

Enhancement of wettability and *in vitro* dissolution properties of lercanidipine hydrochloride by solid dispersion technique

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Abstract:

The aim of the present study was to improve lercanidipine HCl solubility and *in vitro* dissolution rate by preparing solid dispersion with polyethylene glycol (PEG) 6000 using the solvent evaporation technique. Solid dispersions with PEG 6000 (as carriers) were prepared in drug: carrier (1:1, 1:5 and 1:10) ratios along with the corresponding physical mixtures. Analytical techniques, FT-IR spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were used to characterize the drug in the physical mixtures and solid dispersions. The solubility and wettability studies of solid dispersions as well as physical mixtures showed greater improvement compared to the pure drug. Higher *in vitro* dissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. Solid dispersion in 1:10 drug to carrier ratio exhibited the highest drug release (100.2%) in comparison with solid dispersion in 1:5 drug to carrier ratio (85.25% drug release), whereas there was no significant improvement in dissolution of solid dispersion in 1:1 drug to carrier ratio in comparison with its physical mixture. The FT-IR spectra suggested that there was no interaction between lercanidipine HCl and PEG 6000 when prepared as a solid dispersion. No representative DSC peaks for drug were observed for solid dispersion indicating the transformation of crystalline structure of lercanidipine HCl. The absence of XRD peaks of the drug in solid dispersion demonstrated that drug was present in amorphous structure suggesting the transformation of crystalline form of lercanidipine HCl to amorphous form. This polymorphic transformation contributes to faster dissolution rate of solid. The dissolution efficiency values for pure drug and solid dispersion compared also support this aspect.

Keywords: Solid dispersion; Amorphization; Saturation solubility; PEG 6000; Lercanidipine HCl

Introduction

Lercanidipine hydrochloride is chemically 2-[(3,3-diphenyl propyl) methylamine]-1,1-dimethylethylmethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5 pyridine carboxylic ester hydrochloride. Lercanidipine is an antagonist of type-L calcium channels, due to its selectivity and specificity on the smooth vascular cells; it is the very active antihypertensive and thus useful agent for the treatment of angina and coronary diseases. [1, 2]. Owing to the lipophilic character of such compounds, considerable concentration occurs in lipid-containing membrane depots and slowly released from these depots to reach their L-type calcium channel's targets. This phenomenon explains both slower onset and longer duration of action against the drug. The pharmacokinetics of lercanidipine is unique in comparison to other dihydropyridines. The drug is administered orally at a dose of 10-20 mg daily as its hydrochloride salt, reducing significantly the diastolic blood pressure [3]. After oral administration, lercanidipine HCl is completely and erratically absorbed from the upper gastrointestinal. However, absolute bioavailability is reduced to approximately 10% because of extensive first-pass metabolism to inactive metabolites. The literature suggested that mean plasma half-life of lercanidipine HCl is 2.8 and 4.4 hours in humans after a single dose of 10 and 20 mg respectively [4]. Lercanidipine shows polymorphism and available as amorphous forms, several crystalline forms and both mixture of crystalline forms with amorphous forms [5]. The polymorph of the lercanidipine in a dosage form may play a significant role; it may turn to influence its pharmacokinetic properties such as solubility, dissolution, etc. and thus influence absorption and subsequently therapeutic effect [6, 7]. In such cases it is very important that the polymorphic form of the lercanidipine remains constant during the process of preparing formulation and its shelf life in order to ensure the consistent therapeutic activity of the drug. Lercanidipine and its salts are practically insoluble in water and show low permeability and high first-pass metabolism resulting in low and highly variable bioavailability; this is creating a challenge to develop immediate release composition

for lercanidipine. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods [8-12]. Solid dispersion is one of the effective and widely used techniques for dissolution enhancement. The two basic procedures used to prepare solid dispersions are the melting or fusion and solvent evaporation techniques. The increase in dissolution rate for solid dispersions can be attributed to a number of factors [13], which include reduction in particle size, absence of aggregation or agglomeration of fine crystallites of the drug, the possible solubilization effect in the polymer, excellent wettability and dispersability of the drug from solid dispersion and conversion of the drug into its amorphous form. Polyethylene glycol (PEG 6000) is used in the preparation of solid dispersions. A particular advantage of PEG 6000 for the formation of solid dispersions is that they have good solubility in many organic solvents. The melting point of PEG 6000 lies below 65°C [14], which is advantageous for the manufacture of solid dispersions. Additional attractive features of PEG 6000 include their ability to solubilize and improve compound's wettability [15, 16]. Therefore, in the present study, PEG 6000 was chosen as a suitable polymer for the preparation of solid dispersions.

