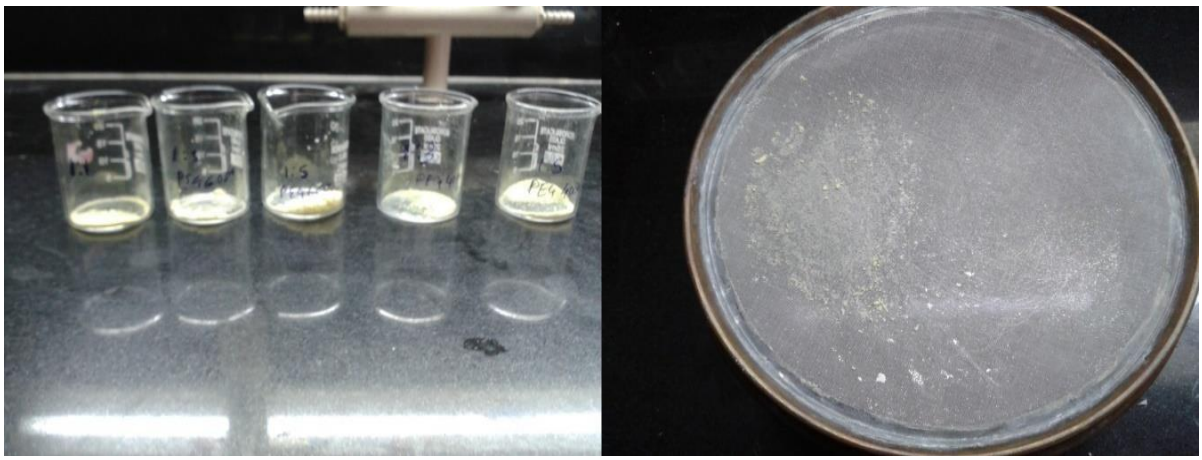


Fig. 4. Phase solubility study diagram of LER with PEG6000

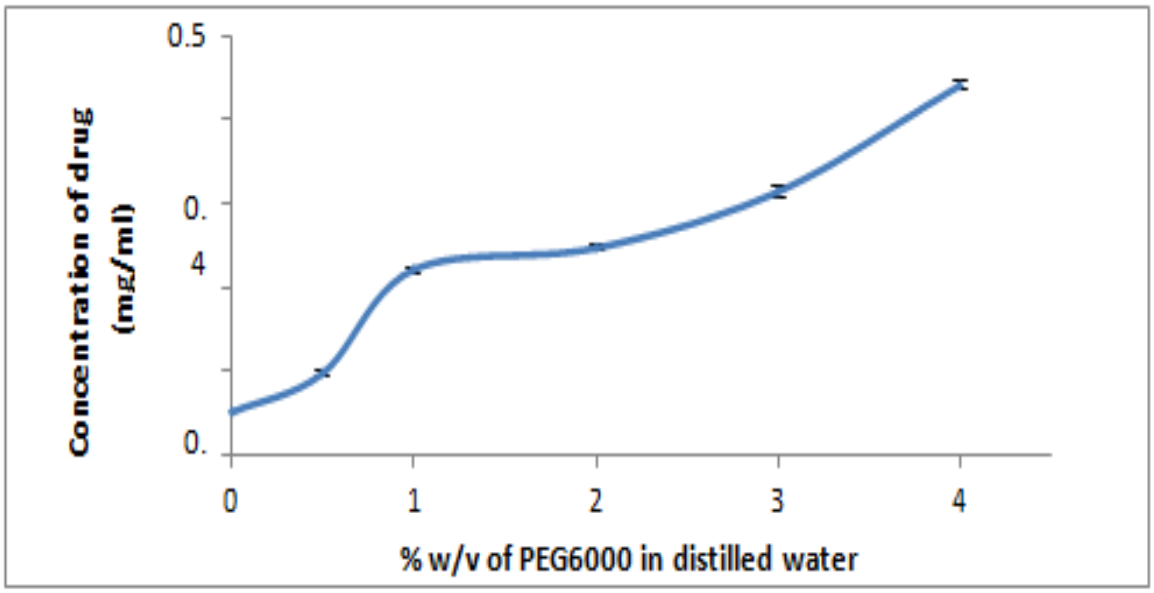


Fig. 5. Dissolution Profile of LER, Physical Mixtures and Solid Dispersions obtained with PEG6000 in 0.1 N HCl at 75 rpm

