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ENHANCEMENT OF RATE OF DISSOLUTION OF ANTI HYPERTENSIVE DRUG (LERCANIDIPINE) BY USING SOLUPLUS AS A CARRIER

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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 a molecular level. Solid dispersions of LER were prepared by solvent evaporation 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 techniques showed improved release compared to pure LER and physical mixture. No interaction of LER and polymer was confirmed by 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.

Keywords: Lercanidipine, Soluplus, Solid dispersions, Solvent evaporation method.

INTRODUCTION

Lercanidipine Hydrochlorideis an antihypertensive (blood pressure lowering) drug. It belongs to the dihydropyridine class of calcium channel blockers, which work by relaxing and opening the blood vessels allowing the blood to circulate more freely around the body. This lowers the blood pressure and allows the heart to work more efficiently. Lercanidipine, a widely prescribed drug belongs to class II. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy.[1]

HYPERTENSION:

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease, vision loss, chronic kidney disease, and dementia.[2][3][4][5]

TYPES OF HYPERTENSION:

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[6]

a)Primary hypertension: defined as high blood pressure due to nonspecific lifestyle and genetic factors. About 90–95% of cases are primary. [5][6] Lifestyle factors that increase the risk include: excess salt in the diet, excess body weight, smoking, alcohol use.

b)Secondary hypertension:defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills. 5–10% of cases are categorized as secondary high blood pressure.

ANTI HYPERTENSIVE DRUGS:

Anti hypertensives are a class of drugs that are used to treat hypertension (high blood pressure).Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mm Hg can decrease the risk of stroke by 34%, ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[10]

- **TYPES OF ANTI HYPERTENSIVES:**

There are many classes of antihypertensives, which lower blood pressure by different means. Among the most important and most widely used drugs are: Diuretics, Calcium channel blockers, ACE inhibitors, Angiotensin II receptor antagonists (ARBs), Adrenergic receptor antagonists, Vasodilators, Renin Inhibitors, Aldosterone receptor antagonists, Alpha-2 adrenergic receptor agonists & Endothelin receptor blockers

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SOLUBILITY:

Solubility is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous solvent. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and presence of other chemicals (including changes to the pH) of the solution. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units [11]. When an active agent given orally, it must first dissolves in gastric and intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving the oral bioavailability of active agentsinclude:

1.Enhancing solubility and dissolution rate of poorly water-soluble drugs
2. Enhancing permeability of poorly permeable drugs.

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Almost More than 90% drugs are orally administered. Drug absorption, bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble. Solvent is defined as the component which forms major constituent of a solution and is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level. Solute is defined as a substance that present in small quantity and dissolves in solvent.

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Oral drug delivery is the simplest and easiest way of administering drugs due to its convenience, good patient compliance, greater stability, accurate dosage and easy production. Drug solubility is the maximum concentration of the drug dissolved in the solvent under specific condition of temperature, pH and pressure. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in Table.

Table.1: Solubility description table

Definition	Parts of solvent required for one part of solute
Very Soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100

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Slightly	100 – 1000
Very slightly soluble	1000 – 10,000
Insoluble	> 10,000

CLASSIFICATION OF DRUGS BASED ON SOLUBILITY:

The Biopharmaceutics Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability.

CLASS I: HIGH PERMEABILITY AND SOLUBILITY:

Formulation independent: The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

Ex: Loxoprofen, Benzapril, Sumatriptan etc.
CLASS II: HIGH PERMEABILITY AND LOW SOLUBILITY:
Formulation dependent: The bioavailability of class II compounds is limited by drug solubility/dissolution.

EX: Aceclofenac, Valsartan, Nimesulide, Loratadine etc.
CLASS III: LOW PERMEABILITY BUT HIGH SOLUBILITY:

Dependent on barrier properties: The bioavailability of class III compounds is limited by intestinal permeability.

EX: Atropine, Gabapentine, Topiramate etc.
CLASS IV: LOW PERMEABILITY AND LOW SOLUBILITY:

Formulation and barrier properties dependent: The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

EX: Hydrochlorthiazide, Meloxicam, Furosemide etc.
TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

- PHYSICAL MODIFICATIONS:Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.
- CHEMICAL MODIFICATIONS:Change of pH, use of buffer, derivatization, complexation, and salt formation.
- MISCELLANEOUS METHODS:Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

There are various techniques available to improve the solubility of poorly soluble drugs. Most widely used method is Solid dispersion method.
SOLID DISPERSION [11]**:**

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

TYPES OF SOLID DISPERSIONS:

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- **EUTECTIC MIXTURES:** A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution[12-15].
- **AMORPHOUS PRECIPITATION IN CRYSTALLINE MATRIX:** This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form[16-17]
- **SOLID SOLUTION:** Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions[18] and the dissolution rate is determined by the dissolution rate of the carrier. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).
- **CONTINOUSSOLID SOLUTIONS:** In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date.
- **DISCONTINOUS SOLID SOLUTIONS:** In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg et al.[18] that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.
- **SUBSTITUTIONAL SOLID DISPERSIONS:** Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules[19]. Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the intrsticies between the solvent molecule.
- **INTERSTITIAL SOLID SOLUTIONS:** In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter. [20]
- .**LASS SOLUTIONS AND SUSPENSIONS:** Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solution and suspension.