Materials and Methods

Lercanidipine hydrochloride was a generous gift from Torrent Pharmaceuticals, Ahmadabad (India). Polyethylene glycol 6000 was from Alkem labs (India). Ethanol was purchased from Rankem, (India). All other reagents were of analytical grade. Double distilled water was freshly prepared whenever required throughout the study.

Preparation of solid dispersion and physical mixtures

Solid dispersions prepared by solvent evaporation technique

Solid dispersions (SDs) of lercanidipine HCl with three different mass ratios (1:1, 1:5 and 1:10) of PEG 6000 were prepared by solvent evaporation technique [16]; weight amount of PEG 6000 was dissolved in ethanol followed by the drug. The resulting solution was afterwards homogenized thoroughly and then solvent

was evaporated at reduced pressure at 40°C in rotary evaporator (Sabar Scientific, India). The dried mass obtained was kept in the oven at 40°C for 24 h for complete removal of solvent. The prepared solid dispersions at different mass ratios (denoted as SDDPEG 1/1, SDDPEG 1/5 and SDDPEG 1/10 respectively) were then ground, sieved through a #100 sieve and stored under desiccator until further use.

Physical mixtures

Physical mixtures (PMs) of lercanidipine HCl with three different mass ratios (1:1, 1:5 and 1:10), were prepared by thoroughly mixing appropriate amounts of lercanidipine HCl and PEG 6000 in a glass mortar by light trituration until a homogeneous mixture was obtained. The resulting mixtures were sieved through a #100 sieve (denoted as PMDPEG 1/1, PMDPEG 1/5 and PMDPEG 1/10, respectively). The prepared mixtures were then filled-in glass bottles, sealed and stored in a desiccator until further use.

Saturation solubility study

Solubility studies were performed according to the method reported by Higuchi and Connors [17]. Lercanidipine HCl pure drug, its physical mixtures and solid dispersions in amounts that exceeded its solubility, were transferred to screw-capped vials containing 20 ml water, pH 1.2 buffer and pH 6.8 phosphate buffer solutions. The contents were stirred on an electromagnetic stirrer (Remi, India) at 21°C for 48 h and 100 rpm. This duration was previously tested to be sufficient to reach equilibrium, after that no improvement in solubility was observed. After reaching equilibrium, samples were filtered through a 0.45 µm membrane filter (Millipore India), (suitably diluted if needed) and analyzed for drug content at the λ_{max} of 241.5 nm using a spectrophotometer (Shimadzu-1601, UV-Vis spectrophotometer, Shimadzu Corp, Kyoto, Japan). All experiments were performed in triplicate.

Determination of percent yield

The percent yield of lercanidipine HCl solid dispersions was determined by using the following formula:

$$\text{Percent Yield} = \frac{\text{Weight of prepared solid dispersion}}{\text{Weight of drug + Carriers}} \times 100 \quad (1)$$

Determination of percent drug content

Solid dispersions of lercanidipine HCl (equivalent to 10 mg of drug) were placed in 25 ml volumetric flask. Ethanol (15 ml) was added, mixed thoroughly using a rotating shaker for 1 h. The volume was made up to the mark with ethanol. The solution was suitably diluted with ethanol and spectrophotometrically assayed for drug content at 241.5 nm using the following formula:

$$\text{Percent drug content} = \frac{\text{Practical drug content in solid dispersion}}{\text{Theoretical drug content in solid dispersion}} \times 100 \quad (2)$$

Characterization of solid dispersion

Infrared (IR) spectroscopic analysis

FTIR spectra of moisture-free powdered samples of lercanidipine HCl and its PMs and SDs were obtained using a spectrometer FTIR-8300, Shimadzu Co., Kyoto, Japan) by potassium bromide (KBr) pellet method. For the production of KBr compacts approximately 2 mg sample was powdered with 200 mg of KBr. The spectra were recorded in transmission mode. The scanning range was 400-4500 cm^{-1} , and the resolution was 1 cm^{-1} .