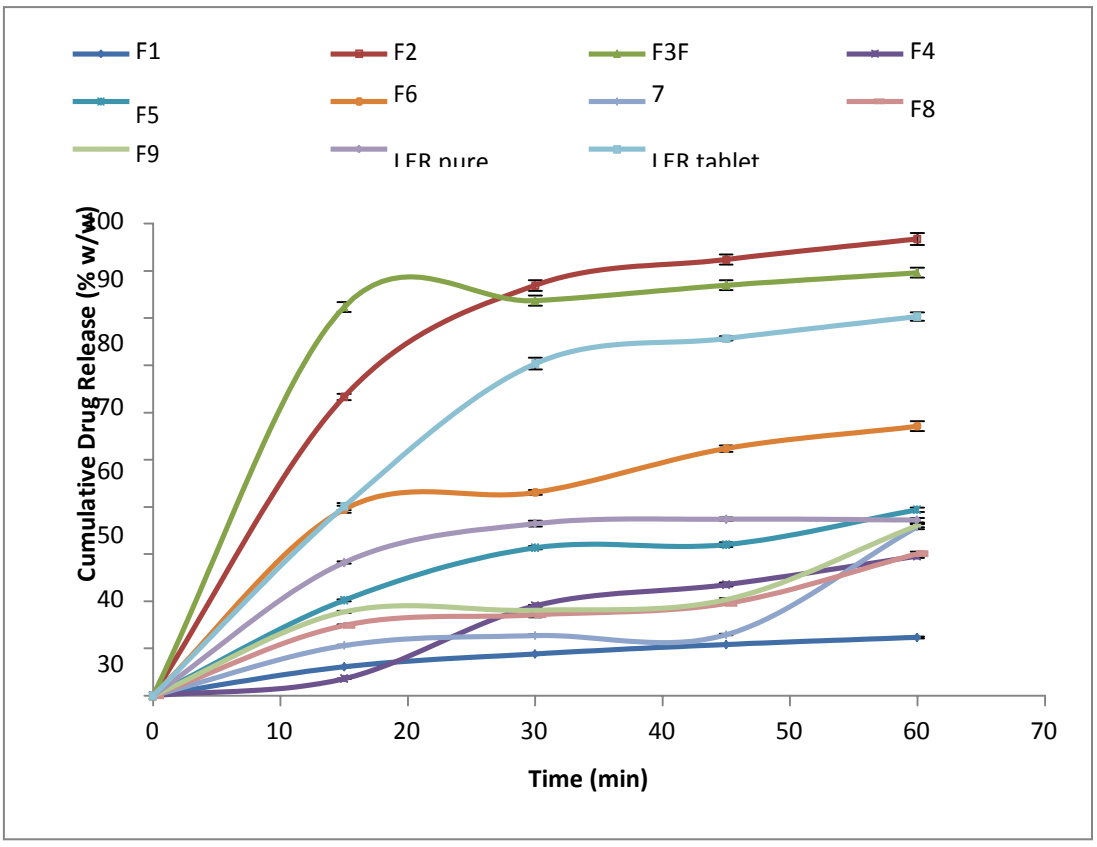


Fig. 6. Dissolution profile of Optimized Solid Dispersion (F2), LER pure and LER marketed tablet in 0.1 N HCl at 100 rpm

