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# SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG LERCANIDIPINE

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## ABSTRACT

The aim of the study was to enhance the solubility and dissolution rate of poorly water soluble drug lercanidipine by solid dispersion technique. Solid dispersion of lercanidipine was prepared by solvent evaporation and kneading technique by using polymer PVP K30 in 1:1, 1:3, 1:5 drug: polymer ratio respectively. Drug excipient compatibility study indicates that there is no interaction between the excipient and the drug. Total six batches were prepared and subjected to evaluation parameters. Prepared solid dispersion of lercanidipine was evaluated for solubility, drug content, in vitro drug release and short term stability studies. Solubility study of all the SD formulation's shows increased in solubility of drug as compare to pure lercanidipine and physical mixture. It was observed that as the concentration polymer increases the drug solubility also increases. The in vitro dissolution profile of all the formulation was rapid and all the formulation showed more than drug 50% release within 30 min. The optimized formulation of F6 prepared with PVP K30 by kneading method containing drug to polymer in a ratio of 1:5 was consider as the optimized formulation with respect to drug content, solubility and in vitro drug release pattern for 60 min. Formulation F6 showed highest 99.11% drug release at the end of 60 min. Optimized formulation F6 was found to be stable during the stability studies for 3 month indicating good stability of the formulation.



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# INTRODUCTION

The Biopharmaceutics Classification System (BCS) was introduced by US food and Drug Administration (FDA) to assess oral drug product. In this system, drug are classified in to four groups based on the ability of a given drug substance to permeate biological membranes and aqueous solubility. The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral drug absorption from IR solid oral dosage forms. It was first introduced into regulatory decision-making process in the guidance document on immediate release solid oral dosage forms: Scale-up and post approval changes. The drugs are divided into high/low-solubility and permeability classes. Currently, BCS guidelines are provided by USFDA, WHO and EMEA. Solid dispersion is a crucial formulation strategy employed in pharmaceutical science to enhance the solubility and bioavailability of poorly water-soluble drugs. This theory elucidates the principles underlying the formation and behavior of solid dispersions, offering insights into their utility and applications.[1] Solid dispersion refers to a dispersion of one or more active pharmaceutical ingredients (APIs) in an inert solid matrix or carrier, where the drug is uniformly dispersed at the molecular or colloidal level. The primary objective of solid dispersion is to overcome the inherent solubility limitations of drugs, particularly those with low aqueous solubility, by increasing their surface area and improving their dissolution rate upon administration. One of the fundamental mechanisms underlying solid dispersion formation is the conversion of crystalline drug particles into an amorphous state. Amorphous drugs exhibit higher solubility and dissolution rates compared to their crystalline counterparts due to the absence of ordered crystal lattice structures, facilitating interactions with the solvent. Solid dispersion techniques often involve reducing the particle size of the drug to enhance its surface area and dissolution kinetics. This can be achieved through methods such as milling, micronization, or nanonization, leading to increased drug wettability and dissolution. The choice of inert carriers or matrices in solid dispersion formulations is crucial, as these carriers can interact with the drug molecules through hydrogen bonding, van der Waals forces, or other interactions. These interactions can stabilize the amorphous form of the drug and prevent its re-crystallization, thereby maintaining enhanced solubility.[2,3] Lercanidipine has very low solubility in water. Lercanidipine is more soluble in organic solvents such as ethanol, methanol, chloroform, and acetone. Lercanidipine is a dihydropyridine calcium channel blocker that primarily acts on the cardiovascular system. Lercanidipine selectively inhibits the influx of calcium ions through L- type calcium channels in the smooth muscle cells of the arterial wall. By blocking calcium entry, lercanidipine causes relaxation of the vascular smooth muscle, leading

to vasodilation (widening) of the arteries.[4]

# MATERIALS AND METHODS

## Materials

Lercanidipine was kind sample gifted by Sun Pharma, Baroda., PVP K30 and Methanol was purchased from S.D. Fine Chem. Ltd.All other chemicals are analytical grade.

## Method

**Preformulation Study of Drug:** A preformulation study is a crucial preliminary stage in the drug development process, aiming to evaluate the physicochemical properties of a drug substance before formulating it into a dosage form. This stage provides valuable insights into the drug's intrinsic characteristics, which are essential for designing an effective and stable formulation Preformulation testing's main goal is to produce data that will help the formulator create a dosage form that is safe, effective, and stable. They help in identifying potential formulation challenges and risks early in the development process, allowing for proactive problem- solving and mitigation strategies.