X-ray diffraction (XRD) analysis

The X-Ray diffraction of lercanidipine HCl in the various preparations was measured by X-ray diffractometer equipped with CuKa-radiation (40 kV, 40 mA) in wide angle x-ray diffractometer of BRUKER axs, D8 ADVANCE. The sample was analysed by using the following parameter: measuring range of 4-60° 2theta; step with 0.01579°; and measuring time per step 0.11 sec.

Differential scanning calorimetry (DSC) analysis

DSC measurements of all powdered samples were performed with a differential scanning calorimetry (DSC Q1000, TA Instruments, New Castle, Delaware, USA) at the scan rate of 10°C per minute and nitrogen gas purge at 50 ml/min. The instrument was calibrated for temperature and heat flow using pure water and indium as primary standard to calibrate the DSC temperature scale and enthalpy response as standard. All samples were weighed (8-10 mg) and encapsulated into close aluminium pans subsequently crimped to

ensure a tight seal. Data's acquisition and analysis were performed using universal analysis 2000 software (TA Instrument).

Wettability and dissolution studies

A wettability study was performed using open tubes containing lercanidipine HCl and its PMs and SDs with PEG 6000; these were placed with their lower capillary ends dipped into colored water (0.01% eosin in water). The upward migration of the colored front was registered as a function of time [18]. Dissolution studies of lercanidipine HCl in powder form and its PMs and SDs with PEG 6000 were performed to evaluate *in vitro* drug release profile. Dissolution studies were performed using tablet dissolution tester USP24 (Electro lab TDT-06) type 2 with 1000 ml; pH 1.2 buffer as dissolution media (degassed on 40°C for 30 min under vacuum with constant stirring) at 37 ± 0.5°C and 50 rpm for 60 min [19]. Samples of pure lercanidipine HCl and PMs and SDs (equivalent to 20 mg of the pure drug) were dispersed throughout the dissolution medium. At fixed time intervals, 5 mL aliquots were withdrawn, filtered through a 0.45 µm membrane filter (Millipore India), suitably diluted (if needed) and assayed for lercanidipine HCl content by measuring the absorbance at 241.5 nm using an UV-Visible spectrophotometer. Equal volume of the fresh medium prewarmed at the same temperature was replaced in the dissolution medium after each sampling to maintain constant volume throughout the test. Each test was performed in triplicate and % cumulative release was plotted using calculated mean values of cumulative drug release. Preliminary tests demonstrated that there was no change in the λ_{max} of lercanidipine HCl due to the presence of PEG 6000 dissolved in the dissolution medium.

Results and Discussion

Various solid dispersions using drug and PEG 6000 at different mass ratios (1:1, 1:5 and 1:10) were successfully prepared by solvent evaporation technique to increase the solubility and dissolution of poorly aqueous soluble drug, lercanidipine HCl. The solubility of lercanidipine HCl in water at 21°C is 5 µg/mL, in

pH 1.2 buffer is 20 µg/mL and in 6.8 pH phosphate buffer is less than 5 µg/mL. Log p value of lercanidipine 6.4, shows maximum solubility in acidic medium; therefore, lercanidipine HCl can be considered to be a water-insoluble drug. The phase solubility graph of lercanidipine HCl at 21°C is shown in Fig 1. Solid dispersions of lercanidipine HCl showed increased drug solubility over the pure lercanidipine HCl and its physical mixture of drug with PEG 6000. With the increase in the drug to the PEG 6000 ratio, increased in solubility was found, this is due to the solubilization effect of PEG 6000.

Percent yield and drug content

The percent yields of various lercanidipine HCl solid dispersion were within the range of 89.09 ± 2.21% to 95.18 ± 3.27% (Table 1). The percentage drug content in various newly prepared, lercanidipine HCl solid dispersions ranged from 97.15 ± 2.91% and 99.63 ± 1.73%, as reported in Table 1. This indicated that lercanidipine HCl was uniformly distributed in all of these prepared solid dispersions.