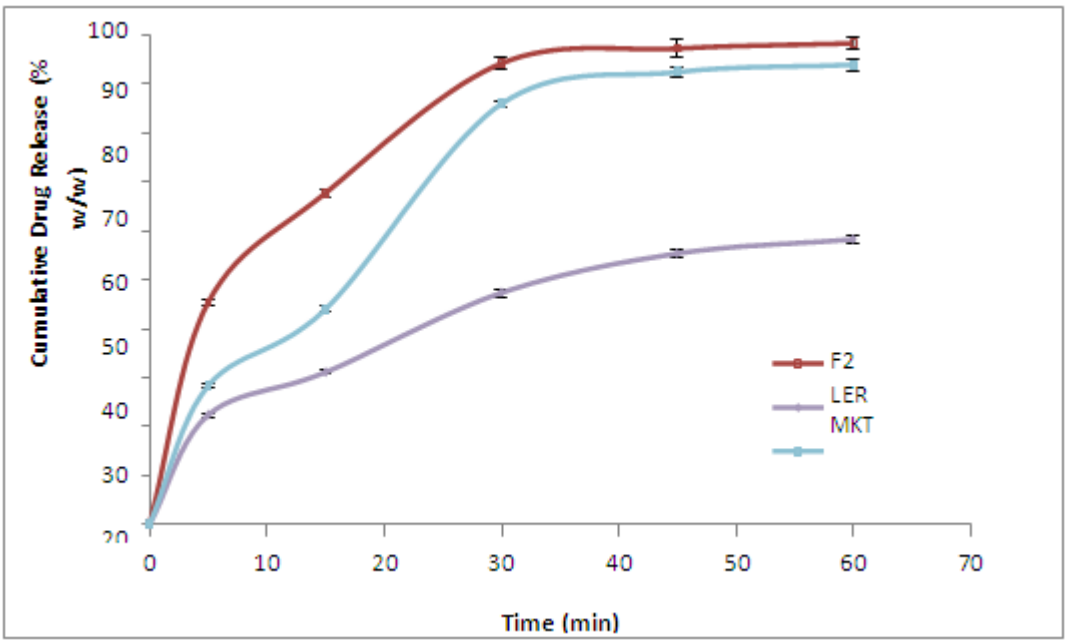


Fig. 7. FTIR spectra of (a) LER pure (b) PEG 6000 (c) Physical mixture of LER: PEG 6000 (1:6) and (d) Optimized Solid Dispersion (F_2)

