COMPARATIVE SOLUBILITY ENHANCEMENT OF OLMESARTAN MEDOXOMIL BY USING SOLID DISPERSION, COMPLEXATION AND SELFEMULSIFICATION TECHNIQUES

By

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Under the guidance of,

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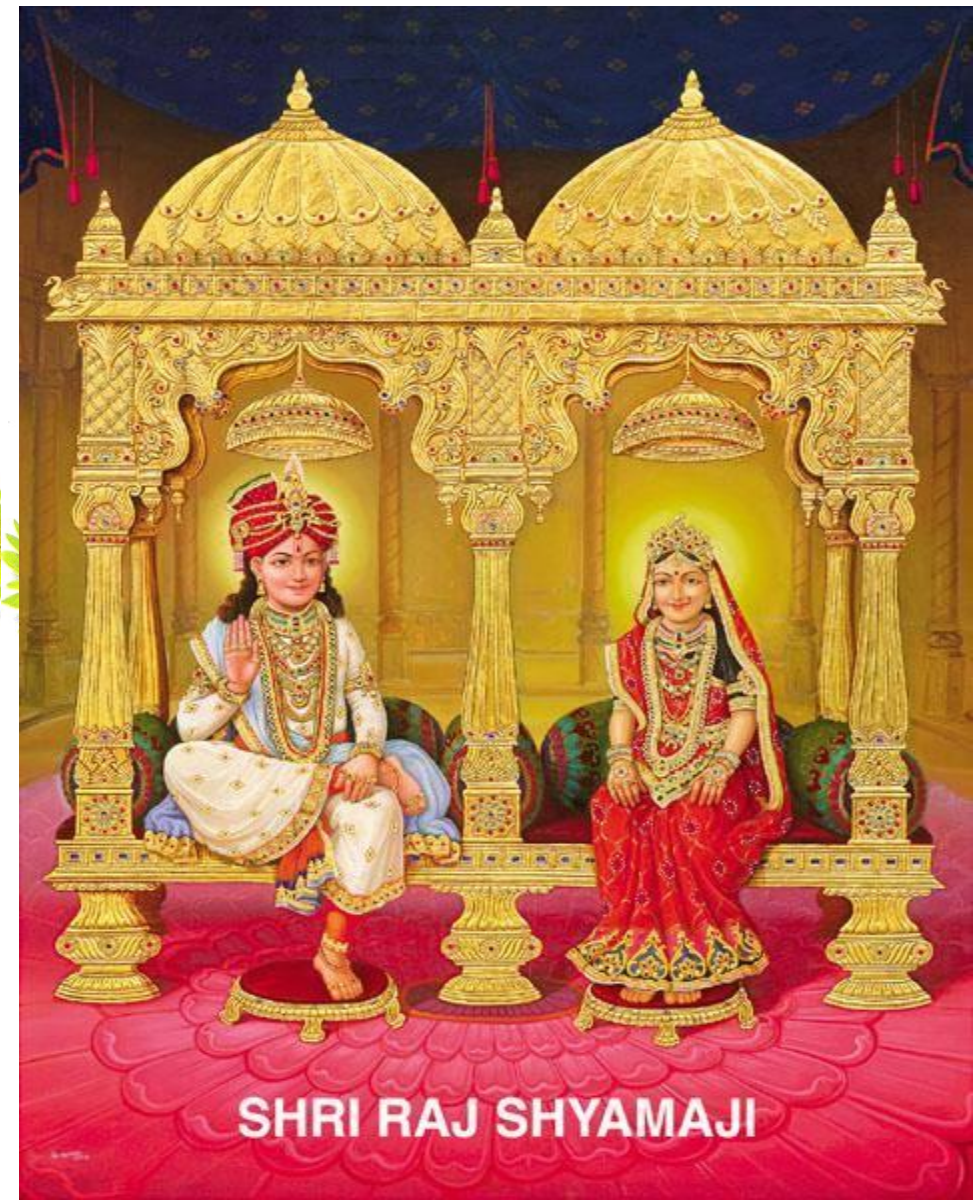

Dedicated to my family members & friends...

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ABSTRACT

Olmesartan medoxomil is a prodrug of Olmesartan, a selective AT1 subtype angiotensin-II receptor antagonist for the treatment of hypertension. It belongs to class II under BCS and posses low oral bioavailability (< 26%) due to its poor aqueous solubility. The purpose of the study was to enhance the aqueous solubility of Olmesartan medoxomil by three different approaches; solid dispersion, complexation and selfemulsification. The solid dispersion was prepared by solvent evaporation method using poloxamer 188 as a carrier. In complexation technique, inclusion complex of drug and β-cyclodextrin was formulated following solvent evaporation technique. In selfemulsification method soya bean oil, tween 80 and PEG 400 were used as oil, surfactants and co-surfactant respectively. The prepared formulations were characterized for compatibility, solubility phase, SEM and dissolution studies. FT-IR study revealed no interaction between drug and excipients. SEM of optimized formulation SD3 showed reduction in particle size with regular surface morphology compared to that of pure drug, poloxamer188 and β-CD. In comparison to pure drug and the physical mixtures of the different carriers used, both the drug solubility and its dissolution rate were significantly increased from the different preparations. Among all methods solid dispersion (SD_3) containing drug: poloxamer188 in the ratio of 1:4 showed rapid and higher drug release (88.36% within 45 min). The in-vitro drug release data was fitted to various kinetic models and all the formulations showed first order kinetics following super case II mechanism. The increase in dissolution rate of Olmesartan medoxomil from solid dispersion of poloxamer 188 might be due to reduction of crystal size of the drug, conversion of drug to amorphous or microcrystalline state and hence decreasing the hydrophobicity of the drug. The increase in solubility of Olmesartan medoxomil was found in the order; solid dispersion> complexation > selfemulsification > pure drug.

Key words: Aqueous solubility, Olmesartan medoxomil, poloxamer188, solid dispersion, complexation, selfemulsification

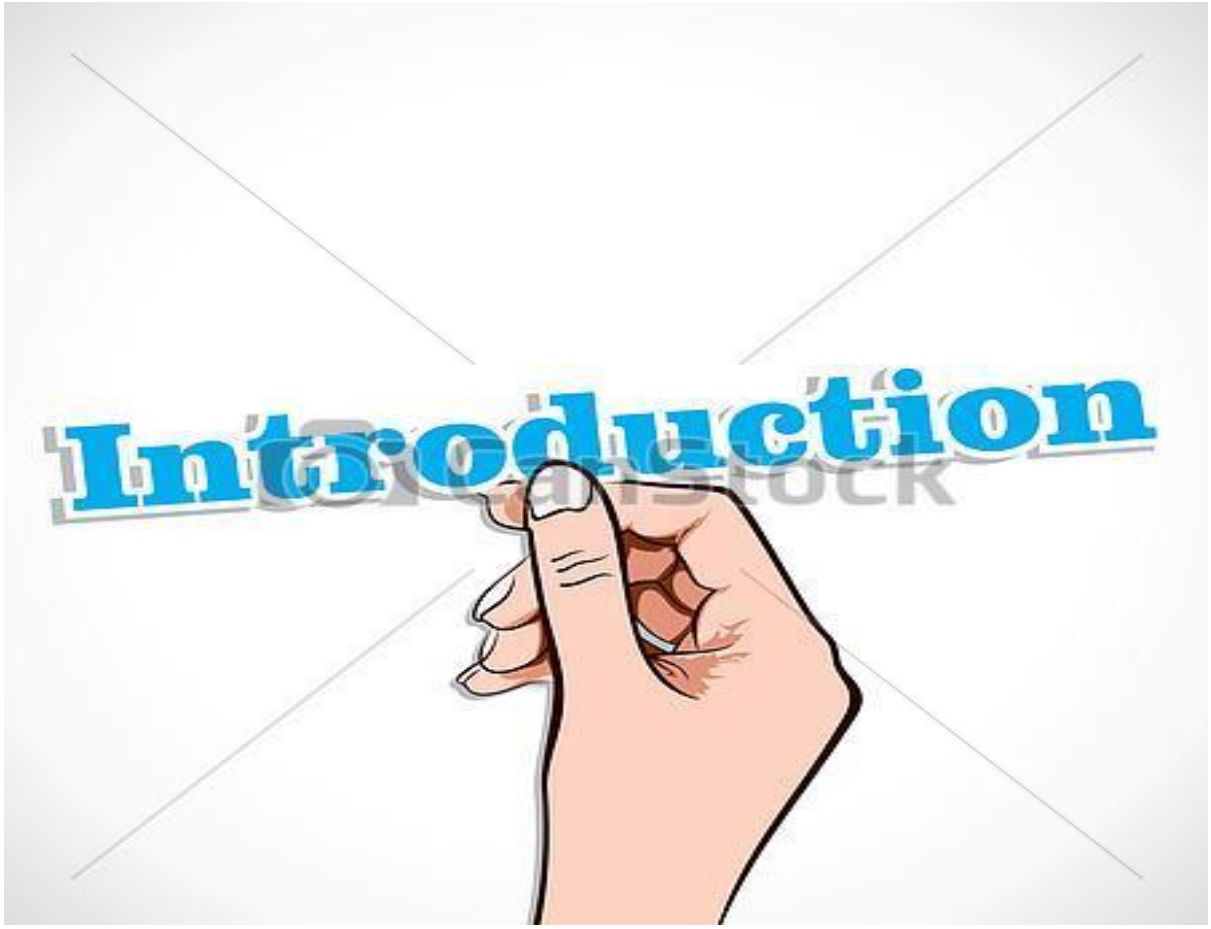
LIST OF ABBREVIATIONS

ABBREVIATIONS	EXPANSIONS
%	Percentage
^{0}C	Degree centigrade
µg	Micro gram
kHz	Kilohertz
pKa	Dissociation rate constant
SCF	Super critical fluid
λ_{max}	Maximum wavelength
%CDR	Percentage cumulative drug release
Conc.	Concentration
Abs	Absorbance
BCS	Biopharmaceutical classification system
SEDDS	Selfemulsifying drug delivery system
SD	Solid dispersion
OLM	Olmesartan medoxomil
β-CD	Beta Cyclodextrin
PEG	Poly ethylene glycol
ACE	Angiotensin converting enzyme
AUC	Area under curve
Cm	Centimetre
Cmax	Maximum plasma concentration of the drug
FTIR	Fourier transform infrared radiation
NMR	Nuclear magnetic resonance
Gm	Gram
Hrs	Hours
DSC	Differential scanning calorimetry
PXRD	Powder x-ray diffraction
Kg	Kilogram

Mg	**Milligram**
Min	**Minute**
Ml	**Millilitre**
Nm	**Nanometre**
pH	**Negative logarithm of hydrogen ion concentration**
RH	**Relative humidity**
RPM	**Revolution per minute**
UV	**Ultraviolet**
w/v	**Weight by volume**
w/w	**Weight by weight**
Vs	**Versus**
SEM	**Scanning Electron Microscopy**
KV	**kilovolt**
ICH	**International Conference of Harmonization**
>	**Is greater than**
<	**Is less than**

LIST OF TABLES

Chapter 1



Introduction

1. INTRODUCTION

1.1 General introduction

The popularity of the oral delivery is being increased day by day around the globe due to its ease of administration and better patience compliance. It has been preferred as the easiest and most common route of drug delivery system. In the formulation design and development of these dosage forms, aqueous solubility and poor dissolution of insoluble drugs remains a major problem for pharmaceutical industry[1].