SELECTION OF A CARRIER:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug. [21, 22, 23, 24]

- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
- Able to preferably increase the aqueous solubility of the drug.
- Chemically compatible with the drug and not form a strongly bonded complex with the drug.

SELECTION OF SOLVENTS:

Solvent to be included for the formulation of solid dispersion should have the following criteria:

- Both drug and carrier must be dissolved.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane[25].
- Ethanol can be used as alternative as it is less toxic.
- Water based systems are preferred.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

ADVANTAGES OF SOLID DISPERSION:

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- **Particles with Reduced Particle Size:** Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability[26].
- **Particles with Improved Wettability:** Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Even carriers without any surface activity, such as urea, improved drug wettability. Carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

- **Particles with Higher Porosity:** Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.
- **Drugs in Amorphous State:** Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier[27]. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

METHODS OF PREPARATION OF SOLID DISPERSION:

- **Melting method:** The melting or fusion method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature[28].
- **Solvent method:** In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents[29].
  However, some disadvantages are associated with this method such as

i. The higher cost of preparation.

ii. b. The difficulty in completely removing liquid solvent.

iii. The possible adverse effect of traces of the solvent on the chemical stability d. The selection of a common volatile solvent.

iv. The difficulty of reproducing crystal form.

v. In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.

- **Melting solvent method (melt evaporation):** It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property[30]. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

- **Melt extrusion method:** The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules,

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pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40%(w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355μm.

- **Lyophilisation Technique:** Freeze-drying involves transfer of heat and mass to and from the product under preparation[31]. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

- **Melt Agglomeration Process :** This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer[32]. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

- **The use of surfactant :**The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.

- **Electrospinning :** Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle[33]. This process involves the application of a strong electrostatic field overa conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried [38]. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest,the cheapest, this technique can be utilized for the preparation of solid dispersions in future.

METHODOLOGY:

PREFORMULATION STUDIES: Preformulation studies are an investigation of physical and chemical properties of the drug substances alone and combined with Excipient like colour, form, melting point, and solubility studies, micrometric properties, compatibility studies, analytical studies etc.

MELTING POINT: Melting point of lercanidipine was determined by using melting point apparatus.

SOLUBILITY: Lercanidipine solubility was studied in water and other solvents like methanol, ethanol, chloropharm and acetone .

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MICROMERITIC PROPERTIES[51-53]:

Bulk density: Weighted accurately 5gms of lubricated granules which was previously passed through 20# sieve and was transferred in to 50 ml graduated cylinder. Powder was carefully levelled without compacting and read the unsettled apparent volume (V_o). Apparent bulk density in gm/ml was calculated by the following formula:

Bulk density = Weight of powder/Bulk volume

Tapped density: Weighted accurately 5gms of lubricated granules which was previously passed through 20# sieve and was transferred in to 50 ml graduated cylinder. Then the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provide a fixed drop of 14± mm at a normal rate of 300 drops per minute. Cylinder was tapped for 500 times initially and then measured the tapped volume (V1) to the nearest graduated units, tapped was repeated for an additional 750 times and tapped volume (V2) was measured to the nearest graduated units. If the difference between the two volumes is less than 2% then final volume (V2) should be taken. Calculated the tapped density in gm/ml by the following formula:

Tapped density = Weight of powder/tapped volume

Angle of Repose: The angle of repose of lubricated granules was determined by the funnel method. The accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such away the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on top the surface. The diameter of the powder cone was measured and angle of repose Θ was calculated using the following equation.

$$\mathbf{Tan\ \Theta = h/r}$$

Where h and r are height of the cone and radius of the powder cone respectively.

Hausner ratio:The **Hausner ratio** is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

Hausner ratio = freely settled bulk density/ tapped bulk density of the powder

The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The Hausner ratio (H) is related to the Carr index (C), another indication of flowability. Both the Hausner ratio and the Carr index are sometimes criticized, despite their relationships to flowability being established empirically, as not having a strong theoretical basis. Use of these measures persists, however, because the equipment required to perform the analysis is relatively cheap and the technique is easy to learn.

Carr index:The **Carr index** (Carr's Compressibility Index) is an indication of the compressibility of a powder. The Carr index is calculated by the formula

Cars index = (tapped density – bulk density) * 100 /tapped density

The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. In a free-flowing powder, the bulk density and tapped density would be close in value, therefore, the Carr index would be small. On the other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore, the Carr index would be larger. A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Solubility studies of Lercanidipine Hydrochloride solid dispersion by solvent evaporation method:

Solubility measurements of Lercanidipine Hydrochloride were performed according to a published method**.** Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Lercanidipine Hydrochloride in UV 240 nm.