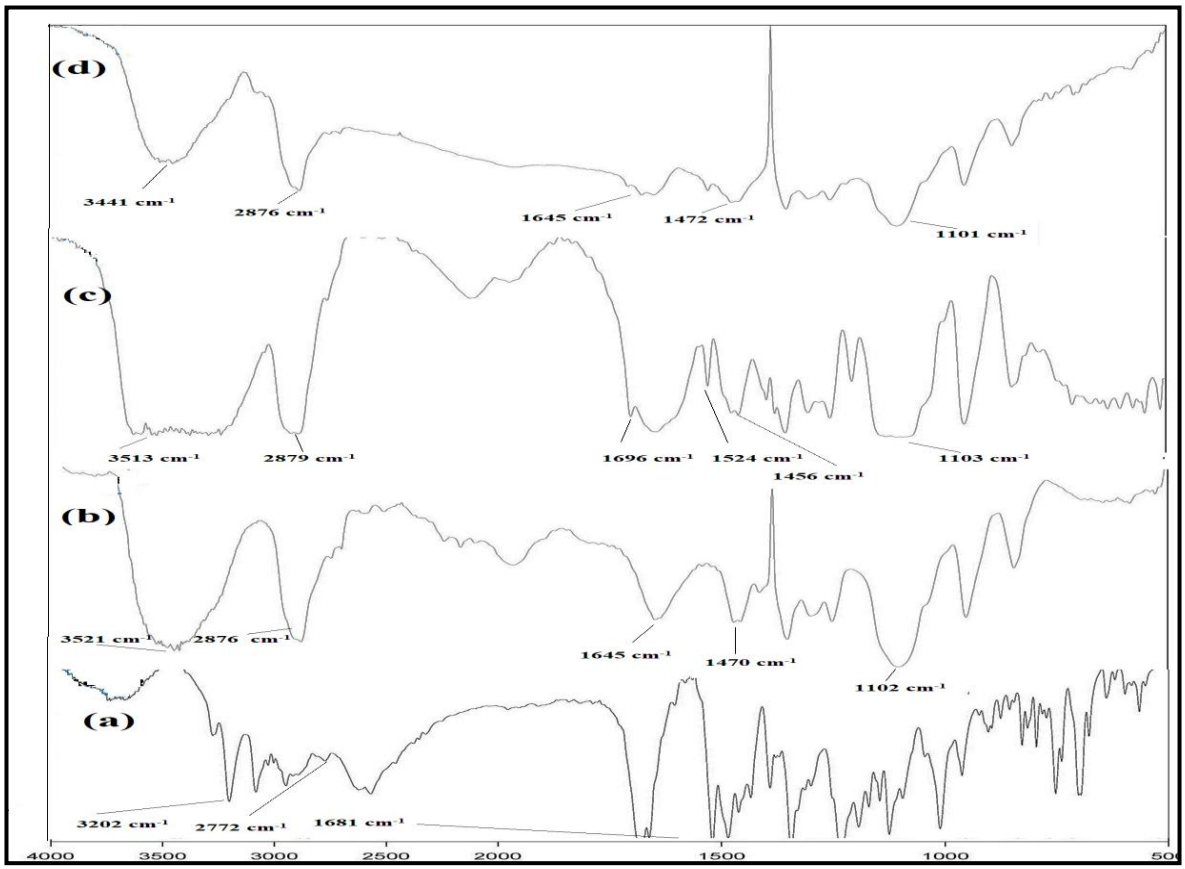


Fig. 8. DSC thermogram of (a) LER pure (b) Physical mixture (c) Optimized Solid Dispersion (F_2)

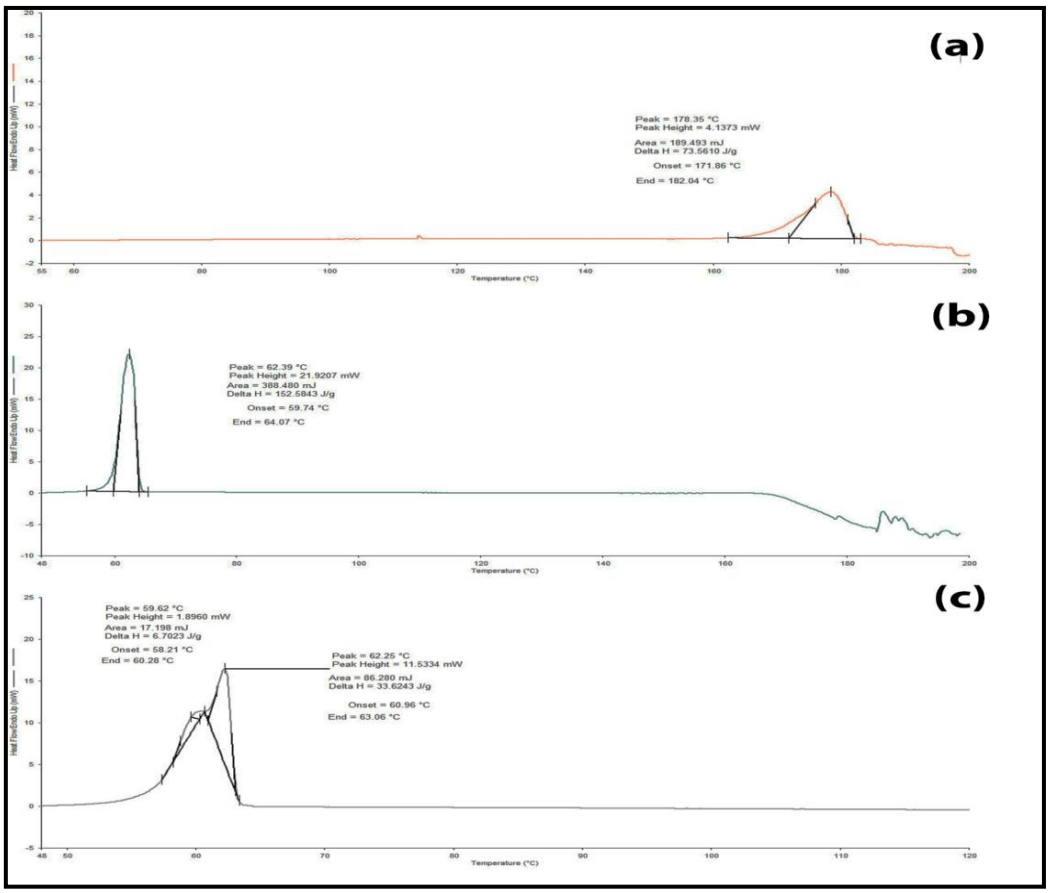


Fig. 9. Powdered X Ray diffraction patterns of (a) LER pure (b) PEG 6000 (c) Optimized Solid Dispersion (F2)