**Drug Excipient Compatibility study:** Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture of drug and polymer in 1:1 ratio was prepared and mixed with suitable quantity of potassium bromide. The mixture was compressed to form a transparent pellet using a hydraulic press. It was scanned from 400 $cm^{-1}$ to 4000 $cm^{-1}$ in a Shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks.[5,6]

***Saturation Solubility Study of Drug (Lercanidipine):*** Saturation solubility study of drugs was determined in different solvents like distilled water, 0.1 N Hcl, phosphate buffer pH 6.8 and phosphate buffer pH 7.5. The saturation solubility of a drug was determined as per the method recommended by Higuchi and Connor's. An excess amount of drug was added in a glass vial containing 10 ml of selected solvent,. Samples were then shaken for 48 hr at a constant speed on a rotary shaker at 25°±2°C. After that, the saturated solutions were filtered through a Whatman filter paper no 1. Filtrates was then diluted appropriately and analysed using UV spectrophotometer.[7]

***Preparation of Physical Mixture:*** Physical mixture of drug lercanidipine was prepared using carrier PVP K30 in 1:1 ratio. Physical mixture of drug and carrier PM1 (Lercanidipine + PVP K 30) was prepared by simple triturating the drug and carrier n mortar and pestle. The appropriate amounts of drug and carrier were blended with minimum stirring pressure in a mortar and pestle to form physical mixture. The mixture was passed through sieve number 60 so as to obtain uniform size distribution and stored in desiccator till further use.[8]

**Preparation of Lercanidipine Solid Dispersion:** In order to study the effect of different methodology on the formulation development and solubility enhancement of drug. Solid dispersion of lercanidipine was prepared by two different method viz solvent evaporation and kneading method.[9]

***Solvent Evaporation Method:*** Solid dispersion of Lercanidipine was prepared using PVP K30 as carrier. The drug and polymer were taken in ratio of 1:1, 1:3 and 1:5. The polymer was taken and dissolved in an adequate amount of methanol and then drug was added slowly with stirring. The solvent methanol was then rapidly evaporated with the help of mild heat on water bath to form a uniform solid mass. The precipitate solid mass was then crushed and kept in desiccator for 24 h. The resultant mas was then pulverized and powder was then passed through 50 mesh sieve to get uniform size powder. The product was then kept in suitable container until further use.[10,11]

***Kneading Method:*** Solid dispersion of Lercanidipine was prepared using PVP K30 as carrier by kneading method. The drug and polymer were taken in ratio of 1:1, 1:3 and 1:5. The drug and carrier were combined in a mortar and then vigorously kneaded for 20 minutes with water and methanol (1:1 ratio). The kneaded compositions were then dried in an oven until they attained a consistent weight. After drying the resultant dried mass was then crushed and screened through a 60-mesh screen before being kept in a desiccator for further use.[12,13]

**Table 1. Composition of Lercanidipine Solid Dispersion**

| Formulation Code | Lercanidipine (mg) | PVP K 30 (mg) | Method |
|---|---|---|---|
| **F1** | 10 | 10 | Solvent Evaporation |
| **F2** | 10 | 30 | |
| **F3** | 10 | 50 | |
| **F4** | 10 | 10 | Kneading |
| **F5** | 10 | 30 | |
| **F6** | 10 | 50 | |

## Characterization of Physical Mixture and Solid Dispersions of Lercanidipine

## Determination of Solubility

Solubility study of physical mixture and solid dispersion was performed using shake flask method. The solubility of PM and SD was determined in distilled water and 0.1 N Hcl as a solvent. Excess quantities of physical mixture and solid dispersions were added in 25 ml of study solvent in conical flask and shaken for 24 hours at room temperature on rotary flask shaker. After shaking resultant samples filtered using whatman filter paper. Further sample ware suitably diluted and analysed by UV- Spectrophotometer at 236 nm.[14]

***Fourier Transform Infra-Red Spectroscopy (FTIR):*** FTIR spectroscopy was used to determine the drug's compatibility with the selected carrier. The FTIR spectrum of a pure drug, a physical mixture, and a solid dispersion was recorded throughout a selected frequency range of 400 to 2000 cm-1 (Shimadzu, Japan). Any kind of incompatibility between drug and selected carrier in the formulation ware observed.15

***Differential Scanning Calorimetry (DSC):*** Thermal analysis gives an idea of the physical nature of solid dispersed powder and melting and crystallization behaviour. The DSC study was done to analyse the samples with the application of controlled heat. Thermal analysis of solid dispersion was performed by using differential scanning calorimetry (DSC) method (Shimadzu Thermal Analyzer, Japan). Sample was placed on aluminum pan of DSC and the sample was heated at the rate of 10°C/min from the temperature range of 30–200°C.Nitrogen was used as a purge gas and flow was adjusted to 50 ml/min.