COMPATABILITY STUDIES[54]: Drug and carrier compatability studies performed by using FT-IR spectra. Pure drug (Lercanidipine), pure polymers (Soluplus, Poloxamer, PEG 4000), and solid dispersions of

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drug with polymers were scanned using FT-IR spectrophotometer. Infrared spectrum of material gives the information regarding drug-polymer interactions. The materials were scanned through a range from 400 to 4000/cm with a resolution of 4/cm.

ANALYTYCAL STUDIES:

Calibration curve of Lercanidipine in 0.1N HCL:

Preparation of 0.1N HCL:

8.5ml of HCL is dissolved in 1000ml of water in 1000ml volumetric flask.

Preparation of stock solution:

Stock solution was prepared by dissolving 10mg of Lercanidipine in 10ml of ethanol (mg/ml). 1ml of the above solution was taken in 10ml volumetric flask.To this 6ml of 0.1N HCL was added, shaken for 20 mins. Volume was made up to 10ml using 0.1N HCL solution (100µg/ml).

Preparation of standard solution:

Different aliquots were taken from stock solution in to 10ml volumetric flask. To this 6ml of 0.1N HCL was added, shaken for 20mins and sonicated for 5mins. Volume was made up to 10ml using 0.1N HCL solution to prepare the series of concentration 5,10,15,20,25µg/ml. Absorbance of these solution were measured at λ max 240 nm using UV-Visible spectrophotometer and standard plot was plotted between concentration on X-axis and absorbance on Y-axis which gives straight line.

MANUFACTURING METHODS:

PROCEDURE:

Preparation of Lercanidipine Hydrochloride solid dispersions

Solid dispersions of Lercanidipine Hydrochloride were prepared by using Kolliphor P 407, Soluplus and PEG 4000 different drug-polymer ratios (1:1 to 1:6) are weighed and mixed together in a porcelain dish. Eighteen formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of Ethanol as a common solvent. Then the solvent was evaporated. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a sieve before packing in an airtight container, stored in a desiccator and used for further investigations. In the present investigation Eighteen formulations were prepared and their complete composition was shown in **Table.** All the solid dispersions prepared were found to be fine and free flowing powers.

Table-2: Compositions of solid dispersions:

S .NO	FORMULATIONS	AMOUNT OF DRUG LERCANIDIPINE (gm)	AMOUNT OF SOLUPLUS (gm)	AMOUNT OF POLAXIMER(gm)	AMOUNT OF PEG 4000(gm)	DRUG CARRIER
1	F1	0.5	0.5	-	-	1:1
2	F2	0.5	1	-	-	1:2
3	F 3	0.5	1.5	-	-	1:3
4	F4	0.5	2	-	-	1:4
5	F5	0.5	2.5	-	-	1:5
6	F6	0.5	3	-	-	1:6
7	F7	0.5	-	0.5	-	1:1
8	F8	0.5	-	1	-	1:2
9	F9	0.5	-	1.5	-	1:3
10	F10	0.5	-	2	-	1:4
11	F11	0.5	-	2.5	-	1:5
12	F12	0.5	-	3	-	1:6
13	F13	0.5	-	-	0.5	1:1
14	F14	0.5	-	-	1	1:2
15	F15	0.5	-	-	1.5	1:3
16	F16	0.5	-	-	2	1:4
17	F17	0.5	-	-	2.5	1:5
18	F18	0.5	-	-	3	1:6

EVALUATING METHODS:

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Evaluation of Lercanidipine Hydrochloride solid dispersions: Solid dispersions obtained from the above method were tested for their % Practical yield, Drug content, micromeretic properties, FTIR study and in-vitro release studies.

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. SDs were collected and weighed to determine practical yield (PY) from the following equation.

$$\% \text{ Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer)}} \times 100$$

Drug content estimation: The percentage drug content in physical mixtures and solid dispersions was estimated by dissolved 20 mg quantities of physical mixtures and solid dispersions in ethanol, mixed thoroughly by shaking and the volume was made-up to the mark with solvent (0.1N HCl). The solution was filtered and the filtrate was diluted suitably with 0.1N HCl (1.2) pH and absorbance was measured at 240 nm using UV/Visible spectrophotometer.

The actual drug content was calculated using the following equation.

Drug content (%) = Actual amount of Solid dispersion x 100/ Theoretical amount of Solid dispersion

IN-VITRO DISSOLUTION STUDIES[l]:

In- vitro dissolution studies of Lercanidipine in pure drug from and solid dispersions were performed by using the US pharmacopoeia (USP) model digital capsule dissolution test apparatures 2 (Lab India, DS 8000) at the paddle rotation speed of 50 rpm in 900ml of 0.1N HCL solution. The dissolution rate was studies by placing Lercanidipine 50mg and solid dispersions equivalent to50mg of drug on the surface of dissolution medium. A5ml aliquot was withdrawn at different time intervals, filtered and replaced with 5ml of fresh dissolution medium. The samples were estimated for dissolved Lercanidipine by measuring absorbance at 240nm

Dissolution parameters:

Apparatus	---	USP-II, paddle method
Dissolution Medium	---	0.1N HCL solution
Revolutions per minute	---	50 rpm
Sampling intervals (mins)	---	5, 10,15,20,30,45,60,90,120
Temperature	---	37˚c ± 0.5˚c

RESULT AND DISCUSSION:

Preformulation Studies:

Table.3:

Parameter	Results
Form	Crystalline
Colour	Pale yellow
Solubility	Poorly soluble in water, Soluble in methanol, ethanol acetone and chloroform.
Melting point	185 ^{0}C
Micrometric properties	
Bulk density	0.96 g/ml

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Tapped density	1.05 g/ml
Angle of repose	28.84 º
Compressibility index	14.5%
Hausner's ratio	1.10

Compatibility studies:

Fig.1:FTIR : Pure API (Lercanidipine)

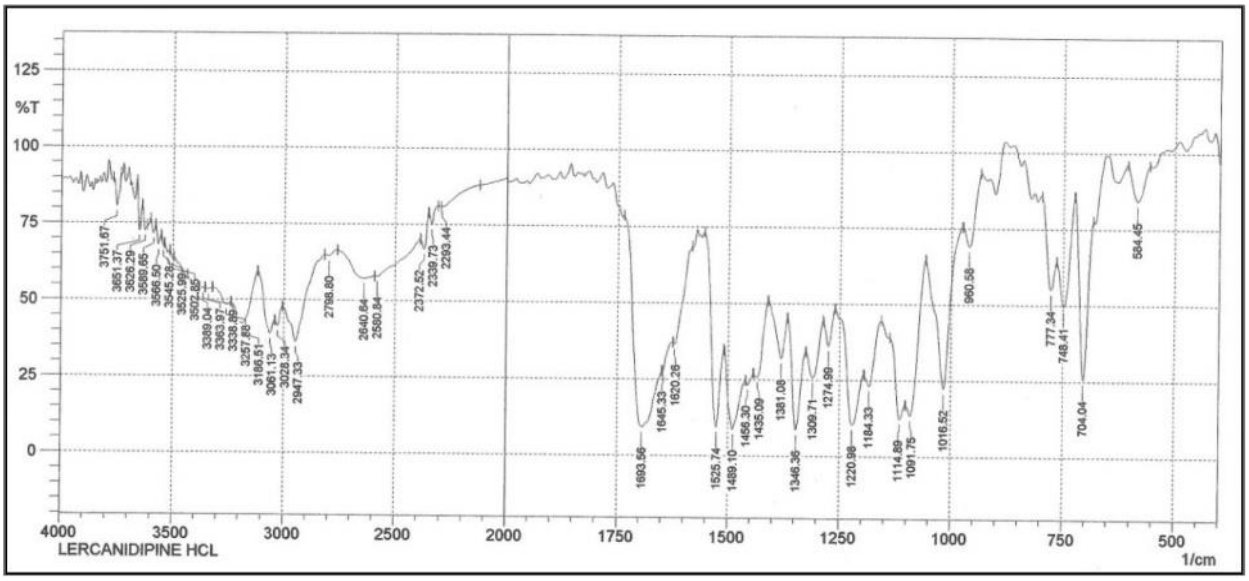

Fig.2:FTIR : API and Carrier (Lercanidipine and Soluplus) – F18

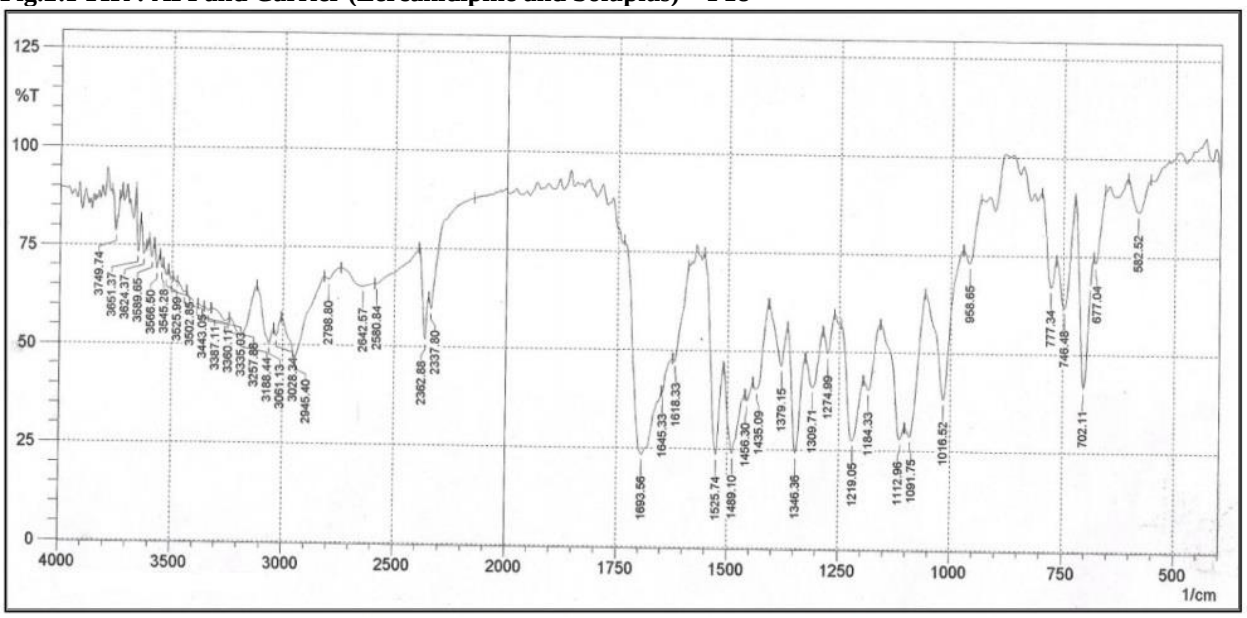

Table.4: Comparision of FTIR spectra between Pure API Lercanidipine and Optimized formulations.

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S. NO.	FUNCTIONAL GROUP	Wave length Cm^{-1}	