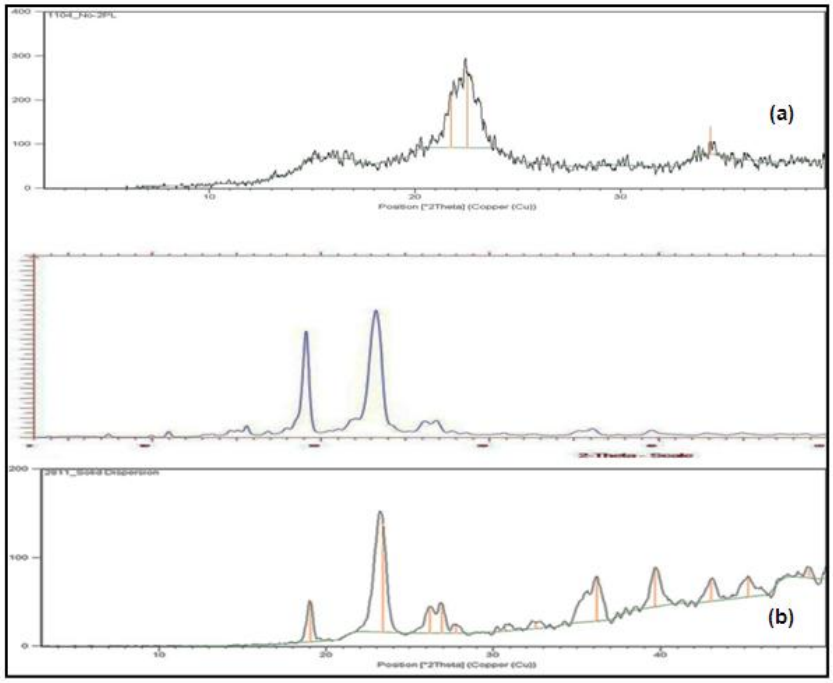


Fig. 10. Dissolution profile of optimized solid dispersion after stability study

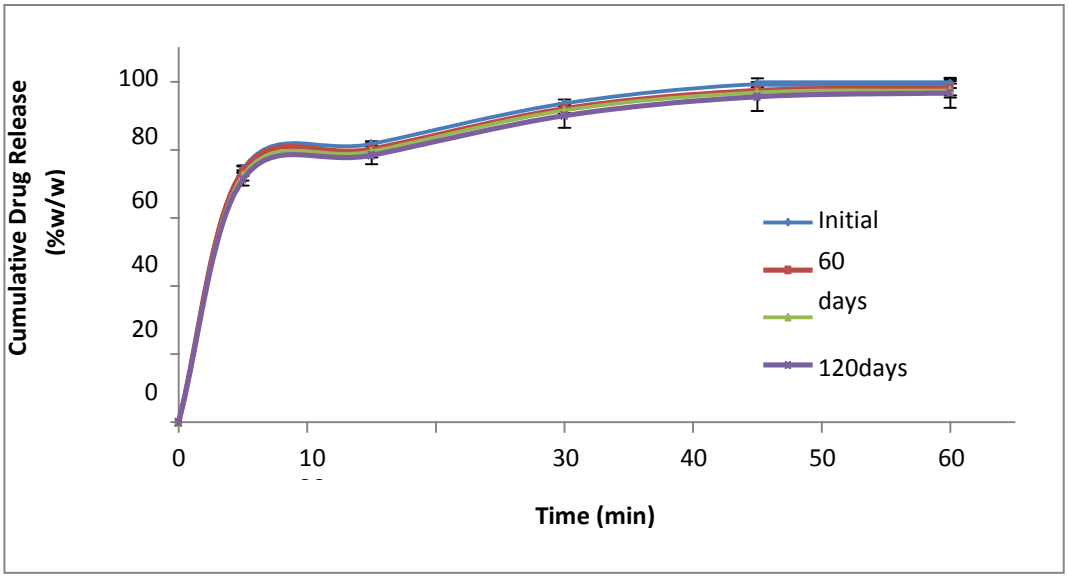


Fig. 11. Powdered X Ray diffraction patterns of Optimized solid dispersion of LER and PEG6000 (a) at zero time (b) after storage of 6 months