***In Vitro Drug Dissolution Study:*** In vitro dissolution study of pure Lercanidipine, physical mixtures and solid dispersions were determined using USP dissolution test apparatus II (Paddle type) (Esico International, Mumbai). Accurately weighted preparation equivalent to 10 mg of Lercanidipine ware added to 900 ml of 0.1 N Hcl as dissolution medium, maintained at 37±0.5°C and stirred at 50 rpm. 5 ml samples were withdrawn at time interval of 10, 20, 30, 40, 50, 60 min and same volume was replaced with fresh media in order to maintain the sink condition. After suitable dilution, collected samples were analysed at 236 nm using UV-visible spectrophotometer against the blank.[16,17]

***Drug Content:*** Solid dispersions equivalent to 10 mg of Lercanidipine was weighed accurately and dissolved in 100 ml of methanol. The solution was shaken vigorously and filtered. After

suitable dilution drug content was analyzed at 236 nm against blank by UV spectrophotometer.[18]

***Percentage Practical Yield:*** Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersion was collected and weighed to determine practical yield.

***Stability Studies:*** The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Stability studies was carried out on optimized formulations as per ICH guidelines by keeping the formulation sample at 40°C ± 2°C/75% RH ± 5% RH for 6 months. The optimized solid dispersion formulation F2 were stored in stability chamber (Remi, India) at 400 C and 75% RH for 6 months. Periodically samples were withdrawn and estimated for the drug content and solubility.[19]

# RESULTS AND DISCUSSION

***Drug Excipient Compatibility Study:*** The IR spectra of a drug-polymer physical mixture was compared to that of a plain drug. Characteristic sharp distinctive peaks seen in pure drug lercanidipine, was compared with the spectra of drug and polymer mixtures. It was observed that characteristic peaks those found on pure drug spectra were still detectable in spectra of drug polymer mixture spectra, showing that the drug and polymer have no interaction. FTIR spectra of pure drug lercanidipine and drug polymer physicam mixture was shown in figure 8.1, 8.2 and 8.3 respectively.