Characterization of solid dispersions and physical mixtures

Fourier transform infrared (FTIR) spectroscopy

FTIR has been used to assess the interaction between carrier and guest molecules in the solid state. In the SDs preparation, there is a peak band shift along the absorption spectrum of the guest. However, some of the changes are very subtle requiring careful interpretation of the spectrum. The FTIR spectra of all samples are shown in Fig. 2. The spectrum of pure lercanidipine HCl presented characteristic peaks at 3183 cm⁻¹ (NH stretching vibration), 3100-2800 cm⁻¹ (alkyl and phenyl stretching), 2684 cm⁻¹ N⁺-H stretching, 1705 cm⁻¹, 1675 cm⁻¹ c=o stretching, 1526 cm⁻¹; 1350 cm⁻¹ (asymmetric and symmetric stretching of NO₂ group), 1402 cm⁻¹; 1380 cm⁻¹ (bending of germinal methyl groups); 800 cm⁻¹-650 cm⁻¹ (out of place bending of 5 and 3 adjacent hydrogen on aromatic rings). Important vibrations detected in the spectrum of PEG 6000 are the C-H stretching at 2890 cm⁻¹ and the C-O

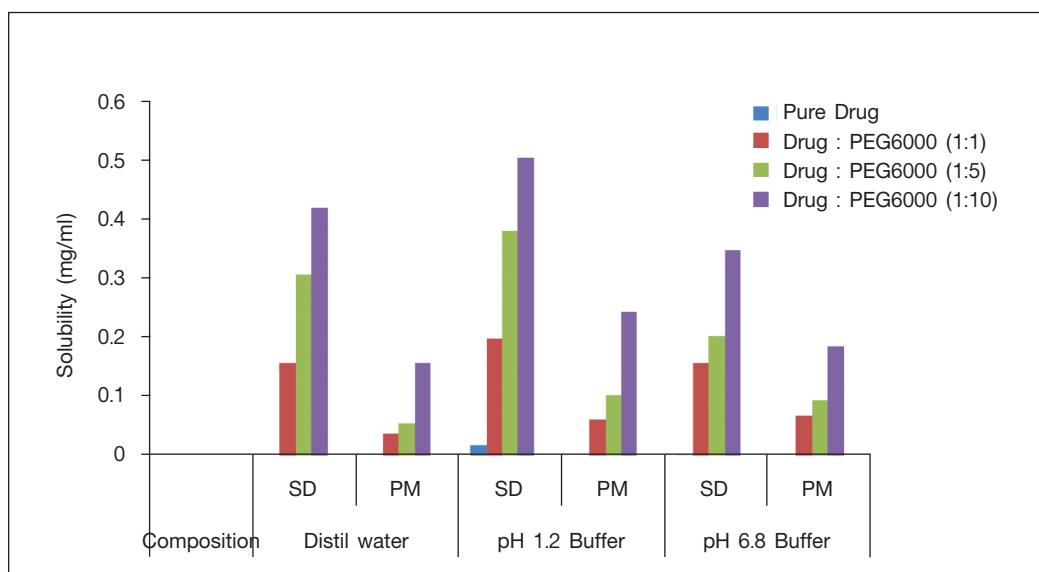


Figure 1 Phase solubility profile of pure drug (lercanidipine HCl), its physical mixtures (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., PMDPEG 1/1, PMDPEG 1/5 and PMDPEG 1/10) and solid dispersions (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., SDDPEG 1/1, SDDPEG 1/5 and SDDPEG 1/10)

Table 1 Percent yield and percent drug content of lercanidipine HCl solid dispersion (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., SDDPEG 1/1, SDDPEG 1/5 and SDDPEG 1/10)

Solid dispersion type	Percent yield (%)	Percent drug content (%)
SDDPEG 1/1	89.09 ± 2.21	94.13 ± 0.22
SDDPEG 1/5	95.18 ± 3.27	97.15 ± 2.91
SDDPEG 1/10	94.21 ± 1.32	99.63 ± 1.73

(ether) stretching at 1125 cm^{-1} . The spectra of PMDPEG 1/10 can be simply regarded as the superposition of those of lercanidipine HCl and PEG 6000. No difference was seen as the position of the absorption bands of lercanidipine HCl and PEG 6000. In the spectra of SDDPEG 1/10, the characteristic peaks of PEG 6000 were present at almost the same positions, whereas peaks due to lercanidipine HCl were absent indicating trapping of lercanidipine HCl inside the PEG 6000 matrix. Moreover, all the spectra showed no peaks other than those assigned to lercanidipine HCl and PEG 6000 which indicates the absence of any well-defined chemical interactions.