		Lercanidipine (API)	Lercanidipine and Soluplus (F18)
1	O-H	3186	3190
2	N-H	3389	3390
3	C-H	3061	3063
4	C-H3	2875	2854
5	C=O	1489	1489
6	C=C	1525	1525
7	C-N	1346	1346

The FTIR scan of lercanidipine HCl, and optimized FD 18 are depicted in figures. The FTIR scan of lercanidipine HCl shows distinct and sharp peaks at 3389 cm-1 (N-H stretching vibration), 1489 cm-1 C=O stretching. The FTIR spectra of F18 displayed same characteristic peaks and no possibility of any chemical interaction between the drug and excipients used in the formulation.

Analytical studies:

TABLE.5: STANDARD CURVE FOR LERCANIDIPINE IN PHOSPHATE BUFFER pH1.2:

CONC(µg/ml)	ABSORBANCE			
	TRAIL 1	TRAIL 2	TRAIL 3	AVERAGE
0	0.00	0.00	0.00	0.00 ± 0.00
5	0.24	0.30	0.26	0.27±0.02
10	0.48	0.55	0.55	0.53±0.04
15	0.69	0.80	0.78	0.76±0.04
20	0.90	1.06	1.00	0.99±0.06
25	1.13	1.25	1.20	1.19±0.02

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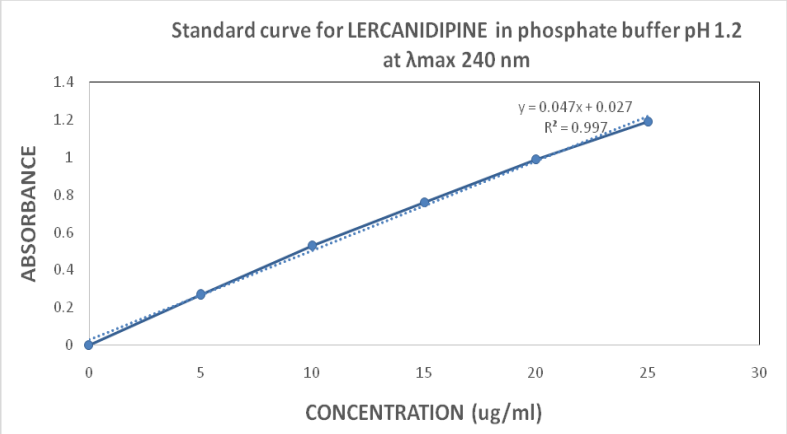
Fig.3:: STANDARD CURVE FOR LERCANIDIPINE IN PHOSPHATE BUFFER OF pH 1.2