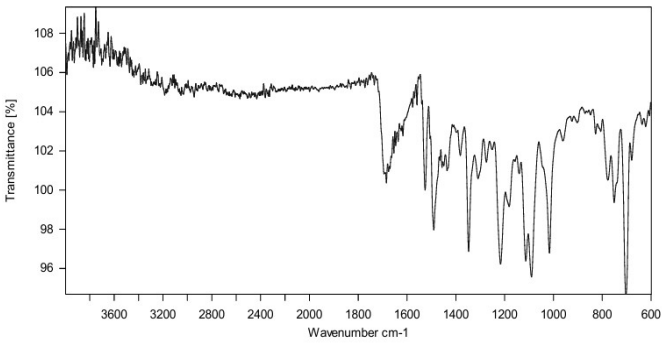


**Figure 1. IR spectra of pure drug Lercanidipine**

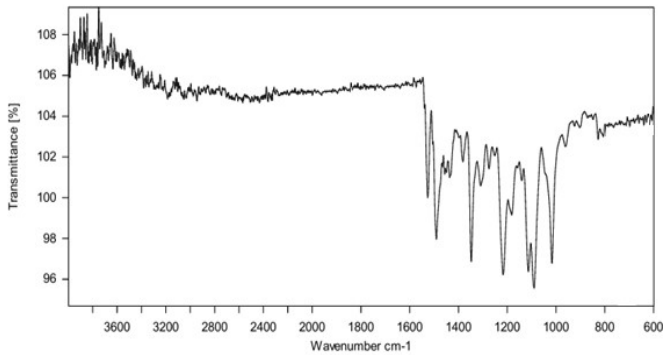


**Figure 2. IR Spectra of Lercanidipine and PVP**

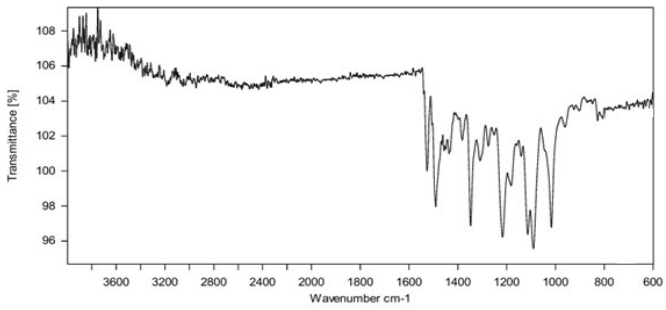


**Figure 3. IR Spectra of Lercanidipine Solid dispersion**

***Saturation Solubility Study of Drug (Lercanidipine):*** Saturation solubility of drug lercanidipine was studied in different solvent like and distilled water, 0.1 N Hcl, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.5. Lercanidipine showed very low solubility of 64.31±1.86 µg/ml in water, which showed its basic hydrophobic nature. The solubility of lercanidipine in 0.1 N Hcl. phosphate buffer pH 6.8 and 7.5 was found to be 97.26 ± 1.78 µg/ml, 34.11 ± 2.13 µg/ml and 23.46 ± 1.96 µg/ml respectively. From the solubility study it was observed that drug lercanidipine exhibited pH dependent solubility. Lercanidipine solubility was found to be maximum in 0.1 N Hcl and lowest in phosphate buffer pH 7.5. Solubility data of lercanidipine in different solvents are shown in Table 2.

**Table 2. Solubility of Lercanidipine in different Solvents**

| Sr. No | Solvents | Solubility (µg/ml) |
|---|---|---|
| 1 | Water | 64.31 ± 1.86 |
| 2 | 0.1 N Hcl | 97.26 ± 1.78 |
| 3 | Phosphate buffer pH 6.8 | 34.11 ± 2.13 |
| 4 | Phosphate buffer pH 7.5 | 23.46 ± 1.96 |

**Characterization of Formulations**

**Solubility Determination of Physical Mixture and Solid**

**Dispersions:** The solubility of drug lercanidipine physical mixture (PM) and Solid Dispersions (SD) was determined in distilled water using the shake flask technique. Lercanidipine has very limited water solubility, showed maximum solubility of 64.31±1.26 µg/ml in water. Physical mixture of lercanidipine prepared with PVPK30 showed improved drug solubility, compare to its pure form, indicating a positive interaction among the drug and carrier. Solid dispersion formulation (F1, F2, F3) prepared by solvent evaporation method using carrier PVP K30 in the ratio of 1:1, 1:3 and 1:5 showed solubility of 125.35 ±2.67, 177.61 ±1.26 and 210.36 ±2.12 µg/ml respectively. While formulation F4, F5 and F6 formulated by kneading method in the ratio of 1:1, 1:3 and 1:5 using PVP K30 showed solubility of 134.32±1.86, 193.56 ±2.14 and 246.76 ±2.47 µg/ml respectively. Solid dispersion formulation of leracnidipine prepared by both the technique using PVK 30 as a carrier showed multifold increase in solubility of drugs. From the study it was noticed that solubility of drug increases with increase in PVP concentration. Solid dispersion prepared kneading method gives higher drug solubility than solvent evaporation method. All solid dispersion formulations showed improved solubility, compared to pure and physical mixtures, this indicate that crystalline lercanidipine was converted in to amorphous form in the presence of PVP. Among all solid dispersion formulation batch F6 showed highest drug solubility as compare to other SD formulations. Solubility study data for pure lercanidipine, its physical mixture and solid dispersion are shown in table .3

**Table 3. Solubility Study of Pure Lercanidipine, Physical Mixture and Solid**

**Dispersion in Distilled Water**

| Formulation Code | Solubility (µg/ml) |
|---|---|
| Pure LER | 64.31 ± 1.26 |
| PM | 78.18 ±2.17 |
| F1 | 125.35 ±2.67 |
| F2 | 177.61 ±1.26 |
| F3 | 210.36 ±2.12 |
| F4 | 134.32 ±1.86 |
| F5 | 193.56 ±2.14 |
| F6 | 246.76 ±2.47 |

Values are mean ± SD (n=3)

**Differential Scanning Calorimetry (DSC):** The DSC thermogram of pure lercanidipine showed a sharp single endothermic peak at176.03°C, which corresponds to the melting temperature of