X-ray diffraction (XRD) studies

X-ray diffractograms of lercanidipine HCl, PEG 6000, their PMs and SDs are shown in Fig. 3. The presence of numerous distinct peaks on the XRD

spectrum indicated that lercanidipine HCl was present as a crystalline form with major characteristic diffraction peaks appearing at a diffraction angle of 2θ at 42.0854 and 49.0803 with relative intensity (1/10) 100 and 33.81. PEG 6000 also exhibited a distinct pattern with diffraction peaks at 2θ at 15.00, 18.75, 23.15, 26.60, and 29.35. The diffraction patterns of all the samples of SDs showed peaks due to PEG 6000 and an absence of major diffraction peaks corresponding to lercanidipine HCl, with most of the diffraction indicating lercanidipine HCl was present as amorphous material inside the PEG 6000 matrix [7]. Moreover, no peaks other than those that could be assigned to pure lercanidipine HCl and PEG 6000 were detected in the SDDPEG 1/10, indicating no chemical interaction in the solid state between the two entities. In the case of the physical mixture, diffractograms of PMDPEG 1/10 showed more

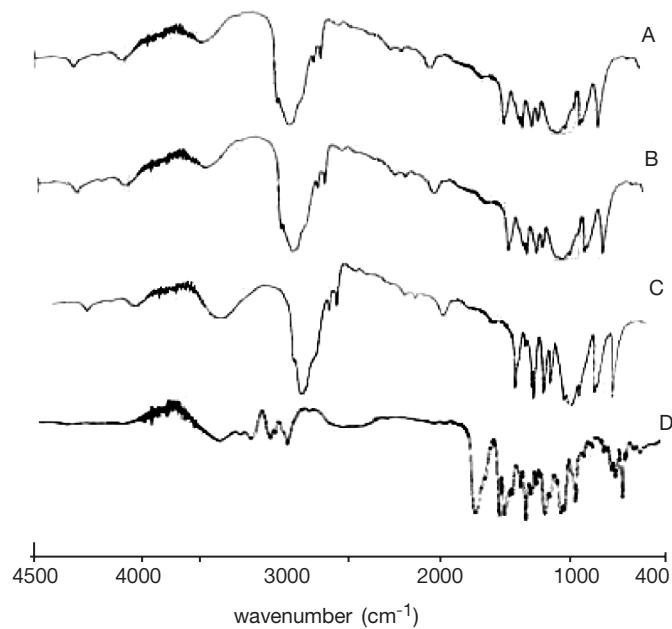


Figure 2 FTIR spectra of (A) solid dispersion, drug and PEG 6000 ratio 1:10 (SDDPEG 1/10); (B) physical mixture, drug and PEG 6000 ratio 1:10 (PMDPEG 1/10); (C) PEG 6000; (D) lercanidipine HCl

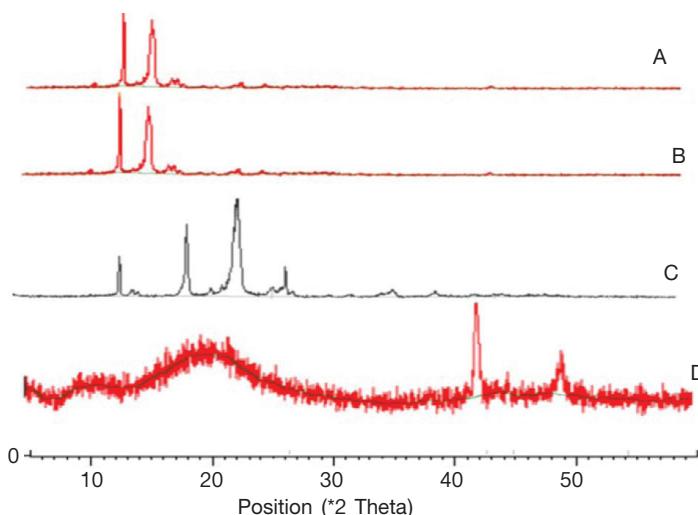


Figure 3 X-ray diffractograms of (A) solid dispersion, drug and PEG 6000 ratio 1:10 (SDDPEG 1/10); (B) physical mixture, drug and PEG 6000 ratio 1:10 (PMDPEG 1/10); (C) PEG 6000; (D) lercanidipine HCl

resemblance; PEG 6000 to lercanidipine HCl due to presence of free drug.