Table 2. Details of LER solid dispersion prepared by different composition with different Drug: Polymer ratio

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)	MeltMethod
F5	Drug: Polymer(1:6)	MeltMethod
F6	Drug: Polymer(1:9)	MeltMethod
F7	Drug: Polymer (1:3)	Physical Mixture
F8	Drug: Polymer(1:6)	Physical Mixture
F9	Drug: Polymer(1:9)	Physical Mixture

Table 3. Results of Preliminary Trials of Solid dispersions of LER

Batch Code	Polymer	Drug : Polymer Ratio	Preparation Technique	Solubility* (mg/mL)	Drug Release at 60 min*
LER	-	-	-	0.051±0.001	37.26±0.43
SDPS1		1:1		0.070±0.002	39.23±0.50
SDPS2	PVP K30	1:3		0.093±0.001	48.74±0.45
SDPS3		1:5	Solvent Evaporation	0.107±0.002	55.27±0.43
SDMS1		1:1		0.085± 0.002	40.13±0.43
SDMS2		1:3		0.097± 0.002	62.59±0.84
SDMS3		1:5	Solvent Evaporation	0.109±0.001	74.36±1.3
SDMM1		1:1		0.060±0.002	40.25±0.45
SDMM2	Mannitol	1:3		0.115±0.001	51.36±0.64
SDMM3		1:5	Melt Fusion	0.139±0.003	58.67±0.97
SDP4S1		1:1		0.058±0.001	42.56±0.74
SDP4S2		1:3		0.241±0.004	78.47±0.84
SDP4S3		1:5	Solvent Evaporation	0.097±0.001	52.69±0.78
SDP4M1		1:1		0.056±0.001	39.68±0.57

Batch Code	Polymer	Drug : Polymer Ratio	Preparation Technique	Solubility* (mg/mL)	Drug Release at 60 min*
SDP4M2	PEG4000	1:3		0.186±0.002	57.39±0.84
SDP4M3		1:5	Melt Fusion	0.114±0.002	77.59±1.4
SDP6S1		1:1		0.0.045±0.001	10.26±0.14
SDP6S2		1:3		0.064±0.005	12.34±0.19
SDP6S3		1:5	Solvent Evaporation	0.096±0.002	90.53±1.05
SDP6M1		1:1		0.015±0.0005	24.36±0.41
SDP6M2	PEG6000	1:3		0.030±0.0030	29.57±0.45
SDP6M3		1:5	Melt Fusion	0.048±0.0008	39.47±0.68

**Data Expressed as Mean ± SD (n=3)*

Table 4. Phase solubility and $\Delta G°_{tr}$ of LER at different concentrations of PEG6000*

Concentration of Polymer (% w/v)	Solubility of LER* (mg/mL)	$\Delta G°_{tr}$ (J K^{-1} mol^{-1})
0.5	0.0976±0.002	-1673.13
1	0.220±0.004	-3777.02
2	0.246±0.004	-4059.34
3	0.313±0.006	-4679.18
4	0.439±0.005	-5552.12
Stability Constant ($mL^{-1}mol$)	1245.42	
R^2	0.948	
Type of curve	A_L	

**Data expressed at Mean ± SD (n=3)*

Table 5. Saturation solubility data of LER solid dispersions and physical mixtures with PEG6000

S.N.	Formulation#	Solubility in mg/mL*
1.	F1	0.065±0.0006
2.	F2	0.330±0.0172
3.	F3	0.113±0.0121
4.	F4	0.029±0.0101
5.	F5	0.153±0.0153
6.	F6	0.051±0.0032
7.	F7	0.007±0.0014
8.	F8	0.009±0.0076
9.	F9	0.027±0.0070

**Data expressed at Mean ± SD (n=3), # Refer Table 6A.2 for Composition of formulation*

Table 6. Cumulative Drug Release of LER from Solid Dispersions prepared with PEG6000