Recently more than 40% of the new chemical entities developed in the pharmaceutical industry are practically insoluble in water. Orally administered drug completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. There is a chance of slow drug absorption and variable bioavailability due to poor aqueous solubility of the drug. To overcome these problems several methods and techniques have been defined. The techniques generally employed to enhance the solubility of poorly water soluble drugs includes micronization, nanonization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, salt formation, self emulsification, etc. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system[2].

1.2 Solubility:

Solubility is one of the important phenomenon having very effective and significant role in the formulation of various dosage forms. Solubility of any compound in a particular solvent can be defined as the concentration of a solute in a saturated

solution at a certain temperature[3]. It is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at specified temperature. As the solubility increases bioavailability also increases[4]**.** The solubility of drug molecule is a critical factor for determining its usefulness since the solubility indicates the amount of compound that will dissolve and hence the amount available for absorption into the systemic circulation. The molecule having low aqueous solubility is subjected to dissolution rate limited absorption within the gastrointestinal residence time. The solubility of molecules can also be expressed by variety of concentration such as quantity per quantity, percentage, parts, molarity, molality, mole fraction, milliequivalents, and parts of solvent required to solubilize for one part of solute as explained in U.S pharmacopeia which is shown in table [3].

Table 1: Examples of drugs with their solubility[3]

Terms	**Parts of solvent required for 1 part of solute**	**Examples of drugs**
Soluble	From 10-30	Cyclophosphamide, propananolol
Very soluble	Less than 1	Metoprolol, deltiazem
Freely soluble	From 1- 10	Ipratropium bromide
Sparingly soluble	From 30-100	Fluorouracil, ramipril
Slightly soluble	From 100-1000	Atenolol, valsartan
Very slightly soluble	From 1000-10,000	Lomustine, busulphan
Practically insoluble	More than 10,000	Chlorambucil, candesartan

In 1995 Amidon et al devised BCS (Biopharmaceutics classification system) which categorized the drugs into four classes based on their solubility and permeability.

Table 2: BCS classification of drug

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

According to BCS solubility challenges are faced in the classII and classIV where the dissolution becomes rate limiting step for the absorption of drug[4].

1.2.1 Process of solubilization:

Solubilization is defined as the spontaneous passage of poorly water soluble solute molecules into an aqueous solution of surfactant. When different molecules interact there appears both the repulsive as well as attractive forces. The intramolecular forces and valence bond involved are[5]:

Intramolecular forces

- Dipole-dipole interaction (Keesome interactions)
- Dipole- induced dipole interaction (Debye interactions)
- Induced-dipole interaction-Induced-dipole interaction (London dispersion forces)
- Ion-dipole interaction
- Hydrogen bonds

Valence Bonds

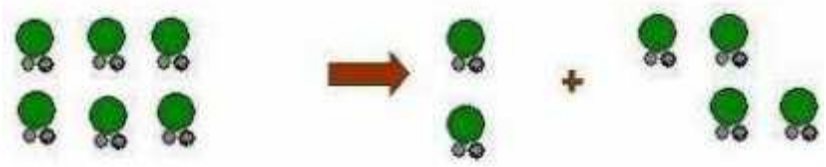
- Electrovalent Bond
- Covalent Bond
- Homo-polar Bond
- Ionic Bond

- Heteropolar Bond

The process of solubilization involves the breaking down of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. During the process, breaking of solute bond occurs leading to the formation of holes. When solubilization process occur solid molecules break down because of breaking of inter molecular bonding and integrating of freed solute molecule in the solvent [6]. The different steps involved in the process of solubilization can be illustrated in the figures as given below[7]:

Step 1: Holes opens in the solvent

Step 2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

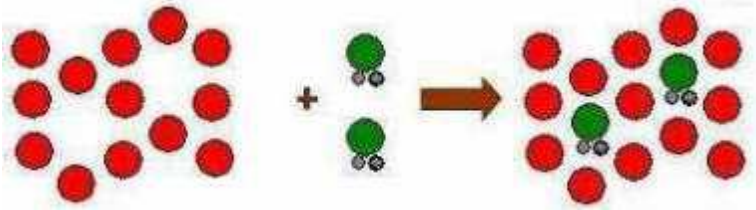


Fig. 1: Process of solubilization.

1.2.2 Factors affecting solubility:

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature, pressure of system. The different factors that show great impact on the solubility of molecules are described below [8].

1. Particle size: The effect of particle size on solubility is given by Kelvin equation[9]:

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where, S is the solubility of infinitely large particles

S_0 is the solubility of fine particles

V is the molar volume

r is the radius of the fine particle

T is the absolute temp in degree Kelvin

R is universal gas constant

γ is the surface tension of solid

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent[10].

2. Temperature: If the solution process absorbs energy then the temperature is increased thereby increasing the solubility. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases[11].

3. Pressure: For gaseous solutes, an increase in pressure increases solubility and decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility[12].

4. Nature of solute and solvent: While only 1 gram of lead chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility of these two substances is due to the result of differences in their nature[13].

5. Molecular size: Molecular size will affect the solubility of drug. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent[11].

6. Polarity: Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces which give the non-polar solvent a chance to solvate the solute molecules[12].

7. Polymorphs: A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always

constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities [13].

1.2.3 Approaches to enhance the solubility:

A number of methodologies can be adapted to enhance solubility of poorly water soluble drugs and further to improve their bioavailability. Some of these methodologies are described below [14].

Particle size reduction: The solubility of drug is related to the particle size. Particle size reduction can be achieved by micronization and sonocrystallization. Each technique utilizes different equipments for reduction of the particle size.

Micronization: By reducing the particle size, the increased surface area improves the dissolution properties of the drug. The micronization is used to increased surface area for dissolution. Micronization increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

Sonocrystallization: Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel

approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallization. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients [15].

Nanosuspension technology: Nanosuspension technology has been developed as a promising candidate for effective delivery of poor water-soluble drug. Nanomilling process reduces the particle size of active pharmaceutical ingredient down to the sub-micron range. As the dissolution rate of the poorly soluble drug is proportional to the surface area, therefore nanomilling or nanosizing of poorly soluble drugs is a potential technique to achieve better in vitro dissolution and high in vivo exposure. Further, the saturation solubility of the drug also increases with reduction of particle size of the API. Finally the nanosystems have been known to reduce variability of drug absorption due to food effects for orally administered drug. Nanosuspension are submicron colloidal dispersion systems which compromises of particle size usually less than one micron ranging between 200 and 600 nm. It can be prepared by two basic methods. One is the bottom-up approach and other is the top down approach. Due to limitation of the bottom-up process during scale-up, the top-down techniques are frequently used as the potential technology for different commercial products. The top down process involves the particle size reduction of compounds using different wet milling techniques like media milling, microfluidization, high pressure homogenization, etc. The media milling comprises mechanical attrition of drug particles using milling media such as yttrium stabilized zirconium oxide beads of definite size range. During the milling process there is chance

of formation of thermodynamically unstable suspension due to the change of Gibbs free energy, which results in agglomeration or crystal growth and may have impact on dissolution and in vivo performance due to formation of larger particles with decreased surface area. Therefore proper selection of stabilizers is required during the preparation of nanosuspension to stabilize the nanoparticles[16].

Use of surfactant: The use of surfactants to improve the dissolution performance poorly soluble drug products has also been successfully employed. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), an example of poloxamers based micelles, Poly (beta-benzyl-Laspartate) -b- poly (ethylene oxide), Poly (caprolactone) -b- poly (ethylene oxide) etc are used as carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. Micelles are supramolecular self assemblies of macromolecules where unimers are held by non-covalent interactions. The core of the micelles solubilizes drugs whereas the corona/shell allows for their suspension in aqueous media. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. Examples of poorly soluble compound that uses surfactants to enhance their solubility are gliclazide, glyburide, glimepiride, glipizide, albendazole, rofecoxib, piroxicam, etc. Their enhanced in solubility and higher dissolution is due to the solubilization effect in diffusion layer, increased wettability and surface availability to the dissolution medium[17].

Salt formation: The interest in salt formation has grown greatly over the past half a century and, in recent years, it has become the most commonly applied technique of increasing solubility and dissolution rate in drug product development Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. Salt formation to increase aqueous solubility is the most preferred approach for the development of liquid formulations for parenteral administration. For solid dosage forms, the dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal pH conditions were much higher than those of their respective free acid forms. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts or not. pH-solubility interrelationships also dictate what would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different gastro intestinal pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ions or not[18].

pH adjustment: It is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading. Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment principle can be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2-7.4. To assess the suitability of the approach, the

buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds. Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs. The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug[19].

Hydrotrophy solubilization: The term hydrotropy refers to the process where the solubility of insoluble or slightly soluble drugs in aqueous media is increased by the addition of excess amount of additives or second solute. The mechanism by which it increases solubility is more closely associated to complexation involving a weak interaction between the hydrotropic agents and the solute. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Some hydrotropic agents used are sodium benzoate, urea, sodium alginate, sodium acetate etc. In hydrotropy techniques many different class of drugs like anti-viral, antipyretic, antitumor, anti-inflammatory and analgesic drugs are used for solubility enhancement.

Hydrotrophy technique is applied for solubility enhancement of riboflavin, nimesulide, nifidepine and xanthine derivatives such as caffeine and theophylline[19,20].

Solid dispersion: Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. 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 where matrix can be either crystalline or amorphous is dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [21]. The process of dispersion is individualized depending on the interaction between drug and carrier. One of the underlying principles of formulation of solid dispersion is achievement of the amorphous state which is considered to be more soluble than the crystalline state because in the amorphous state, no energy is required to break the crystal lattice found in the crystalline phase[22].

Mechanism of solid dispersion:

Numbers of theories have been proposed yet, for the mechanism by which solubility and the dissolution rate enhancement occurs in solid dispersion but not fully understood. The currently accepted range of possible mechanisms of enhanced dissolution effectively includes the following [23]:

- By particle size reduction and reduced agglomeration
- Formation of amorphous structure replacing crystalline structure
- By improving local solubility and wettability of the poorly soluble drug in the solid dispersion matrix
- Interactions of the drug with carrier functional groups

- Complex formation of drug with inert soluble carriers
- Swelling and capillary action of carrier
- Surface activity and miscellar solubilization
- By increasing the porosity of solid dispersion

Classification of solid dispersion:

Solid dispersions have been classified mainly into five major categories namely; Simple eutectic mixtures, solid solutions, glass solutions of suspension, compound or complex formations between the drug and the carrier and amorphous precipitations of a drug in a crystalline carrier.

Simple eutectic mixture: A eutectic mixture of sparingly water soluble drugs and a highly water- soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These components are assumed to crystallize simultaneously in very small particulate sizes. The increase in specific surface area, therefore, is mainly responsible for the increased rate of dissolution of poorly water- soluble drugs[24].

Solid solutions: Solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. It was reported that a solid solution of a poorly soluble drug in a fast dissolving carrier achieves a faster dissolution rate than a eutectic mixture because the drug particle size is reduced to its absolute minimum as it is molecularly dispersed in the carrier in a solid solution[25].

Glass solution of suspension: Glass suspension is a two-phase system consisting of a carrier in amorphous state with the incorporated drug substance in crystalline form. Method to obtain glass suspensions consists in crystallization of the drug substance in

amorphous carrier, while particle size of dispersed phase is dependent on the rate of cooling/ evaporation of solvent[26].

Compound or complex formations: Drug and matrix strongly interact and form complexes in aqueous medium e.g. Cyclodextrins. Low association constant is necessary for dissolution enhancement. The formation of soluble complex possibly takes place when low or intermediate fraction of carrier is employed in the preparation of solid dispersion. Using a high fraction of carrier, drug dissolution may be promoted owing to the formation of a solid solution[27].