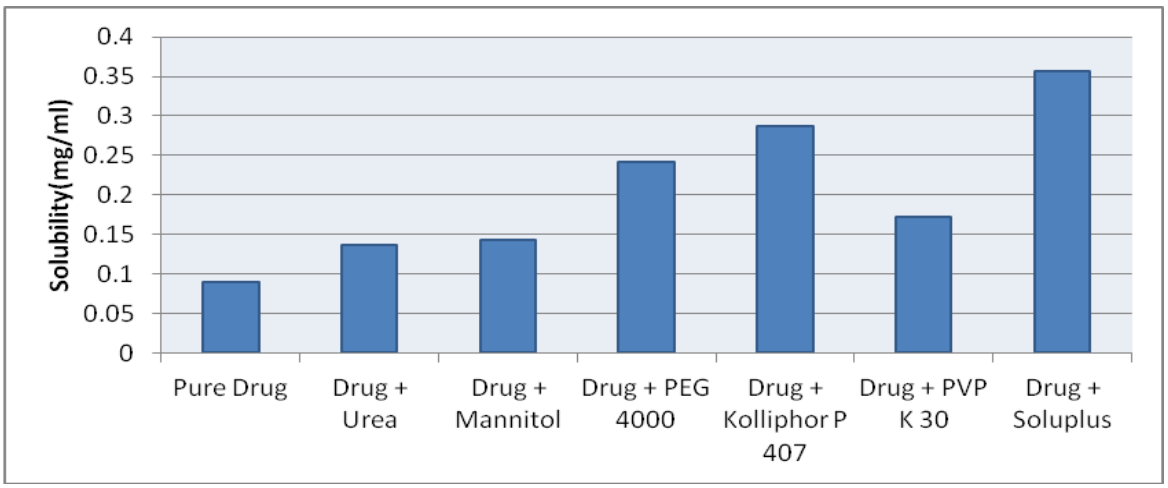


Solubility studies: In case of solid dispersions initially preliminary solubility analysis was carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility was found to be 0.0889±0.013mg/ml. From this study, drug and Soluplus in the ratio of 1:1 shown highest drug solubility i.e. 0.3556±0.028 mg/ml, almost 4-fold increase compared to that of pure drug. For all the water soluble carriers used in preliminary solubility studies, PVP K30, Mannitol and Urea shown low solubility when compared with other carriers and did not included in the preparation of Lercanidipine Hydrochloride solid dispersions. The graphical representation of solubility studies of Lercanidipine Hydrochloride physical mixtures was shown in **Figure.**

Table.6 :Preliminary solubility studies of Lercanidipine Hydrochloridein different polymers

Physical Mixture	Solubility(mg/ml)
Pure Drug	0.0889±0.013
Drug + Urea	0.1360±0.028
Drug + Mannitol	0.1423±0.012
Drug + PEG 4000	0.2421±0.051
Drug + Kolliphor P 407	0.2874±0.009
Drug + PVP K 30	0.1721±0.114
Drug + Soluplus	0.3556±0.028

Fig. 4: Solubility studies of Lercanidipine Hydrochloride physical mixture (1:1 Ratio)



Preparation of Lercanidipine Hydrochloride solid dispersions

Solid dispersions of Lercanidipine Hydrochloride were prepared by using Kolliphor P 407, Soluplus and PEG 4000 different drug-polymer ratios (1:1 to 1:6) are weighed and mixed together in a porcelain dish. Eighteen formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of

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Ethanol as a common solvent. Then the solvent was evaporated. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a sieve before packing in an airtight container, stored in a desiccator and used for further investigations. In the present investigation eighteen formulations were prepared and their complete composition was shown in **Table.** All the solid dispersions prepared were found to be fine and free flowing powers.

Evaluation parameters:

Solubility studies of Lercanidipine Hydrochloride solid dispersions:

Different formulations of Lercanidipine Hydrochloride solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (F18) with Drug and soluplus in the ratio of 1:6 shown highest solubility i.e.0.4281±0.005 mg/ml, almost 4.8 fold compared to that of the pure drug (Pure drug solubility is 0.0889±0.021 mg/m**l**). The results are tabulated in **Table** and graphical representation was shown in **Figure**

Table.7 : Solubility studies of Lercanidipine Hydrochloride solid dispersions prepared by solvent evaporation method:

S. No.	Formulation code	Solubility (mg /ml) *
1	Pure drug (Lercanidipine)	0.0889±0.021
2	F1	0.2421±0.045
3	F2	0.2551±0.012
4	F3	0.2655±0.015
5	F4	0.2789±0.017
6	F5	0.2805±0.085
7	F6	0.2955±0.037
8	F7	0.2874±0.045
9	F8	0.2912±0.014
10	F9	0.2955±0.034
11	F10	0.3119±0.007
12	F11	0.3169±0.012
13	F12	0.3279±0.037
14	F13	0.3556±0.021
15	F14	0.3635±0.017
16	F15	0.3798±0.047
17	F16	0.3846±0.018
18	F17	0.3991±0.009
19	F18	0.4281±0.005

Fig.5: Solubility studies of Lercanidipine Hydrochloride solid dispersion

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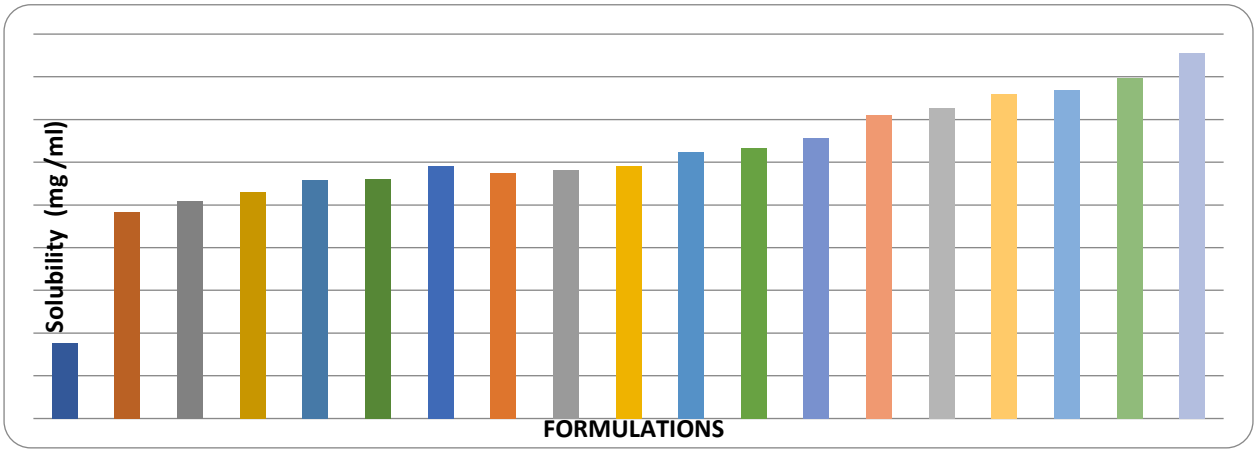