Differential scanning calorimetry (DSC) studies

The thermal behaviour of the prepared solid dispersions and physical mixtures of lercanidipine HCl with PEG 6000 was studied by DSC which allows determination of thermotropic phase transition behaviour in a quantitative manner. The thermograms recorded during analysis display pronounced melting peaks. The DSC thermograms for pure lercanidipine HCl, PEG

6000, their PMs and SDs are shown in Fig. 4. The lercanidipine HCl showed a melting peak at 198.34°C with an enthalpy of fusion (ΔH) of -52.48 J/g (Fig. 4A) infers presence of crystalline form of lercanidipine HCl. DSC thermograms of prepared SD showed the melting peak of the drug at 68.27°C due to depression of melting point in the presence of PEG 6000 (melting point of PEG 6000 is 58–65°C). DSC thermograms of PMDPEG 1/10 showed the melting peak of the drug at 76°C due to loosely bind PEG 6000. Samples of PM and SD

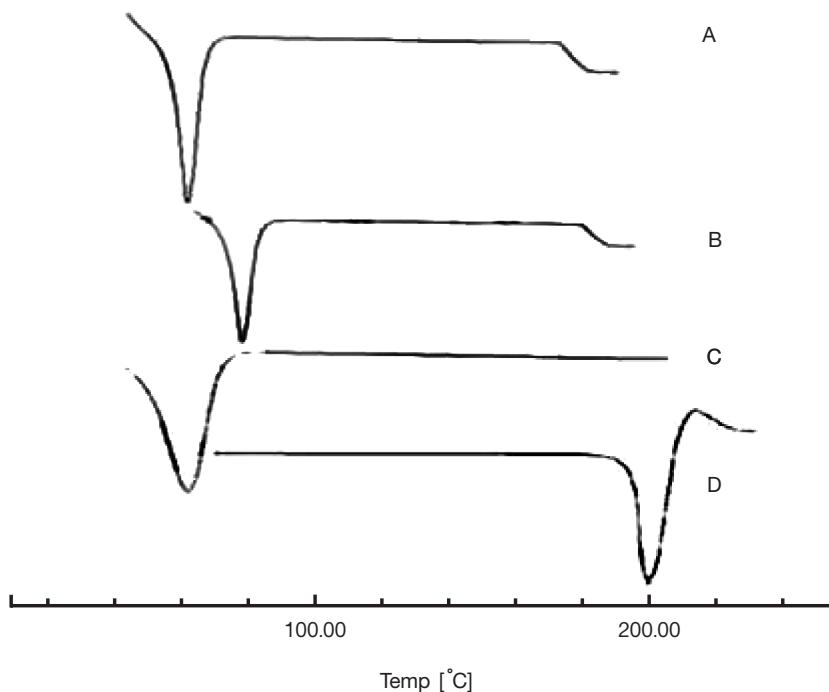


Figure 4 DSC thermograms of (A) solid dispersion, drug and PEG 6000 ratio 1:10 (SDDPEG 1/10); (B) physical mixture, drug and PEG 6000 ratio 1:10 (PMDPEG 1/10); (C) PEG 6000; (D) lercanidipine HCl

Table 2 Percent drug dissolve within 30 minutes (DP 30 min), time to dissolve 50% drug (t50%) for pure drug (lercanidipine HCl), its physical mixtures (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., PMDPEG 1/1, PMDPEG 1/5 and PMDPEG 1/10) and solid dispersions (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., SDDPEG 1/1, SDDPEG 1/5 and SDDPEG 1/10)

Sample	DP 30 min	t50% (min)
Pure Drug	31.80	> 260
PMDPEG 1/1	42.40	29
SDDPEG 1/1	50.01	26
PMDPEG 1/5	59.27	25
SDDPEG 1/5	87.21	11
PMDPEG 1/10	62.46	20
SDDPEG 1/10	100.00	5

showed complete absence of drug peak at 198.34°C. This complete absence of the lercanidipine HCl peak indicates that lercanidipine HCl is amorphous or is in a solid solution inside the PEG 6000 matrix.

Wettability and dissolution studies

The wettability of lercanidipine HCl was significantly improved by preparing its solid dispersions with PEG 6000. The greatest improvement of wettability in water was observed with SDDPEG 1/10 (74.3% after 30 min). A significant improvement in the wettability of lercanidipine HCl was also observed in PMDPEG 1/10 as compared

with pure lercanidipine HCl (36%) after 30 min. This might be imputed to an improvement of wetting of drug particles and localized solubilization by the hydrophilic carriers (PEG 6000) in the diffusion layer. DP30 min values (percent drug dissolved within 30 min) and t50% (time to dissolve 50% drug), values in different samples are reported in Table 2. Carefully observing these value we can find the DP30 and t50% value of SDs were less than their corresponding PMs, due to the solubilising effect of the PEG 6000 and or transformation of crystalline form of lercanidipine HCl to amorphous form (XRD studies support this aspect). *In vitro* dissolution