Amorphous precipitation in crystalline carrier: This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form. Drug gets precipitate in an amorphous form in the crystalline carrier from a melting or solvent method of preparation. Amorphous form produces faster dissolution rate than the crystalline form[28,29].

Preparation of solid dispersion:

Various preparation methods for solid dispersion have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while drug and matrix are poorly miscible. During many of the preparations techniques, demixing and formation of different phases is observed which are difficult to control and therefore unwanted. It can be minimized by maintaining the low molecular mobility of matrix and drug during preparation and also by maintaining the driving force for phase separation low by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility as long as possible. The different preparation methods for solid dispersion are described below[30].

1. Solvent evaporation method:

This technique involves dissolving the drug and the carrier in a suitable organic solvent or a combination of solvents to get a clear solution. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent is then evaporated directly on a water bath or hot plate or using a rota-vapour. The resulting solid dispersion is stored in the desiccators under vaccum and pulverized to obtain the desired size fraction. The important prerequisite for the manufacturing of solid dispersion using the solvent method is that both drug and the carriers are sufficiently soluble in the solvent. A basic process of preparing solid dispersion of this type consists of dissolving the drugs and the polymeric carrier in a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane[31.]

2. Kneading method:

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary[32].

3. Melting or fusion method:

This 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. The modification in the method can be done by 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. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures[33].

4. Melt extrusion method:

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 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, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets[34].

5. Co-Precipitation Method (Co-Evaporates):

Accurately weighed carrier is dissolved in water and drug in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then heated and evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried[35].

6. Spray Drying Method:

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing[36].

7. Gel Entrapment Technique:

Carrier is dissolved in organic solvent to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved[35].

8. Supercritical fluid technology:

In the pharmaceutical field, the SCF technology was industrially applied in the early 1980s, in the same period, interest in using SCFs for precipitation and crystallization processes was developing for pharmaceutical materials. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). It is safe, environmentally friendly, and economical and also due to its low operating conditions (temperature and pressure) makes SCFs attractive for pharmaceutical research. Carbondioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.10C) and pressure (Pc = 73.8 bar). At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilized within SCF, they may be recrystallised at greatly reduced particle sizes SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels[37-38].

9. Lyophilization technique:

Freeze-drying involves transfer of heat and mass to from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization 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. Then the prepared sample is freezed to a temperature of - 45˚C and lyophilized in a freeze dryer at a temperature of - 40˚C and vacuum of 90 x 10-3 Mbar. The freeze dried mass was then sifted through 60 mesh sieve and stored in air tight container until further evaluation[39,40].

Evaluation and characterization of solid dispersion[41,42]:

Solid dispersion can be characterized with several analytical methods. FT-IR Spectroscopy, scanning electron microscopy, X-ray diffraction, dissolution rate determination and thermal analysis methods like thermo-microscopic method, differential thermal analysis (DTA), and differential scanning colorimetry (DSC) can be employed for solid dispersion evaluation. Characterization of polymorphic and solvated forms involves quantitative analysis of these different physicochemical properties are listed along with the sample requirements for each test.

Drug –carrier miscibility

- Hot stage microscopy
- DSC (Conventional modulated)
- PXRD (Conventional and variable temp)
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure

- Scanning electron microscopy

- Surface area analysis

Surface properties

- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarized light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC
- PXRD

Stability

- Humidity studies
- Isothermal calorimetry
- DSC (Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

Advantages of solid dispersion[43]:

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug in to amorphous form.
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceuticals.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.

Disadvantages of solid dispersion[44]:

- There is possibility of crystallization of amorphous state during processing and storage.
- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state thereby decreased in solubility and dissolution rate.
- Poor scale-up of manufacturing as well as laborious and expensive methods of preparation.
- Reproducibility of physicochemical characteristics.
- Difficulty in incorporating into formulation of dosage forms.

Selfemulsification:

Self-emulsifying drug delivery systems (SEDDS) or self-emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid

surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/surfactants[45].

Properties of SEDDS[46]:

- They are able to self emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.
- They require lower dose of drug with respect to conventional dosage forms.

Mechanism of Selfemulsification:

Self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by equation:

$$DG = SN_1pr_12s$$

Where, "DG" =free energy associated with the process (ignoring the free energy of mixing)

"N" = number of droplets; "r"= radius of droplets and "S" = interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence[47].

Basic components of self emulsifying drug delivery system:

1. Oils: In the self-emulsifying formulations oil can solubilize the lipophilic drug in a specific amount. And increase the fraction of lipophilic drug transported via the intestinal lymphatic system, therefore increasing absorption from the GI tract. In contrast, modified or hydrolyzed vegetable oils have been widely used because of the higher fluidity and better solubility properties. Examples: Corn oil, olive oil, oleic acid, sesame oil, hydrogenated soyabean oil, hydrogenated vegetable oils, Soyabean oil, peanut oil, etc[48].

2. Surfactants: Surfactants or surface-active agents are amphiphilic molecules and consist of both hydrophilic and lipophilic parts. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows[49];

i). Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3-) or sulphate (ROSO3-). Examples: Potassium laurate, sodium lauryl sulphate.

ii). Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

iii). Ampholytic surfactants: (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

iv). Nonionic surfactants: where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or Polyoxyethylene (OCH2CH2O). Examples: Sorbitan esters (Spans), polysorbates (Tweens)[49].

3. Co-solvents: Relatively high surfactant concentrations (usually more than 30% w/w) are needed in order to produce an effective self-emulsifying system. Organic solvents,

suitable for oral administration (ethanol, propylene glycol, polyethylene glycol, etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems, although alcohol- free self-emulsifying micro-emulsions have also been described in the literature[50].

Evaluation of SEDDS formulations:

The prepared SEDDS formulations are evaluated for the following properties[51,52]:

- Thermodynamic stability study
- Dispersibility test
- Turbidimetric test
- Viscosity determination
- Droplet size analysis
- Drug content
- *In-vitro* dissolution

Advantages of SEDDS[53]:

- Protection of sensitive drugs
- More consistence drug absorption
- Selective targeting of drug towards specific absorption window in GIT
- Control of delivery profiles
- Reduced variability including food effects
- Enhanced oral bioavailability enabling reduction in dose
- High drug loading efficiency
- For both liquid and solid dosage forms

- Protection of drug from the gut environment

Disadvantages of SEDDS[54]:

- Due to presence of high surfactant concentrations there may be chances of instabilities of drugs.
- Also the high content of surfactant in self emulsifying formulations irritates the gastrointestinal tract. This problem may be avoided by utilizing optimum less amount of surfactants.
- Sometime co-solvents remain into the formulation and cause degradation of drugs.
- It may allow less drug loading.

COMPLEXATION

Another method to increase drug solubility is by complexation with cyclodextrin which is advantageous over the above mentioned technique because of low hygroscopicity, less toxicity, (as compared with solid dispersions) high fluidity, excellent compatibility and compressibility of cyclodextrin complexation improves the stability of drugs in a formulation, resulting in longer shelf life. The unique structure of cyclodextrin has allowed to serve as modalities as diverse as enzyme mimics, chiral separation tools and complexing agent in pharmaceutical industries.[55]

Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be prepared simply by adding the drug and excipients together, resulting in enhanced drug solubilization. Inclusion complexes are formed by the insertion of the nonpolar molecule (known as guest) into the cavity of another molecule (as host). The most commonly used host molecules are cyclodextrin[56].

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α, β or γ respectively) obtained by the enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Out of the three parent cyclodextrins, β- cyclodextrin (β-CD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties. Natural cyclodextrins have limited water solubility. However, a significant increase in water solubility has been obtained by alkylation of the free hydroxyl groups of the cyclodextrin resulting in hydroxyalkyl, methyl and sulfobutyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group[57].

Mechanism of complexation:

The mechanism of complexation processes were discussed as CDs can be regarded as cylinders with hydrophilic outside and hydrophobic inside. The hydrophobic cavity forms an ideal harbour in which poorly water soluble molecules are to be protected from the surrounding atmosphere shelter their most hydrophobic parts or whole molecules. These hydrophobic molecules which can fit in the CD cavity are included in it in the presence of water. In aqueous solution the polar CD cavity is occupied by water molecules that are in an energetically unfavoured state (Polar – a polar repulsion) and are therefore, readily replaced by an appropriate guest molecules that is less polar than water

and forms an inclusion complex. The degree of complexation with CD depends upon the dimensions and lipophilicity of the guest molecules. The guest molecule or as part of it must fit into the CD cavity[58,59].

Different approaches for making inclusion complexes:

1. Kneading Method: This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through a sieve if required. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines[60].

2. Physical blending method: A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 min[58].

3. Co precipitation technique: Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex[58].

4. Solvent evaporation method: This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular

dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hrs and evaporated under vaccum at 45 ºc. The dried mass was pulverized and passed through a 60-mess sieve[61].

5. Lyophilization/Freeze-Drying Technique: Lyophilization/freeze drying technique is considered as an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent In order to get porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method[60].

6. Atomization/spray drying method: In spray drying, cyclodextrin is dissolved in 200 ml of a solution previously alkalinized with 25% aqueous ammonia (final pH 9.5). The guest is dissolved in 100 ml of 96% ethyl alcohol. Both solutions are mixed and sonicated and the final solution is spray-dried to get the complexes[62].

Techniques for characterization of inclusion complexation:

The complexation depends largely on the dimensions of the cyclodextrins and the particular sterical arrangement of the functional groups of the molecules, which characterized both in the solid and solution state by the following techniques[63]:

(A) Inclusion complexation in the solid state characterized by;

(i) Thermo-analytical methods.

(ii) Scanning Electron Microscopy (SEM)

(iii) X-ray diffractiometry and single crystal X-ray structure analysis

(iv) Wettability and dissolution tests

(v) Infra-Red spectroscopy

(vi) Thin Layer Chromatography

(B) Inclusion complexation in solution state characterized by;

(i) Electrochemistry studies

(ii) Solubility studies

(iii) Spectroscopy methods like:

(a) Nuclear Magnetic Resonance spectroscopy

(b) Electron Spin Resonance

(c) Ultraviolet/Visible (UV/VIS) spectroscopy.

(d) Fluorescence spectroscopy.

(e) Circular Dichroism spectroscopy.

1.3 An overview of hypertension:

Cardiovascular diseases are one of the life threatening diseases of mankind and hypertension is one of them, which required constant care and monitoring. It is well known that hypertension is a major risk factor for congestive failure as well as coronary artery disease. The risk of congestive heart failure may be reversed during the control of hypertension[64].

Hypertension is a common disease in industrialized country and accounts for 6% of death worldwide. An elevated arterial blood pressure is a major problem, particularly in developed countries. It is very essential to control the hypertension and maintain

sufficient blood flow to the heart in order to reduce the morbidity and also make the patient to live their normal life. The conventional treatment of chronic illnesses like diabetes, hypertension etc ironically sometimes disturbs the normal rhythm of the life. The ultimate aim of each and every therapy is to restore the normalcy of life without any affects to patient. Conventional dosage forms cause fluctuation of drug level in the plasma and hence, certain adverse effects are seen. Therefore the success of any therapy depends up on the dosage form of the drug which maintains constant drug plasma levels[65, 66].

Blood pressure is continuously distributed in the population and there is no clear cut-off point between hypertensive and normotensive subjects, although a figure of systolic/diastolic blood pressure of 140/90 mmHg is considered the upper limit of 'normal'. The complications of hypertension include stroke, myocardial infarction, heart failure, renal failure and dissecting aortic aneurysm and the risk of cardiovascular disease doubles for 20/10mmHg raise in blood pressure. The World Health Organization reported that suboptimal blood pressure (>115mmHg) is responsible for 62% of all cerebrovascular diseases and 49% of all ischemic heart diseases[67, 68].