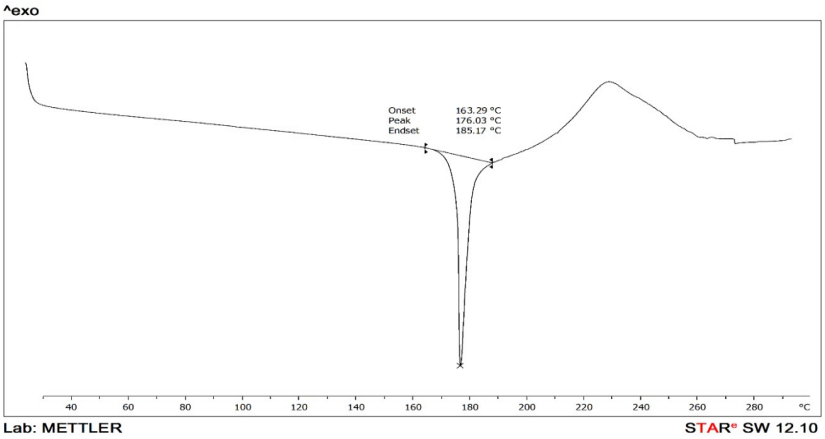


**Figure 4. DCS thermogram of pure Lercanidipine**

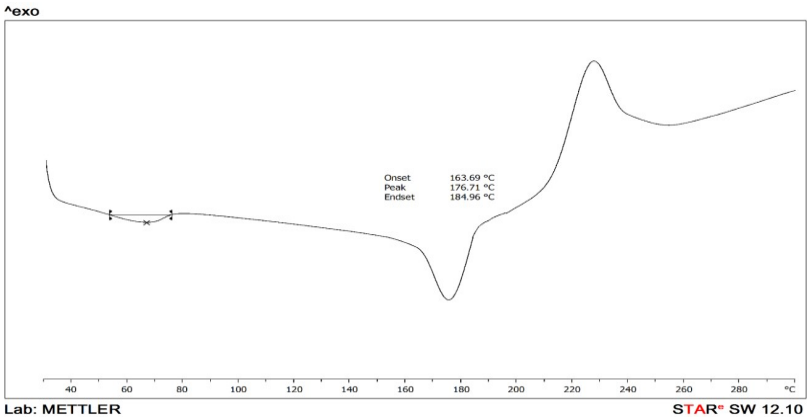


**Figure 5. DCS thermogram of Optimized solid dispersion F6**

**Table 4. *In-vitro* drug release study of Lercanidipine and its Solid Dispersion**

| Time (Min) | Pure LER | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 10.27±1.32 | 40.8±1.80 | 52.56±2.25 | 67.58±1.88 | 48.56±1.41 | 80.54±1.78 | 86.51±2.08 |
| 20 | 15.81±9.78 | 50.8±1.67 | 60.36±3.14 | 75.62±2.89 | 58.36±2.28 | 92.18±1.34 | 96.63±2.71 |
| 30 | 20.55±2.10 | 61.82±1.33 | 70.47±2.17 | 81.92±1.60 | 65.47±3.10 | 96.54±3.26 | 97.51±1.66 |
| 40 | 24.51±1.87 | 69.32±1.80 | 77.25±0.56 | 87.65±1.55 | 71.25±3.04 | 97.26±0.98 | 98.12±2.65 |
| 50 | 29.24±0.67 | 75.21±2.12 | 83.36±3.28 | 92.23±2.95 | 78.36±2.76 | 97.4±1.66 | 98.82±1.89 |
| 60 | 34.14±2.42 | 80.12±1.74 | 91.74±2.30 | 94.54±1.90 | 82.74±1.30 | 98.55±2.28 | 99.11±2.10 |

lercanidipine. The sharp endothermic peak indicated that the lercanidipine crystalline in nature. Figure 8.9 shows the DSC thermogram of Optimized solid dispersion formulation (F6). Thermogram showed that sharpness of peak in SD formulation is reduced and broadening is observed. Peak showed endothermic peak at endothermic peak at 176.71°C corresponds to the peak of lercenidipine. Broadening of endothermic peak and reduction in the intensity of peak of drug lercanidipine indicates that the crystallinity of the drug was reduced and drug was converted to more soluble amorphous form.