% Practical yield and drug content:

The results of % practical yield for all formulations of solid dispersions found to be 81.99±0.012% - 98.23±0.015%. The results of % practical yield studies are shown in **Table.** Maximum yield was found to be 98.23±0.015% in formulation F18. Actual drug content of all 18 formulations are shown in **Table**. The drug content of the prepared solid dispersions was found to be in the range of 90.08±0.001 – 97.99±0.114 %. Maximum % drug content i.e. 97.99±0.114 % was found in the formulation F18.

Table.8 : % Practical yield and drug content for Lercanidipine Hydrochloride solid dispersions

S. No	Formulation	% Practical Yield	% Drug content
1	F1	95.21±0.101	91.47±0.114
2	F2	92.46±0.002	94.77±0.171
3	F3	93.68±0.031	97.33±0.001
4	F4	83.88±0.004	90.33±0.008
5	F5	96.55±0.005	92.47±0.004
6	F6	91.68±0.011	94.92±0.110
7	F7	91.98±0.013	93.50±0.116
8	F8	96.22±0.122	94.52±0.118
9	F9	91.87±0.121	91.53±0.015
10	F10	94.26±0.141	92.56±0.155
11	F11	81.99±0.012	94.57±0.004
12	F12	96.12±0.004	91.64±0.016
13	F13	91.87±0.051	92.43±0.141
14	F14	93.27±0.013	94.37±0.114
15	F15	94.26±0.121	92.52±0.125
16	F16	91.28±0.117	90.08±0.001
17	F17	97 .23±0.009	96.01±0.182
18	F18	98.23±0.015	97.99±0.114

Table.9 : Micrometric properties for Lercanidipine Hydrochloride solid dispersions

S. No	Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle Of Repose (Degrees)	Compressibility Index (%)	Hausner's Ratio
1	F1	0.84	0.94	25.18	10.02	1.11
2	F2	0.79	0.86	23.34	8.59	1.09
3	F3	0.88	0.98	26.40	9.63	1.11

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4	F4	0.77	0.84	24.57	8.78	1.10
5	F5	0.75	0.82	22.12	8.98	1.10
6	F6	0.83	0.90	24.57	8.23	1.09
7	F7	0.94	1.03	24.57	9.10	1.10
8	F8	0.96	1.05	28.84	8.94	1.10
9	F9	0.81	0.88	23.95	8.40	1.09
10	F10	0.94	1.03	22.12	9.10	1.10
11	F11	0.90	0.98	27.01	7.59	1.08
12	F12	0.86	0.94	25.79	7.89	1.09
13	F13	0.92	0.99	26.40	7.44	1.08
14	F14	0.94	1.03	24.57	9.10	1.10
15	F15	0.92	1.01	27.62	9.27	1.10
16	F16	0.77	0.84	22.73	8.78	1.10
17	F17	0.92	0.99	28.84	7.44	1.08
18	F18	0.94	1.03	28.23	9.10	1.10

Evaluation of flow properties of the Lercanidipine hydrochloride Solid dispersions:

Flow properties of the Lercanidipine hydrochloride Solid dispersions, Angle of repose were found to be in the range of 22.12 to 28.84 indicating acceptable flow properties .The percent compressibility for all formulations lie within the range of 7.44 to 10.02. Hausner's ratio was found to be in a range of 1.09 to 1.11.

In vitro dissolution studies: The drug release data obtained for formulations F1 to F18 are tabulated in **Table.** It shows the cumulative percent drug released as a function of time for all formulations. The cumulative percent drug released after 60 min was shown in table. In vitro studies reveal that there is marked increase in the dissolution rate of Lercanidipine Hydrochloride from all the solid dispersions when compared to pure Lercanidipine Hydrochloride itself. From the in vitro drug release profile, it can be seen that formulation F18 containing Combination of Dug and Soluplus (1:6 ratio) shows higher dissolution rate i.e. 99.87% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The graphical representation of solid dispersions of F1-F6, F7-F12, & F13-F18 were depicted in **Figures** .