1.3.1 CLASSIFICATION OF HYPERTENSION[69,70]

Hypertension can be classified either essential (primary) or secondary.

- **Essential / primary hypertension** indicates that no specific medical cause can be found to explain a patient's condition where cause for the increase in blood pressure is unknown.
- **Secondary hypertension** indicates that the increase in blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumors

(Pheochromocytoma and Paraganglioma) in which definite cause for the increase in blood pressure is unknown. Secondary hypertension comprises 5-10% cases of hypertension.

Both essential and secondary hypertension may be benign or malignant.

- **Benign hypertension** is moderate elevation of blood pressure where the blood pressure rises slowly over the years. About 90% patients of hypertension have benign hypertension.
- **Malignant hypertension** is marked and rapid increase of blood pressure to 200/140mmHg. Less than 5% of hypertensive patients develop malignant hypertension and life expectancy after diagnosis in these patients is less than 2 years if not treated effectively.

1.3.2 Pathophysiology of Hypertension[71]:

The pathogenesis of essential hypertension is still unknown. Earlier days it was suggested that renal sodium retention, expanded vascular volume, increasing cardiac output etc which led to increased vascular resistance. Later, it was suggested that sympathetic nervous system plays primary role. Syndrome X relationship gives that hypertension is mainly related to obesity, insulin resistance, glucose intolerance and hyperinsulinemia.

1.3.3 Diagnosis[71]:

The diagnosis of hypertension is based on repeated and reproducible measurements of elevated blood pressure. It serves primarily as prediction of consequences for the patient and later includes a statement about the cause of

hypertension. Its diagnosis depends mainly on measurements of blood pressure and not on symptoms reported by patients.

1.3.4 Treatment[71]:

The first step in treatment of hypertension may be non-pharmacologic which includes sodium restriction, weight reduction in obese patients. Pharmacologic management includes a single drug for mild hypertension while for moderate to serve hypertension a combination of two or more drugs.

1.3.5 Classification of Antihypertensive agents[72]:

i. **Diuretics:** eg. Chlorthalidone, Clopamide, Indapamide
ii. **ß-Adrenergic blockers:** eg. Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol
iii. **à-Adrenergic blockers:** eg. Terazosin, Prazosin, Doxazosin
iv. **à + ß Adrenergic blockers:** eg. Labetalol, Carvedilol
v. **ACE inhibitors:** eg. Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, Trandolapril, Benazepril
vi. **Calcium channel blockers:** eg. Amlodipine, Felodipine, Nifedipine, Nimodipine, Verapamil
vii. **Vasodilators:** eg. Hydralazine, Minoxidil, Sodium nitroprusside
viii. **Angiotensin-II receptor antagonists:** eg. Candesartan, Losartan, Valsartan, Olmesartan
ix. **Central sympatholytics:** eg. Clonidine, Methyldopa.

Olmesartan Medoxomil (OLM) is a selective AT1 subtype angiotensin-II receptor antagonist that is approved for the treatment of hypertension. OLM dose dependently reduces blood pressure through arterial vasodilatation and reduced sodium retention, as

do other angiotensin receptor blockers. It is a prodrug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite Olmesartan. Half-life of Olmesartan Medoxomil is 13 hours. Aqueous solubility of OLM is <7.75 μg/ml. Oral bioavailability of this tablet formulation is only 26% in healthy humans due to low aqueous solubility. The unabsorbed drug leads to gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis and nausea. Thus, improving oral bioavailability of OLM can increase clinical efficacy, reduce the oral dose required to achieve the same effect and hence reduce the side effects[73].

In present study, attempt is made for comparative study for enhancing the solubility of Olmesartan medoxomil by using solid dispersion, self emulsification and inclusion complexation methods by using various carriers like cyclodextrin, poloxamer, PEG, tween, etc in different ratios, thereby enables to know which of these formulations shows the better aqueous solubility and dissolution profile.

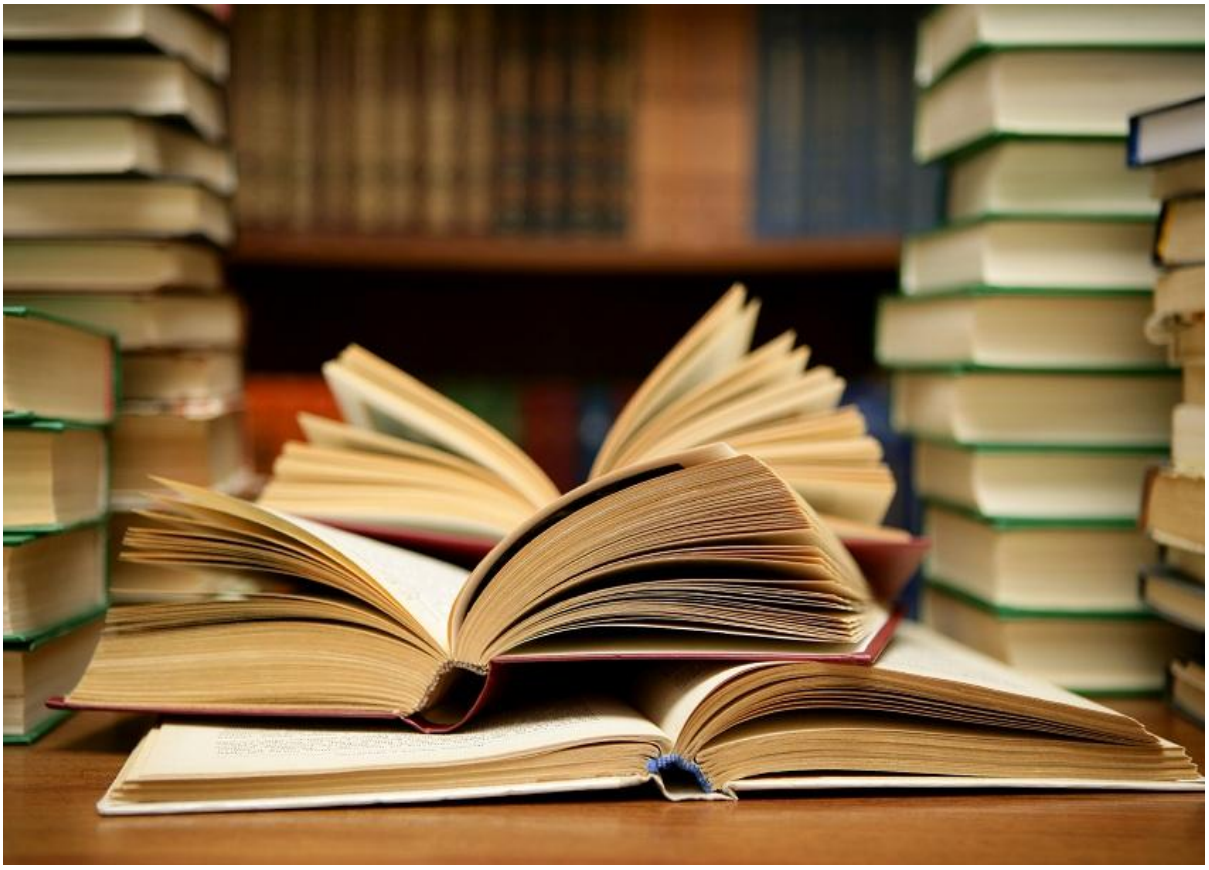
CHAPTER 2

OBJECTIVES

2. AIM OF THE WORK

- The key objective of the work is to enhance in the solubility and dissolution rate of a poorly water soluble drug, Olmesartan Medoxomil by using solid dispersion, complexation and selfemulsification techniques.
- To characterize the physiochemical properties of the model drug, Olmesartan Medoxomil along with the excipients used.
- To carry out the preformulation studies of the drug and the polymers.
- To prepare the solid dispersion of Olmesartan medoxomil with poloxamer 188 by using the solvent evaporation method.
- To characterize and evaluate the prepared solid dispersion for enhanced in the solubility and dissolution rate.
- To formulate the inclusion complex of Olmesartan medoxomil by complexing with the β-cyclodextrin by using solvent evaporation technique.
- To find out the increased in solubility and dissolution of the prepared inclusion complex.
- To formulate the selfemulsifying drug delivery system of Olmesartan medoxomil with oil, surfactant and co-surfactant in different ratios.
- To evaluate the different parameters of selfemulsifying drug delivery system.
- To check the drug excipients compatibility as well as the stability of dosage form.
- Finally, to carry out the comparative study of solubility or dissolution profile of Olmesartan Medoxomil which is prepared by following solid dispersion, complexation and selfemulsification methods.

Chapter 3



Review of Literature

3. REVIEW OF LITERATURE

Tayseer El-nawawy *et al.,*[74] enhanced the dissolution of poorly-water soluble Olmesartan medoxomil by solid dispersion preparation and formation of inclusion complexes. Solubility determinations prepared by solvent evaporation method and by fusion (melting) method. The inclusion complexes of OLM with β-CD were prepared in different D/C ratios (1:1, 1:2, 1:3, 1:4 and 1:5) by kneading method. In comparison to pure drug and the physical mixtures of the different carriers both the drug solubility and its dissolution rate was significantly increased from the different preparations. Particularly, solid dispersions of Drug: Polyethylene glycol 6000 in ratios of 1:3 and 1:5 achieved a rapid and complete drug release. In conclusion, solid dispersion prepared with Polyethylene glycol 6000 by fusion method appeared to alleviate the solubility problems of Olmesartan medoxomil and improved its dissolution profile.

Abdul Hasan Sathali *et al.,*[75] prepared solid dispersions of Olmesartan medoxomil to improve the aqueous solubility and dissolution rate in order to enhance bioavailability. In the present study, solid dispersions of Olmesartan with different carriers like poly ethylene glycol 4000 (PEG 4000), HPMC K4, HPMC K100, Poloxamer-407 and crospovidone in different ratios (1 : 1, 1 : 2, 1 : 4, 1 : 6) were prepared by melting, solvent evaporation and kneading methods. *In vitro* release studies revealed that the solid dispersions prepared by solvent evaporation method showed faster drug release than melting and kneading method. Solid dispersion containing crospovidone (1: 4) was considered as the best formulation because of its faster drug release among all formulations.

Yogesh Singh *et al.,*[76] studied the solubility of the water insoluble drug Olmesartan medoxomil (BCSII) by using polymers like Poloxamer 407, poloxmer188 and PEG 6000. Solid dispersions were prepared by solvent evaporation method. Prepared solid dispersions and pure drug were

evaluated for Compatibility study, Phase solubility, Saturation solubility, XRD analysis and *in-vitro* dissolution study. All the polymers were found to be effective in increasing the dissolution rate of Olmesartan medoxomil in solid dispersions when compared to pure drug.

R.L.C. Sasidhar *et al.*,[77] studied the solubility and dissolution rate of Olmesartan medoxomil by complexation with cyclodextrins. The inclusion complexes were prepared by kneading method. The prepared complexes were characterized by Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC). The FTIR and XRD spectra of Olmesartan/beta-cyclodextrin solid complexes showed that Olmesartan medoxomil could form inclusion complex with beta-Cyclodextrins in solid state. The XRD spectra of Olmesartan/ beta-cyclodextrins solid complexes indicated Olmesartan medoxomil existed in amorphous state, this could be explained the fact that the aqueous solubility of Olmesartan medoxomil was increased.