Time	Cumulative Drug Release (% w/w)*			
Formulation	15	30	45	60
F1	6.10±0.09	8.82±0.15	10.82±0.09	12.34±0.19
F2	63.29±0.63	86.89±1.10	92.37±1.10	96.73±1.26
F3	82.34±1.04	83.68±1.05	86.94±1.02	89.59±1.05
F4	3.60±0.04	19.05±0.20	23.53±0.41	29.57±0.41
F5	20.21±0.22	31.33±0.33	32.01±0.50	39.38±0.45
F6	39.46±0.76	43.06±0.51	52.36±0.67	57.07±1.03
F7	10.62±0.19	12.74±0.25	12.91±0.14	35.79±0.25
F8	14.89±0.22	17.12±0.57	19.55±0.34	30.06±0.45
F9	17.74±0.21	18.10±0.32	20.36±0.27	36.05±0.43
LER pure	28.2±0.24	36.45±0.61	37.40±0.37	37.21±0.43
LER TAB	40.06±0.65	70.33±0.81	75.66±0.81	80.33±0.84

**Data expressed at Mean ± SD (n=3)*

Table 7. *In vitro* release data of F_2, LER MKT and LER pure in 0.1 N HCl at 100 rpm

Time (min)	F_2 *	LER MKT *	LER Pure *
0	0	0	0
5	45.36±0.78	28.36±0.48	22.36±0.42
15	67.72±0.84	44±0.71	31.1±0.37
30	94.26 ±1.22	86±0.57	47.35±0.83
45	97.28±1.79	92.51±1.08	55.39±0.81
60	98.34±1.29	94.01±1.23	58.27±0.91
MDT (min)	9.86	13.64	13.74
DE_{30} (%)	63.12	46.92	28.52

**Data expressed at Mean ± SD (n=3)*

Table 8. Comparison of Dissolution profiles of optimized solid dispersion with LER MKT and LER pure

Comparison	Similarity Factor	Dissolution Profile
LER Pure and F_2	22.91	Dissimilar
Marketed tablet formulation and F_2	44.98	Dissimilar

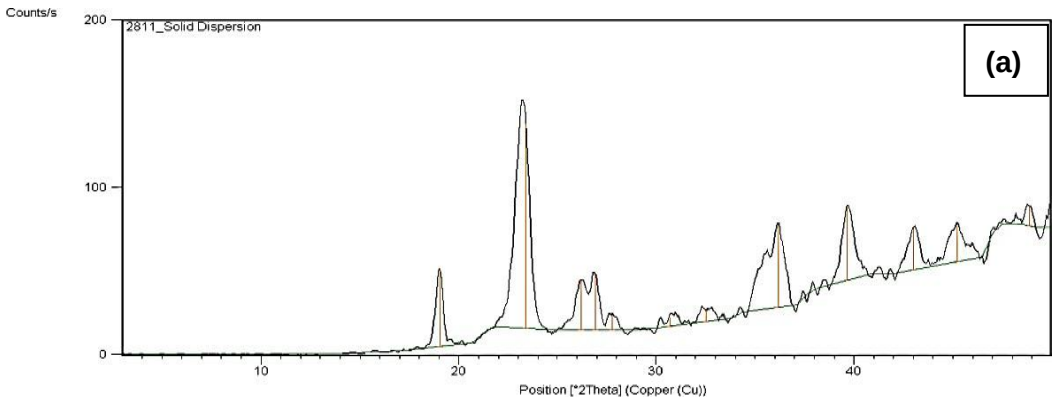
Table 9. Thermal behaviour of DSC Thermogram of LER pure, PEG6000, Physical Mixture and Optimized Solid dispersion (F_2)