Table.10: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F1-F6)

TIME (min)	CUMULATIVE % DRUG RELEASE					
	F1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
0	0	0	0	0	0	0
15	2014	25.73	29.86	31.21	39.23	42.48
30	52.49	65.88	68.68	75.85	75.23	78.48
45	66.91	73.62	75.03	79.15	80.19	83.49

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60	73.53	75.63	79.63	82.75	84.79	85.82

Fig.6: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F1-F6)

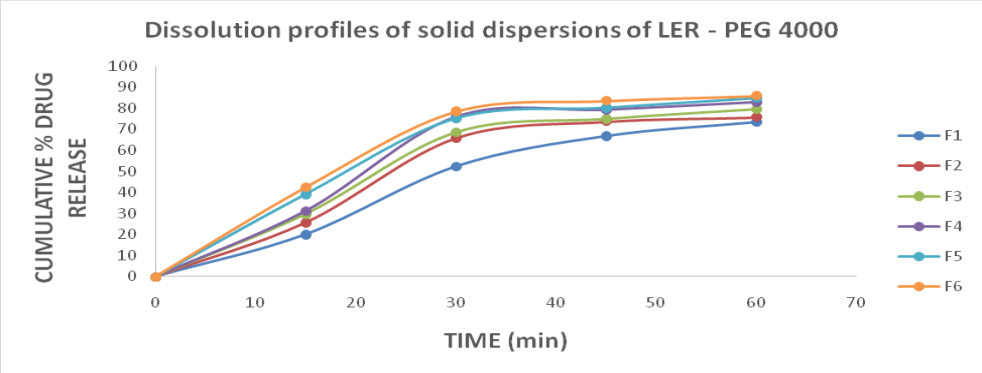

Table.11: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F7-F12)

TIME (min)	CUMULATIVE % DRUG RELEASE					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
15	20.94	35.48	35.52	39.6	40.66	42.86
30	47.15	59.45	65.93	71.29	75.23	80.94
45	56.68	73.96	77.86	79.48	83.06	87.27
60	71.59	78.49	80.74	85.89	90.10	95.32

Fig.7: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F7-F12)

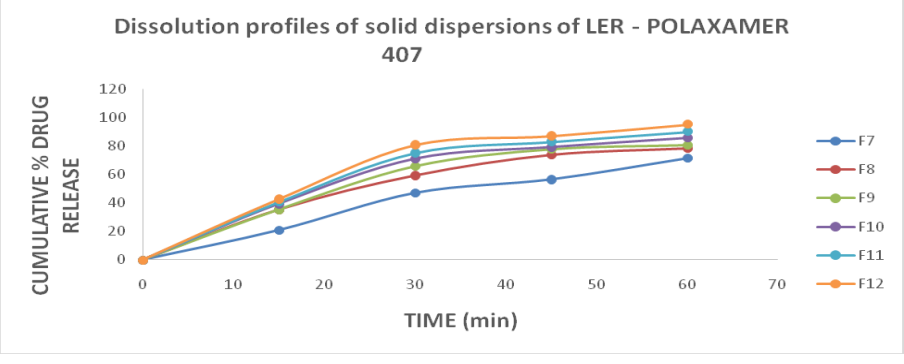

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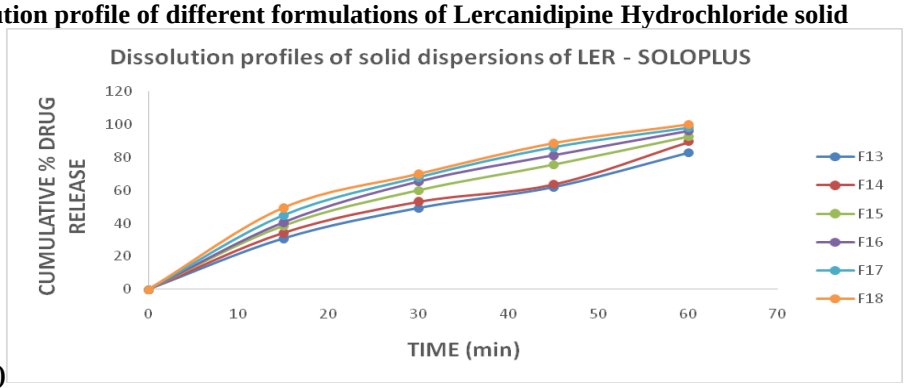
Table.12: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F13-F18)

TIME (min)	CUMULATIVE % DRUG RELEASE					
	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0
15	30.77	34.28	38.59	40.48	44.83	49.49
30	49.16	53.11	60.07	65.15	67.82	69.92
45	61.75	63.62	75.59	81.05	85.98	88.55
60	82.52	89.34	92.62	95.71	97.77	99.87

Fig.8: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (F13-F18)



SUMMARY AND CONCLUSION:

The current investigation established an effective and easy method to formulate lercanidipine HCl solid dispersion with Soluplus to increase its water solubility and also its dissolution. Solid dispersions were prepared by solvent evaporation 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 99% w/w after 60 min. FTIR spectral data of solid dispersion shows interaction between lercanidipine HCl and Soluplus, which confirms that the drug is dispersed at molecular level into polymer matrix. 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.

List of abbrevations: API – active pharmaceutical ingredient, FTIR – fourier transform infrared spectroscopy, LER – lercanidipine, PEG- poly ethylene glycol, SOL – soluplus, UV – ultra violet visible.

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