V. Prudhvi Raj *et al.*,[78] evaluated solubility of Olmesartan medoxomil among which cyclodextrin complexation is predominant. β-cyclodextrin was used since this possess a special ability to complex with drugs enabling them to increase solubility, reduce bitterness, enhance stability and decrease tissue irritation upon dosing. Olmesartan medoxomil-β cyclodextrin complexes were prepared and characterized by FT-IR and SEM, studies. The results showed the formation of true inclusion complexes at molar ratio 1:5. The dissolution of Olmesartan medoxomil from all the prepared complexes has been carried out to determine the most appropriate ratio that can be used for further development like tablet formulation for oral delivery. The complexes prepared by physical mixture method in 1:5 ratio showed superior dissolution profile when compared to complexes prepared in other ratios.

Raval C et al., [79]developed a self-micro emulsifying drug delivery system (SMEDDS) of Olmesartan medoxomil to enhance the its solubility as well as its oral bioavailability. The solubility of Olmesartan medoxomil was determined in various vehicles like oils, surfactants and co-surfactants. Three formulations of Olmesartan medoxomil were prepared and analyzed for phase separation, viscosity, droplet size, zeta potential and *in-vitro* dissolution. Among three formulations, Formulae F1 was found to be optimized formulation. The optimized formulation F1 contained tween 20 (45%), propylene glycol (45%) and Capmul MCM 10 (10%) with the droplet size, polydispersity and viscosity of 36.4 nm, 0.186 and 0. 8872 cP respectively. *In-vitro* drug release of the optimized liquid SMEDDS formulations (99.35%) was comparatively high as compared to marketed conventional tablet and pure drug solution. Thus, from this study it was confirmed that the potential use of SMEDDS to improve dissolution and oral bioavailability of poorly water-soluble Olmesartan Medoxomil.

Patel KB et al,.[80]developed a self-emulsifying drug delivery system (SEDDS) of Valsartan to enhance the solubility and that may enhance its oral bioavailability. The solubility of Valsartan was determined in various vehicles like oils, surfactants and co-surfactants and result showed maximum solubility of Valsartan in Capmul MCM C8 55.62 ± 0.78 mg/ml and was selected as oily phase for SEDDS formulation. Among four prepared formulations, formulation A1 containing Capmul MCM C8 (10%), Tween 20 (45%) and Propylene glycol (45%) with 40 mg 0f Valsartan was best formulation. The developed liquid SEDDS of Valsartan was converted into solid SEDDS (S-SEDDS) formulations by using adsorption carriers i.e. Silysia. The droplet size, polydispersity index, and viscosity of optimized formulation was 29.53 nm, 0.310 and 0. 8879 cp respectively. Results of in-vitro dissolution studies of S-SEDDS formulation of Valsartan showed that there was enhancement of dissolution rate of Valsartan as compared with that of

plain Valsartan. The results of this study showed that, Silysia can be used to develop S-SMEDDS by adsorption technique to enhance dissolution rate of Valsartan.

Nawale RB *et al.,* [81] developed and characterized self-microemulsifying drug delivery system (SMEDDS) of anti-diabetic drug glibenclamide for filling into liquid filling hard gelatin capsules. The solubility of glibenclamide in tween 80 and Transcutol was found to be 8.6mg/ml and 17.6 mg/ml respectively, hence selected for formulation of SMEDDS of glibenclamide. Nine formulations of glibenclamide SMEDDS was prepared by using Peceol (oil), Tween 20 (surfactant), Transcutol P (cosurfactant), in which optimized formulation ME3 contains 15% Peceol, 44% Tween 20 and 41% Transcutol P with droplet size 81.13 nm, PDI 0.270, zeta potential -55.12 mV. The prepared formulation showed 95.16% drug release within 15 min as compared with marketed tablet and plain glibenclamide. The results from this study clarify that SMEDDS could be a means of improving solubility, dissolution, and concomitantly the bioavailability of glibenclamide.

Nainwal P et al., [82] prepared the solid dispersion of Rosuvastatin by evaporation method using Polyethylene glycol 4000, mannitol and urea were used as carriers. Hydrotropic studies and micellar solubilization were using different hydrotropic agents and different surfactant solutions. The solubility enhancement of Rosuvastatin by different solubilization technique was observed that the solubility increased with the increase in the concentration of hydrotropic agents. Among the various hydrotropic agents used the solubility of Rosuvastatin was enhanced greatest to 55 folds with sodium salicylate this might be due to aggregation of the hydrotropic molecules and inclusion of one of these aggregates at high concentration probably by reacting to form an associated product as a result of hydrogen bonding.

Dahima R *et al*,.[83] has made an attempt to enhance the dissolution and solubility of poorly water soluble drug Enalapril by solid dispersion technique using solvent evaporation method and hydrotropic solubilization method for attainment of effective absorption and improved bioavailability. Excipients used for solvent evaporation method are mannitol, methanol and dichloromethane while for hydrotropic solubilization method urea and tripotassium citrate monohydrate are used. Solubility of pure drug was found to be 129 µg/ml, but formulation containing 1:3 ratio of drug: mannitol showed maximum solubility i.e. 15 µg/ml. Thus, this experiment concluded that solubility enhancement through formulation of solid dispersion is better than hydrotropic solubilization method (150 µg/ml).

Nikhil K. Sachan *et al.*,[84] prepared the solid dispersion of Acyclovir in PEG 600 and PVP K30 containing five different ratios using solvent evaporation method and also prepared inclusion complex by kneading method with β-CD, HP β-CD at five different ratios in distilled water. The optimized batches of solid dispersion (AS4, BS5) and inclusion complexes (CI5, DI5) of Acyclovir were analysed by Ir spectroscopy, SEM and DSC. The dissolution studies for solid dispersion and inclusion complexes were performed in 0.1 N HCL and PBS pH 7.4 for all optimized batches. The solubility of AScyclovir was found to be more with the inclusion complexation method as compared to solid dispersion technique. Hence the result showed that HP β-CD inclusion complex could possibly improve the dissolution characteristics of Acyclovir and would provide better bioavailability as compare to conventional dosage form.

Chowdary KPR *et al.*,[85] prepared and evaluated solid dispersions of Olmesartan in crospovidone and poloxamer 188 alone and in combination of both for enhancing the dissolution rate and dissolution efficiency of Olmesartan. Solvent evaporation method was used to prepare solid dispersion of Olmesartan. Solid dispersions of Olmesartan in crosspovidone alone were

prepared using five ratios of drug: carrier namely 9:1, 8:2, 2:1, 1:1 and 1:3 and in Poloxamer 188 alone were prepared using three ratios of drug: carrier namely 19:1, 9:1 and 8: 2 by common evaporation solvent method. All the solid dispersions prepared were evaluated for drug content uniformity, dissolution rate and dissolution efficiency in comparison to Olmesartan pure drug. Solid dispersions prepared employing crosspovidone and poloxamer 188 alone as carriers gave rapid and higher dissolution of Olmesartan. With the both carriers, the dissolution rate and dissolution efficiency of Olmesartan were increased as the percent of carrier in the solid dispersion was increased.

Khandekar AM *et al.,* [86] prepared the solid dispersion of Olmesartan medoxomil orally disintegrating tablets by solid dispersion technique using carriers like PVPK30,PEG6000 and sodium lauryl sulfate in order to improve its solubility and dissolution rate. Altogether fifteen formulation of solid dispersion were prepared by kneading method. The prepared solid dispersion was characterized by FTIR, X-Ray Diffraction (XRD) and Differential Scanning Calorimetry. The FTIR and XRD spectra of Olmesartan and its physical mixture showed that Olmesartan Medoxomil could form complex with carriers in solid state. The XRD spectra of Olmesartan/ carriers solid complexes indicated Olmesartan Medoxomil existed in amorphous state. Prepared tablets were evaluated for physical parameters and drug release by *in-vitro* dissolution studies. Dissolution studies showed fast release of Olmesartan Medoxomil in tablets formulation F15 with 15% CCS showed the rapid drug Release. The rate of drug release of tablet formulations was found to be linear with Hixson-Crowell order rate constant because R^2 values of all tablet formulations were closer to one.

R.S. Hirlekar *et al.,* [87] prepared Carvedilol-Methyl-β-cyclodextrin complex by kneading method and characterized by Fourier Transformation Infrared spectroscopy, Differential Scanning

Calorimetry and powder X-Ray Diffractometry studies. Dissolution rate of complex was compared with plain drug and physical mixture. The complex was incorporated into buccal tablet. The buccal tablets were evaluated for drug release, mucoadhesive strength and *ex-vivo* permeability. Characterization of binary system revealed the formation of inclusion complex of drug with Methyl-β-cyclodextrin. The complex showed complete release as compared to 32.8% and 42.7% from plain drug and physical mixture respectively in 60min.

S Srinivasan et al.,[88] prepared inclusion complexes of Etoricoxib by physical mixing, kneading and solvent evaporation method using β-cyclodextrin. The prepared complexes were confirmed and characterized by FT-IR, DSC, SEM and XRD studies. From the results it was concluded that there was no interference of the functional groups as the principal peaks of the Etoricoxib were found to be unaltered in the spectra of the inclusion complexes. The effect of cyclodextrin on aqueous solution of Etoricoxib was evaluated using phase solubility method and results showed that complexation of Etoricoxib with all 3 β cyclodextrin increases Etoricoxib solubility in a linear pattern. The formulated complexes were evaluated for drug content and in-vitro dissolution studies. Among all method the inclusion complex prepared with cyclodextrin by kneading method exhibited excellent enhancement of solubility and a cumulative drug release of 99.17% was observed in 60 min. Thus, from this study it was concluded that complexation of drug with cyclodextrins is an effective method to improve the aqueous solubility of Etoricoxib.

Prabagar Balakrishnan *et al.,*[89] formulated SEDDS composed of oil, surfactant and co surfactant to enhance the solubility and bioavailability of poorly water-soluble Coenzyme Q10 (CoQ10), for oral administration. The formulations were prepared using two oils (Labrafil M 1944 and Labrafil M 2125), surfactant (Labrasol) and co surfactant (Lauroglycol FCC and Capryol 90). In all the formulations, the level of CoQ10 was fixed at 6% (w/v) of the vehicle.

The optimized SEDDS formulation consist of 65% (v/v) Labrasol, 25% (v/v) Labrafil M 1944 CS and 10% (v/v) Capryol 90 of each excipients showed minimum mean droplet size (about 240 nm) and optimal drug release profile in water. The pharmacokinetic study in rats for the optimized formulation was performed and compared to powder formulation. SEDDS have significantly increased the *C*max and area under the curve (AUC) of CoQ10 compared to powder ($P < 0.05$). Thus, this self-micro emulsifying drug delivery system should be an effective oral dosage form for improving oral bioavailability of lipophilic drug, CoQ10.

Panchal DM et al.,[1] prepared solid dispersion of Olmesartan medoxomil by two techniques namely kneading method and solvent evaporation method to enhance the solubility and dissolution rate of Olmesartan medoxomil. Ten formulations of Olmesartan medoxomil Solid dispersions were prepared by taking different ratio of drug and polymers. The prepared solid dispersion was characterized by FTIR, DSC and XRPD. The XRPD spectra of solid dispersion indicated Olmesartan medoxomil existed in amorphous state, FTIR and DSC showed no interaction between drug and its physical mixture. Formulation code S2 showed 88.66% of drug release within the period of 60 min. Hence it could be concluded that solid dispersions could be one of the effective approaches for improved performance of Olmesartan medoxomil.