***In Vitro Drug Release Study:*** In vitro dissolution study of pure Lercanidipine, physical mixtures and solid dispersions were determined using USP dissolution test apparatus II (Paddle type) (Esico International, Mumbai) using 0.1 N Hcl as dissolution medium. Dissolution study showed that, pure lercanidipine gives only 34.14±2.42% of drug release in 60 min, indicating poor solubility and dissolution of drug. Drug release profile of physical mixture of lercanidipine showed improved drug release as compare to pure drug release. Solid dispersion formulations F1, F2 and F3 formulated using PVP K30 as carrier in different ratio by solvent evaporation method showed drug release of 80.12%, 91.74% and 94.54% respectively at the end of 60 min. Solid dispersion formulation F4, F5 and F6 prepared with PVP K30 as carrier by kneading technique in different ratio showed drug release of 82.74%, 98.55% and 99.11% respectively at the end of 60 min. Among the formulation, F6 showed highest drug release of 99.11%, compare to other formulations. All the solid dispersion formulation showed more than 50% drug release within 30 min. It was observed that as the concentration polymer increases the drug dissolution rate also increases. From the dissolution data it is observed that among the two method of solid dispersion formulation prepared by kneading method gives better solubility and dissolution properties of lercanidipine, this may be due to better wettability and dispersibility along with additional process of grinding during kneading process. Disssolution profile of different solid dispersion formulation along with pure drug lercanidipine was shown in Table. No4

***Drug Content:*** The drug content in each solid dispersion was determined by UV- spectroscopy method. The percent drug content for all the formulation was found to be in the range of 95.26 to 98.61 %. Formulation F6 showed highest drug content of 98.61 %.

Drug content for all the SD formulations are found within pharmacopoeial limit and are shown in Table.5

***Percentage Practical Yield***

Percentage practical yield for all the SD formulations was shown in table 8.6. Formulation F1, F2 and F3 showed yield of 84.26 %, 86.85% and 87.32% respectively, while the F4, F5 and F6 shown 91.56 %, 92.38% and 94.24% respectively. Solid dispersion prepared with carriers PVP by kneading method showed higher % practical yield than the solvent evaporation method. Formulation F6 showed highest % yield while F1 shown lowest yield. Data for % practical yield and graphical representation of percentage practical yield was shown in table 5.

**Table 5. Drug Content & % Practical Yield of Lercanidipine Solid Dispersion**

| Batch | % Drug Content | % Practical Yield |
|---|---|---|
| F1 | 96.10 | 84.26 |
| F2 | 95.26 | 86.85 |
| F3 | 96.82 | 87.32 |
| F4 | 96.78 | 91.56 |
| F5 | 97.40 | 92.38 |
| F6 | 98.61 | 94.24 |

**Stability studies**

Solid dispersion formulations showing maximum solubility, dissolution and drug content, was selected for stability studies. According to ICH guidelines, optimized formulations F6 were stored at 400C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for solubility, drug content at the end of 3 months. At the end of 3 months no significant difference was observed in drug content and solubility. From the stability study it was concluded that solid dispersion formulation F6 was found to be stable. Details of stability study data are shown in table 6

**Table 6. Stability data optimized formulation F6**

| Formulation Code | Parameter | Before storage (0 month) | After storage (3 month) |
|---|---|---|---|
| F6 | Solubility (µg/ml) | 246.76 ±2.47 | 244.11±1.84 |
| | % Drug content | 98.61% | 97.92% |
| | % Drug release | 99.11±2.10 | 97.54±1.29 |

# CONCLUSION

From the present study following conclusion were observed The solid dispersion of lercanidipine can be prepared successfully by solvent evaporation technique and kneading technique using PVP K30 as a polymer.All the prepared SD formulations were showed improved solubility of drug.FTIR- spectroscopic studies indicate no drug-excipient interaction in formulation. The in vitro dissolution profile of all the prepared SD formulations gives rapid drug release in 60 min.Formulation F6 was consider as the ideal formulation which showed multifold rise in drug solubility of 246.76 µg/ml, almost 3.84 fold increase in solubility as compare with pure lercanidipine.Among the two method used for solid dispersion formulation, kneading method showed better solubility and drug release compare to solvent evaporation method. From this study, it was concluded that the solid dispersion prepared using PVK K30 by solvent kneading method is a good approach of enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs lercanidipine.Future detailed investigation is required to established in vivo efficiency of solid dispersion of Lercanidipine and the long term stability study need to be confirm the stability of Solid dispersion of Lercanidipine.

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