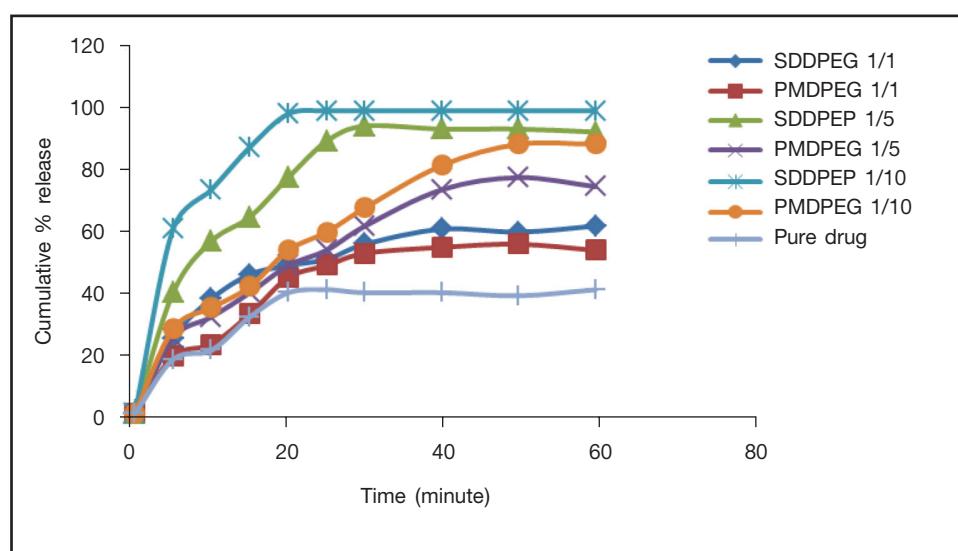


Figure 5 *In vitro* dissolution profiles of pure drug (lercanidipine HCl), its physical mixtures (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., PMDPEG 1/1, PMDPEG 1/5 and PMDPEG 1/10) and solid dispersions (drug and PEG 6000 in 1:1, 1:5 and 1:10 ratio; i.e., SDDPEG 1/1, SDDPEG 1/5 and SDDPEG 1/10)

profiles of pure lercanidipine HCl, its PMs and SDs with PEG 6000 over a period of 60 min are shown in Fig. 5. From data presented in Table 2 and Fig. 5, it is evident that the dissolution rate of pure lercanidipine HCl was very low (DP30 min 32.6%, t50% >>> 4.6 h). SDs of lercanidipine HCl with PEG 6000 (SDDPEG 1/5 and SDDPEG 1/10) significantly enhanced the dissolution rate of lercanidipine HCl (85.27 and 100.02%, respectively) within 1 h as compared with PMs as well as pure lercanidipine HCl. PMs with PEG 6000 (PMDPEG 1/10) also improved the dissolution rate of lercanidipine HCl in comparison of other PMs and SDs of 1/1 and 1/5 (drug/PEG 6000) due to high content of PEG 6000 which gives the higher localized solubilization. The increase in dissolution of lercanidipine HCl from solid dispersion might be due to reduction to the particle size of the drug in the matrix and increase in the solubility of drug in the presence of PEG 6000 carriers and polymorphic transformation contributes to faster dissolution rate of solid dispersion as the material in its amorphous form dissolves at a faster rate due to its higher internal energy and molecular motion when compared to crystalline forms.

Conclusion

Solid dispersion of lercanidipine HCl (poorly water soluble drug) was successfully prepared by solvent evaporation technique using PEG 6000. FTIR indicates the absence of any well-defined chemical interactions. DSC and X-ray diffraction spectroscopic studies indicate that in solid dispersions, drug was present as an amorphous form inside the PEG 6000 matrix. The highest improvement in solubility and in vitro drug release were observed in solid dispersions prepared with drug PEG 6000 ratio 1:10 (i.e.; SDDPEG 1/10). Amorphous nature of the drug in the solid dispersion was confirmed by a decrease in enthalpy of drug melting in the solid dispersion compared to the pure drug. XRD analysis also supported the DSC results as an absence of crystalline nature in lercanidipine hydrochloride.

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