Chapter 4

Materials & Methods

4. MATERIALS AND METHODS

4.1 MATERIALS:

Table 3: List of materials used

SI NO.	INGREDIENTS	SUPPLIERS
1	Olmesartan Medoxomil	Yarrow Chem Products, Mumbai
2	Poloxamer 188	S.D. Fine Chem Ltd, Mumbai
3	β cyclodextrin	S.D. Fine Chem Ltd, Mumbai
4	Soya bean oil	S.D. Fine Chem Ltd, Mumbai
5	Tween 80	S.D. Fine Chem Ltd, Mumbai
6	PEG 400	S.D. Fine Chem Ltd, Mumbai
7	Sodium hydroxide	S.D. Fine Chem Ltd, Mumbai
8	Potassium dihydrogen phosphate	S.D. Fine Chem Ltd, Mumbai
9	Methanol	S.D. Fine Chem Ltd, Mumbai
10	Ethanol	S.D. Fine Chem Ltd, Mumbai

4.2 INSTRUMENTS:

Table 4: Lists of instruments used

SI NO.	INSTRUMENTS	MODEL/COMPANY
1	UV visible spectrophotometer	Spectrophotometer UV-1800, Shimadzu.
2	Dissolution test apparatus	Lab India
3	Magnetic stirrer with hot plate	Techno scientific products, Bangalore, India.
4	Digital pH meter	Techno scientific products
5	Electronic analytical balances	Acculab Sartorius group
6	FT-IR	Thermo Nicolet
7	Scanning electron microscope	HITACHI, Japan
8	Stability chamber(106 Model)	Labtop, sky Lab Instruments & Engineering Pvt. Ltd. Mumbai, India.
9	Hot air oven	Kadavil electro mechanical industries, Kerala.

4.3 DRUG PROFILE

Olmesartan medoxomil[90,91,92]

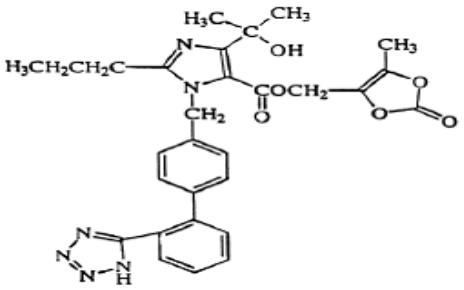
Category: As antihypertensive agent, angiotensin II type1 receptor antagonist.

Chemical name:(5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1*H*-imidazole-5-carboxylate.

Molecular formula: $C_{29}H_{30}N_6O_6$

Molecular weight: 558.59

Chemical structure:



Melting point: 175-180ºC

Physical state: White to almost white crystalline powder.

Solubility: Insoluble in water, sparingly soluble in strong acid, methanol, soluble in strong base.

Mechanism of action: Olmesartan medoxomil (OLM), a prodrug, is hydrolyzed to Olmesartan during absorption from the gastrointestinal tract. It works by blocking the binding of angiotensin II to the AT_1 receptors in vascular muscle; it is therefore independent of angiotensin II synthesis pathways, unlike ACE inhibitors. By blocking the binding rather than the synthesis of angiotensin II, Olmesartan inhibits the negative regulatory feedback on renin secretion. As a result of this blockage, Olmesartan reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance.

Bioavailability: Bioavailability is about 26%. Food does not affect the bioavailability of Olmesartan.

Volume of distribution: The volume of distribution is 17 liters and Olmesartan poorly crosses the blood brain barrier.

Protein binding: Highly bound to plasma proteins (99%) and does not penetrate red blood cells.

Metabolism: Olmesartan is rapidly and completely bioactivated by ester hydrolysis to Olmesartan during absorption from the gastrointestinal tract. There is virtually no further metabolism of Olmesartan.

Route of elimination: Olmesartan is eliminated unchanged in the urine (35% to 50%) and the remainder in the feces.

Half-life: The half-life is approximately 13 hrs.

Clearance: Total plasma clearance=1.3L/h and renal clearance=0.6L/h.

Dose: The usual recommended starting dose of Olmesartan is 20 mg once daily. The dose may be increased to 40 mg after two weeks of therapy, if further reduction in blood pressure is desirable.

Indication: Olmesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Contraindication: Contraindications for treatment with Olmesartan include biliary obstruction. Another major contraindication is pregnancy; reports in the scientific literature reveal fetal malformations for pregnant women taking sartan-derived drugs.

Adverse effects: The incidence of adverse effects is reported as similar to placebo. Olmesartan is contraindicated in pregnancy and can cause injury and even death to the developing fetus. It causes increases in serum creatinine or blood urea nitrogen in patients with unilateral or bilateral

renal artery stenosis. Rarely, Olmesartan can cause severe gastrointestinal issues. The symptoms, which include nausea, vomiting, diarrhea, weight loss and electrolyte abnormalities are common among those who have celiac disease.

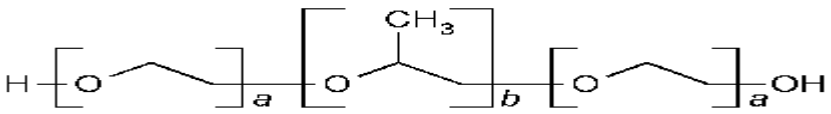
Cautions: It should be used with caution in renal artery stenosis. Monitoring of plasma-potassium concentration is advised, particularly in the elderly and in patients with renal impairment; lower initial doses may be appropriate in these patients.

Interactions: Olmesartan may interact with nonprescription products that contain stimulants, including diet pills and cold medicines, and potassium supplements, including salt substitutes.

Marketed products: Benicar, Olmetec, WinBP, Golme, Erastapex, Olsart.

4.4 POLYMERS PROFILE

Table 5: Poloxamer 188[93]

Non-proprietary name	BP: poloxamers PhEur: poloxamers
Synonyms	Lutrol; Monolan; Pluronic; poloxalkol; poloxamera
Description	Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless.
Structural formula	
Chemical Name	a-Hydro-o-hydroxypoly(oxyethylene)poly(oxypropylene) poly-(oxyethylene)
Empherical Formula	$HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$.
Molar weight	7680-9510
Density	1.06 g/cm^3 at 25 ºC
Melting point	52-57 ºC
Solubility	Freely soluble in water and ethanol (95%)

Moisture content	Contain less than 0.5%w/w water and are hygroscopic only at relative humidity greater than 80%.
pH	5.0–7.4 for a 2.5% w/v aqueous solution.
Functional categories	Dispersing agent, emulsifying agent, solubilizing agent, tablet lubricant, wetting agent.
Stability and storage conditions	Aqueous solutions are stable in the presence of acids, alkalis and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.
Caution	Keep away from water, direct sunlight and flames
Incompatibilities	Incompatible with phenols and parabens.
Safety	Generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.
Applications	In pharmaceutical formulations as emulsifying or solubilizing agents. Used as wetting agents, in ointments, suppository bases and gels and as tablet binders and coatings. Used as an emulsifying agent for fluorocarbons, used as artificial blood substitutes and in the preparation of solid-dispersion systems. Used in drug-delivery systems. Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron.

Table 6: β-cyclodextrin[94]

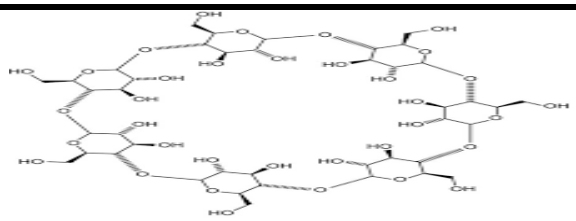
Non-proprietary name	BP: Alfadex Betadex PhEur: Alfadex Betadex
Synonyms	Beta-cycloamylose; beta-dextrin; betadexum
Description	Occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.
Structural formula	
Empherical Formula	$C_{42}H_{70}O_{35}$
Molar weight	1135
Bulk Density	0.523 g/cm3
Melting point	255–2658 ºC
Solubility	Soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 208 ºC, 1 in 20 at 508 ºC, practically insoluble in acetone, ethanol (95%), and methylene chloride.
pH	5-8
Functional categories	Solubilizing agent; stabilizing agent.
Storage conditions	Stored in a tightly sealed container, in a cool, dry place.
Incompatibilities	The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-β- cyclodextrin.
Handling precautions	Should be handled in a well ventilated environment. Efforts should be made to limit the generation of dust, which can be explosive.
Applications	Used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.

Table 7: Tween 80[95]

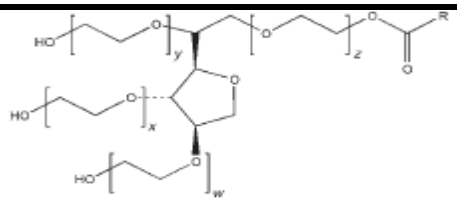
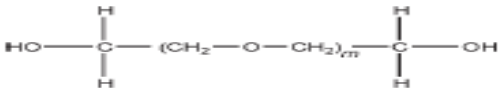
Non-proprietary name	BP: polysorbate 80 PhEur: polysorbate 80
Synonyms	Polysorbate 80, elaic acid, emersol, glycon
Description	Lemon to amber colored oily liquid at 25ºC, with a faint characteristic odour.
Structural formula	
Chemical Name	Polyoxyethylene (20) SorbitanMonooleate
Empherical Formula	$C_{64}H_{124}O_{26}$
Molar weight	1310 g/mol.
Flash point	1498 ºC
Solubility	Soluble in water, ethanol, methanol, ethyl acetate and toluene, insoluble in mineral oil and petroleum ether.
Functional categories	Dispersing agent, emulsifying agent, nonionic surfactant, solubilizing agent, suspending agent, wetting agent.
Storage conditions	Stored in well closed container, protected from light, in cool and dry place.
Incompatibilities	Discoloration or precipitation occur with phenols, tannins, tars and tar like materials. The anti-microbial activity of paraben is reduced in the presence of polysorbate 80.
Safety	Polysorbate 80 is widely used in cosmetics, food products, and topical pharmaceutical formulations and is generally regarded as non-toxic and non-irritant.
Applications	Used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. It is used as solubilizing agents for essential oils and oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for glycoprotein. Widely used in cosmetics and food products.

Table 8: Soyabean oil[96]

Non-proprietary name	BP: Refined Soya Oil PhEur: Soya-Bean Oil, Refined
Synonyms	Aceite de soja, soiae oleum raffinatum, soja bean oil, soyabean oil, soya bean oil.
Description	Soybean oil is a clear, pale-yellow colored, odorless or almost odorless liquid, with a bland taste that solidifies between -10 and -168 ºC.
Chemical Name	Soyabean oil
Empherical Formula and molecular weight	A typical analysis of refined soybean oil indicates the composition of the acids, present as glycerides, to be: linoleic acid 50–57%; linolenic acid 5–10%; oleic acid 17–26%; palmitic acid 9–13%; and stearic acid 3–6%.
Density	0.916–0.922 g/cm^3 at 25 ºC
Autoignition temperature	445 ºC
Solubility	Practically insoluble in ethanol (95%) and water, miscible with carbon disulfide, chloroform, ether, and light petroleum.
Viscosity	50.09 mPa s (50.09 cP) at 25 ºC
Functional categories	Oleaginous vehicle, solvent.
Stability and storage conditions	Soybean oil is a stable material if protected from atmospheric oxygen. Soybean oil should be stored in a well-filled, airtight, light resistant container.
Handling precautions	Spillages of soybean oil are slippery and should be covered with an inert absorbent material prior to disposal.
Incompatibilities	Soybean oil emulsions have been reported to be incompatible at 25 ºC with a calcium chloride, calcium gluconate, magnessium chloride and phenytoin sodium.
Applications	Soybean oil emulsions are primarily used as a fat source in total parenteral nutrition. Emulsions containing soybean oil have also been used as vehicles for the oral and intravenous administration of drugs. Used in the formulation of many drug delivery systems such as liposomes, microspheres, dry emulsions, self-emulsifying systems, microemulsions, nanoemulsions and nanocapsules, solid-in-oil suspensions and multiple emulsions.