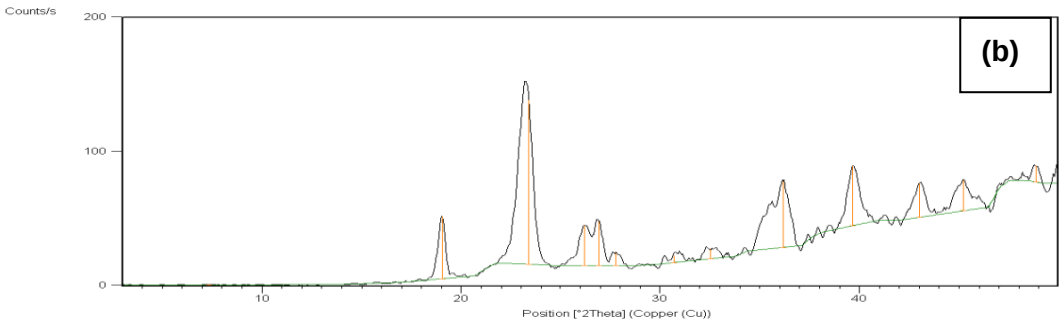
System	Peak point °C	Peak height (mW)	Peak area (mJ)	Heat of fusion (J/g)
LER pure	178.35	4.1373	189.493	73.56
PEG6000 PM (1:6)	62.39	21.91	388.439	152.5683
PEG6000 SD (1:6)	62.25	11.53	86.278	33.62

Table 10. Drug content and *in vitro* dissolution stability data of optimized solid dispersion after storage at 40º C /75% RH

Time (min)	Cumulative Drug Release*			
	Initial	60 days	120 days	180 days
5	45.36±0.78	44.69±1.21	43.65±1.58	41.78±1.87
15	67.72±0.84	66.89±1.14	65.62±2.15	63.40±2.69
30	94.26±1.22	92.81±0.97	91.25±1.97	90.10±3.64
45	97.28±1.79	95.62±1.25	93.12±1.34	93.02±4.21
60	98.34±1.29	96.36±1.87	94.75±2.5	91.37±4.44
Similarity factor between initial release and release after stability	-	94.46 Similar	76.95 Similar	67.15 Similar
Drug Content (%w/w)	98.6±0.5	98.4±0.7	97.7±1.2	97.10±0.9

**Data expressed at Mean ± SD (n=3)*





The solid dispersion of Lercanidipine hydrochloride prepared by solvent evaporation using PEG6000 in ratio of 1:6 has influence on the crystallinity of the drug. As a result of molecular dispersion of Lercanidipine hydrochloride in the PEG6000, the crystalline form of Lercanidipine hydrochloride is converted to its less crystalline form as supported by references [36-38]. Literature suggests that upon storage of the solid dispersion prepared with PEG6000, slight increase in crystallinity can be observed [39]. However, the crystalline form of optimized solid dispersion is not altered upon storage of 6 months as indicated by XRD pattern obtained for the same (Fig. 10). The XRD pattern obtained after storage of 6 month is same as that obtained of freshly prepared solid dispersion suggesting that the crystalline form of Lercanidipine hydrochloride is not changed and hence no change in physicochemical properties is observed upon storage. Photostability studies depicted major effect of UV light on solid state of LER and its formulation while solution state was more sensitive to sunlight. Results of photostability confirmed the reported photostability issue of LER and hence all the experiments were conducted in the amber colored glass apparatus.

4. CONCLUSION

The results obtained from present study projects that solid dispersion of LER can successfully be prepared with the PEG6000 in the ratio of 1:6 using solvent evaporation technique. The solid dispersion can be administered 70-140 mg/day once daily equivalent to 10-20 mg/day of Lercanidipine for effective antihypertensive effect. The prepared solid dispersion exhibited 94 % drug release at 30 minutes which is higher than both LER pure and LER MKT. Better dissolution characteristic of solid dispersion was confirmed by 9.86 min MDT and 63.12 $\%DE_{30}$ which is higher than that of LER MKT (13.64 MDT, 46.92% DE_{30}) Solid state characterization revealed that enhancement of dissolution is the result of conversion of crystalline form of LER to less crystalline and/or amorphous form. As the nature of PEG6000 is sticky, compression of solid dispersion to tablet was avoided and optimized formulation equivalent to 10 mg of LER was filled in capsule shells for administration and *in vitro* dissolution studies. From all these it can be concluded that this can serve as a successful and easy approach for the increase in onset of action of drug after administration and facilitates treatment of cardiovascular diseases. Moreover, the scale-up of this formulation would be easy and can be extrapolated to commercialization.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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