Table 9: PEG 400[97]

Non-proprietary name	BP: Macrogols PhEur: Macrogols
Synonyms	Carbowax, Carbowax Sentry Lutrol E, PEG, Pluriol E, Polyoxyethylene glycol.
Description	Occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.
Structural formula	
Chemical Name	a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)
Empherical Formula	$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.
Molar weight	380-420
freezing point	4-8ºC
Solubility	PEG 400 is soluble in water, acetone, alcohols, benzene, glycerin, and glycols.
Viscosity	90.0 [mm^2/s (cSt)] at 25 ºC
Ph	4.0-7.0 (5%w/v solution)
Functional categories	Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.
Storage conditions	It should be stored in well-closed containers in a cool, dry place.
Incompatibilities	Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents, phenol, tannic acid, and salicylic acid.
Safety	Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight.
Applications	Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. It is used as water-miscible solvents for the contents of soft gelatin capsules.

4.5 METHOLODOGY

4.5.1 PREFORMULATION STUDIES:

Analytical method used in the determination of Olmesartan medoxomil:

The UV spectrophotometric method was developed for the analysis of the drug using Shimadzu 1800 spectrophotometer.

Preparation of 0.2 M potassium di hydrogen phosphate:

27.22g of potassium dihydrogen phosphate was weighed accurately, dissolved in little quantity of distilled water and final volume was made up to 1000 ml with distilled water to get 0.2M potassium dihydrogen phosphate.

Preparation of 0.2 M NaOH stock solution:

8g Sodium hydroxide was weighed, dissolved and diluted up to 1000 ml with distilled water to get 0.2M sodium hydroxide solution.

Preparation of 6.8 pH phosphate buffer solution:

50 ml of 0.2 M potassium dihydrogen phosphate solution was taken into a 200ml volumetric flask and 22.4 ml of 0.2 M sodium hydroxide was added and final volume was adjusted up to 200 ml with distilled water[1].

Determination of λ_{max}:

100 mg of Olmesartan medoxomil was accurately weighed and dissolved in 100 ml of methanol in volumetric flask. 10 ml of above solution was diluted with 100 ml of methanol (=10 µg/ml) in separate volumetric flask and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 200 to 400 nm, using methanol as blank. The λmax of the drug was found to be 257nm[1].

Standard Curve for Olmesartan medoxomil[98]:

100 mg of Olmesartan medoxomil was accurately weighed and dissolved in 50 ml methanol. The solution was sonicated for 10 min and final volume was adjusted to 100ml to give stock solution-I (1000 µg/ml concentration). 10 ml of stock solution-I was placed in 100 ml volumetric flask and volume was adjusted with methanol to give stock solution-II of 100µg/ml concentration. Stock solution-II was further diluted with methanol to get working standard solution of 4, 6, 8, 10, 12, µg/ml of Olmesartan medoxomil to construct Beer's law plot for the pure drug. The absorbance of the solutions was measured at 257 nm using UV-visible spectrophotometer. A graph of concentration vs absorbance was plotted.

Solubility of Olmesartan medoxomil[74]:

The solubility of Olmesartan medoxomil was determined in distilled water, methanol, phosphate buffers pH6.8 and different oils, surfactants and co-surfactants. Briefly, an excess amount of Olmesartan medoxomil was added to each vial containing 10 ml of selected solubilizer. The mixtures were subjected to the mechanical agitation for 24 hrs in isothermal shaker at 25ºC ±1 ºC followed by the filtration through Watmann's filter paper prior to UV. Absorbance was taken at 257 nm by UV-Visible spectrometer. Calculate the drug content by using the standard graph.

Melting point:

Melting point of drug was determined by capillary method in triplicate.

Compatibility study using FT-IR[75]:

Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample (drug and drug-excipient mixture) in KBr (200-400 mg) and compressing into discs by applying

a pressure of 5 tons for 5 min in a hydraulic press. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}. The interaction between drug-excipients was observed from IR-Spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug.

Construction of pseudo ternary phase diagram[79]:

Pseudo-ternary phase diagrams of oil, surfactant/co-surfactant and water were developed using the water titration method. The weight ratio of surfactant: co-surfactant(s/c_os) was varied as 1:1. For pseudo ternary phase diagram at a specific surfactant/co-surfactant weight ratio, oil and surfactant/co-surfactant mixture were mixed thoroughly in different weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1). Water was added drop by drop to the mixture of oil and surfactant/co-surfactant under magnetic stirring at 37 °C until the mixture became clear or persistent turbidity, and then the concentrations of the components were recorded.

4.5.2 Preparation of solid dispersion of Olmesartan medoxomil:

Table 10: Formulation design of solid dispersion of Olmesartan medoxomil

Sl. No.	Formulation code	Drug: polymer
1	SD1	1:1
2	SD2	1:2
3	SD3	1:4

Solvent evaporation method[85]:

OLM and poloxamer188 are dissolved in sufficient quantity of methanol in the ratios 1:1, 1:2 and 1:4 w/w in a separate china dish. The solvent is evaporated at 45ºC in a hot air oven until dried solid mass remains in the china dish. The solid mass is then pulverized and passed through sieve no.60 and kept in a desicator for the further use.

4.5.3 Preparation of OLM-β CD inclusion complex:

Table 11: Formulation design of inclusion complexes

Sl No.	Formulation code	Drug: polymer
1	C1	1:1
2	C2	1:2
3	C3	1:4

Solvent evaporation method[77]:

OLM and β-cyclodextrin were triturated in ratios 1:1, 1:2 and 1:4 w/w with addition of few drops of 40% of ethanol to form a paste in a separate china dish. Then solvent is allowed to evaporate at 40ºC to form a dry solid mass which is further crushed to fine particles and passes through sieve no.60 and kept in a desicator for further use.

4.5.4 Preparation of selfemulsifying drug delivery system:

Table 12: Formulation design for SEDDS

Formulation code	Drug (in mg)	Surfactant: co-surfactant(1:1)	Oil
SE1	20mg	40%	60%
SE2	20mg	50%	50%
SE3	20mg	60%	40%

Method for formulation of SEDDS[79]:

The SEDDS formulations were prepared by initially dissolving the accurately weighed amount of drug (OLM) in co-surfactant (PEG400) at 60 ºC in an isothermal water bath. Oil (soyabean oil) was then added and mixture was cooled to ambient temperature. Then surfactant (tween80) was added and the final mixture was mixed by stirring until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 hrs and

examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies. Final formulation was filled in hard gelatin capsule and stored in well closed container.

4.6 EVALUATION PARAMETERS

4.6.1 Drug content[76]:

All the prepared solid dispersion, inclusion complexes and SEDDS formulations equivalent to 20 mg of OLM were weighed accurately and dissolved in 100 ml of phosphate buffer pH6.8 in a separate volumetric flask. The solution was filtered, diluted suitably with same solvent and drug content is analyzed at 257 nm by UV-spectrophotometer.

4.6.2 Saturation Solubility Studies[76]:

The saturation solubility studies were carried out to determine the solubility of pure drug, prepared solid dispersions and inclusion complexes in distilled water. Weighed amount of OLM, solid dispersions and inclusion complexes were added separately to 100 ml conical flasks containing 25 ml of distilled water. The sealed flasks were shaken for 24 hrs at 37±0.5 ºC. Then aliquots were filtered through Whatman filter paper. The concentration of Olmesartan medoxomil was determined by UV spectrophotometer at 257nm.

4.6.3 Scanning electron microscopy (SEM)[74]:

The surface morphology of OLM, poloxamer188, β-CD and prepared formulation of solid dispersion and inclusion complex were examined by means of scanning electron microscope (Jeol-JSM-5300 scanning microscope). Electron micrographs of individual components, SDs and inclusion complex were obtained using a scanning electron microscope operating at 25 kV. The samples were mounted on a glass stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs

with different magnifications were recorded to study the morphological and surface characteristics of the individual components, SD and inclusion complex.

4.6.4 *In vitro* dissolution studies[78]:

In vitro dissolution study of OLM and all prepared formulations were carried out by using USP rotating basket apparatus (Type I) for 45 min with rotation speed of 50 rpm. Phosphate buffer pH 6.8 was used as dissolution medium (900 ml) and temperature was maintained at 37ºC ± 0.5ºC. Samples equivalent to 20 mg of Olmesartan was filled in hard gelatin capsules and used for dissolution studies. Samples were collected at regular interval of time 5, 10, 15, 20, 30 and 45 min. The absorbances of the samples were measured at λmax 257 nm after suitable dilution using appropriate blank.

4.6.5 Drug release kinetics[99]:

Investigation for the drug release from the SD, SEDDS and inclusion complex of OLM was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model.

a) Zero order kinetics: When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero-order release Kinetics, with a slope equal to K^0.

Zero order release would be predicted by the following equation:-

$$\mathbf{A_t = A_0 - K_0 t}$$

Where, A_t= Drug release at time‘t’.

A_0= Initial drug concentration.

K_0=Zero-order rate constant (hr^{-1}).

b) First order Kinetics: When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

First order release would be predicted by the following equation:-

$$\mathbf{Log\ C = log\ C_0 - K_t / 2.303}$$

Where, C = Amount of drug remained at time't'.

C_0 = Initial concentration of drug.

K = First-order rate constant (hr^{-1}).

c) Higuchi's model: When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

Drug release from the formulation by diffusion has been described by following Higuchi's classical diffusion equation:

$$\mathbf{Q = [D_\varepsilon / \varepsilon\ (2A - \varepsilon C_S)\ C_S t]^{1/2}}$$

Where, Q = Amount of drug released at time't'.

D = Diffusion co-efficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

C_S = Solubility of the drug in the matrix.

ε = Porosity of the matrix.

t = Tortuosity.

d) Korsmeyer equation/ Peppa's model: When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept. To study the mechanism of drug release, the release data were also fitted to the well –

known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where, M_t / M_a = the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug/polymer.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

$$\text{Log } M_t / M_a = \text{Log } K + n \log t$$

For Fickian release 'n' = 0.5 while for anomalous (non- Fickian) transport 'n' ranges between 0.5 and 1.0.

Table 13: Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

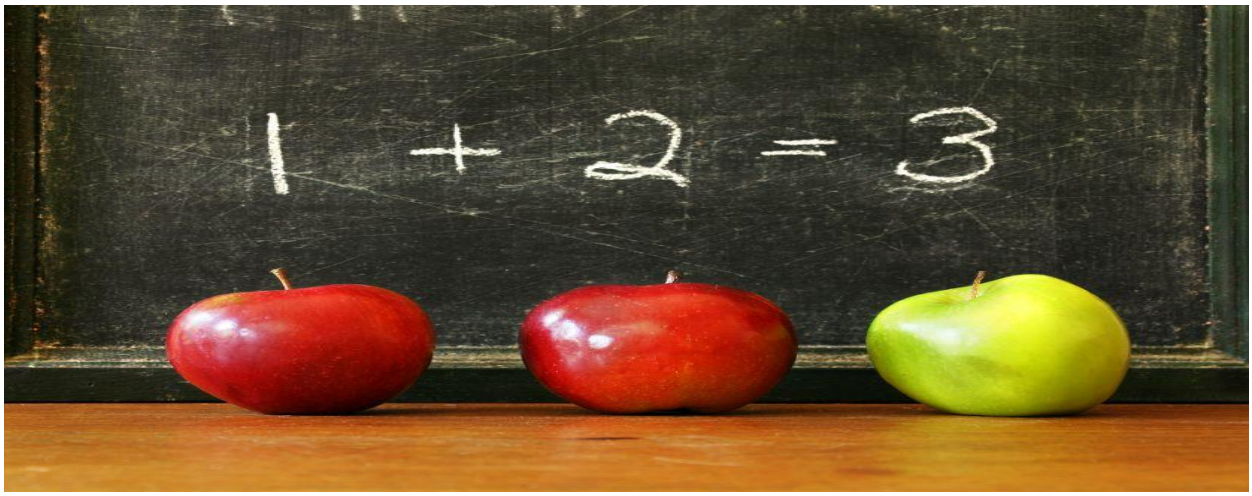
SL. No	'n' value	Drug release mechanism	Rate as a function of time
1.	0.45	Fickian release	$t^{-0.5}$
2.	0.45 <n = 0.89	Non- Fickian transport	t^{n-1}
3.	0.89	Class II transport	Zero order release
4.	Higher than 0.89	Super case II transport	t^{n-1}

4.6.6 Stability studies[75]:

The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence various environmental conditions such as temperature, humidity, light. From this study recommended storage conditions humidity, light, re-test periods and self-life of the drug can be established. The selected formulations were subjected for three month for stability study as per ICH guidelines**.** The selected formulations

were placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 month for the selected formulations.

Chapter 5



Results

&

Discussion

5. RESULTS AND DISCUSSION

5.1. Determination of λ_{max} of Olmesartan medoxomil

The λ_{max} of the Olmesartan medoxomil was found to be 257nm in methanol.

5.2. Calibration curve of Olmesartan medoxomil

The absorbance of Olmesartan medoxomil was measured in a UV spectrophotometer at 257nm against methanol. The absorbance so obtained was tabulated (**table no.14**) and graph was obtained by plotting absorbance vs concentration shown in **figure no.2**.

Table 14: Spectrophotometric data of OLM in methanol

Sl. No.	Concentration (µg/ml)	Absorbance (nm)		Average	Standard Deviation
		Trial 1	Trial 2		
1	0	0	0	0	0
2	4	0.163	0.173	0.168	0.0045
3	6	0.221	0.243	0.232	0.0015
4	8	0.306	0.312	0.309	0.0014
5	10	0.381	0.373	0.378	0.0017
6	12	0.476	0.480	0.478	0.0020

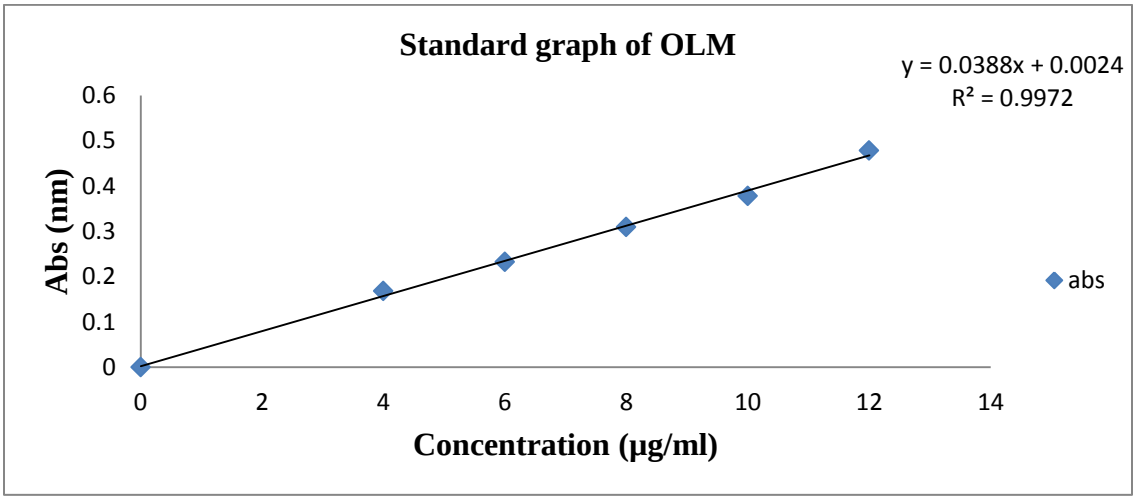


Fig 2: Standard graph of OLM in methanol.

5.3. Solubility studies of OLM

The solubility of Olmesartan medoxomil was determined in different vehicles as well as in different oils, surfactants and co-surfactants. The data for solubility studies in different media are shown in **table no.15.**

Table 15: Solubility of OLM in different media

Media		Solubility at 37ºC(mg/ml)
Solvents	Distilled water	0.037
	Methanol	0.073
	Phosphate buffer (pH 6.8)	0.071
Oils	Sunflower oil	0.059
	Soyabean oil	0.250
	Olive oil	0.056
Surfactants	Tween 20 (surfactant)	59.32
	Tween 80 (surfactant)	65.90
Co-surfactants	PEG 200 (co-surfactant)	57.31
	PEG 400 (co-surfactant)	65.26

Result showed that solubility of OLM was high in methanol when compared to other vehicles, so methanol was choosen for evaluation of OLM. Among different oils, surfactants and co-surfactants, OLM showed maximum solubility in soyabean oil, tween80 and PEG400, which makes them to be selected for the preparation of SEDDS as an oil, surfactant and co-surfactant respectively.

5.4. Melting point

Melting point of drug was determined by capillary method. The result is found to be **175ºC-180 ºC.**

5.5. Compatibility studies using FT-IR

Infra-red spectrum of drug and mixture of drug-polymers were determined by KBr disks method. Samples were prepared in KBr disks by means of a hydrostatic press at 5 tons pressure for 5 min and obtained spectra are shown in the **figure no.3-6.**

All the characteristic peaks of Olmesartan medoxomil were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. The spectrum confirmed that there was no significant change in the chemical integrity of the drug. There was no change in functional group peaks of Olmesartan medoxomil in all the IR-spectra and are tabulated in **table no.16.**

Table 16: Interpretation of FT-IR spectrum

Ingredients	Functional groups with wave number (cm^{-1})			
	C-H (aromatic)	COOH (acid)	C=C (aromatic)	C=O
Olmesartan Pure drug	2931.90	1604.83	1550.82	1388.79
Complexation(C1)	2924.18	1643.41	1543.99	1396.51
Solid dispersion (SD3)	2924.18	1643.41	1552.08	1350.22
SEDDS (SE1)	2924.18	1643.41	1498.23	1350.22

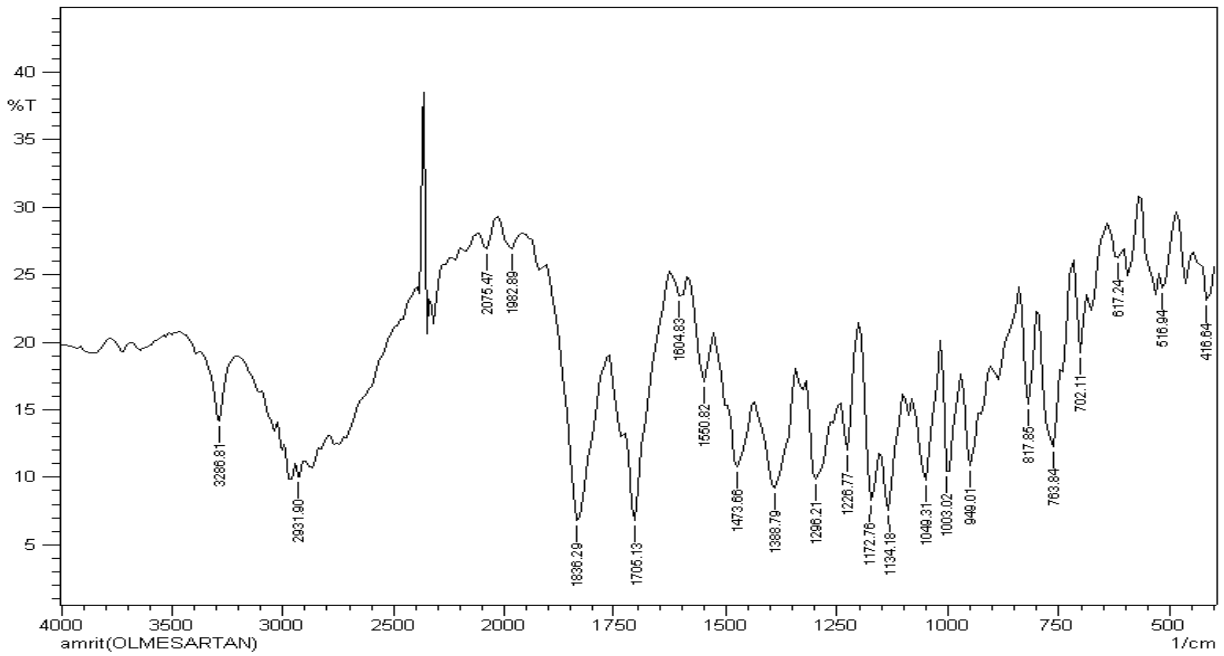


Fig 3: FT-IR spectrum of pure drug, Olmesartan medoxomil.

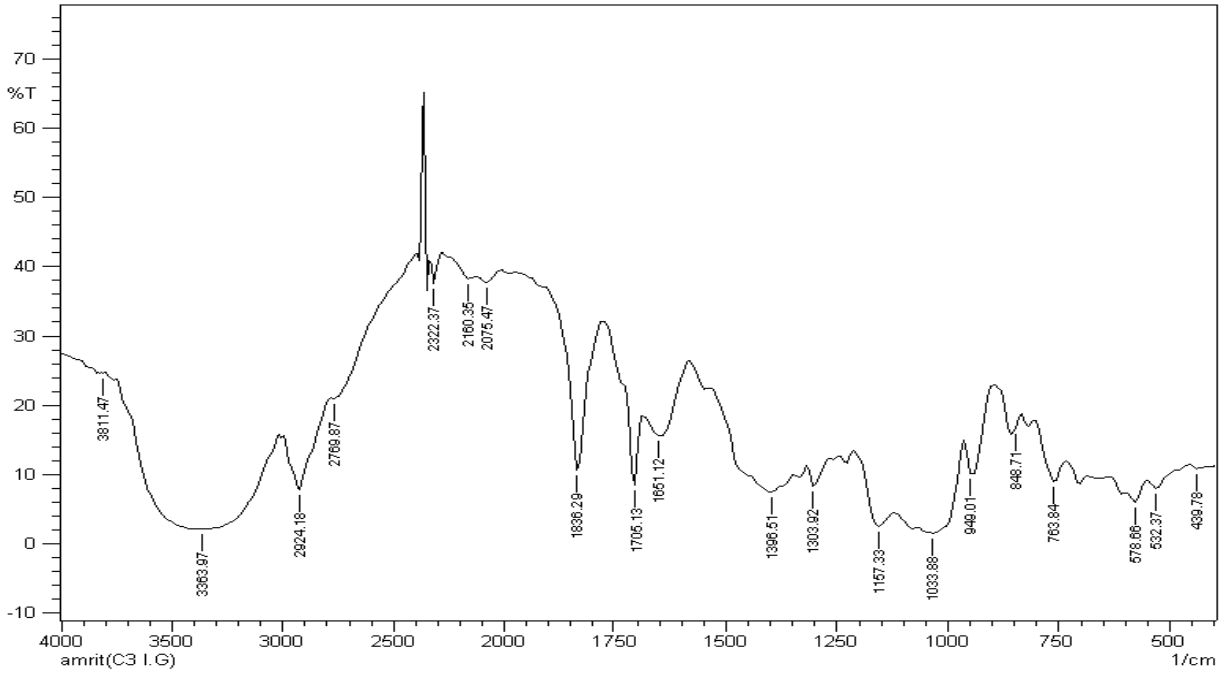


Fig 4: FT-IR spectrum of OLM+β-CD (C3).

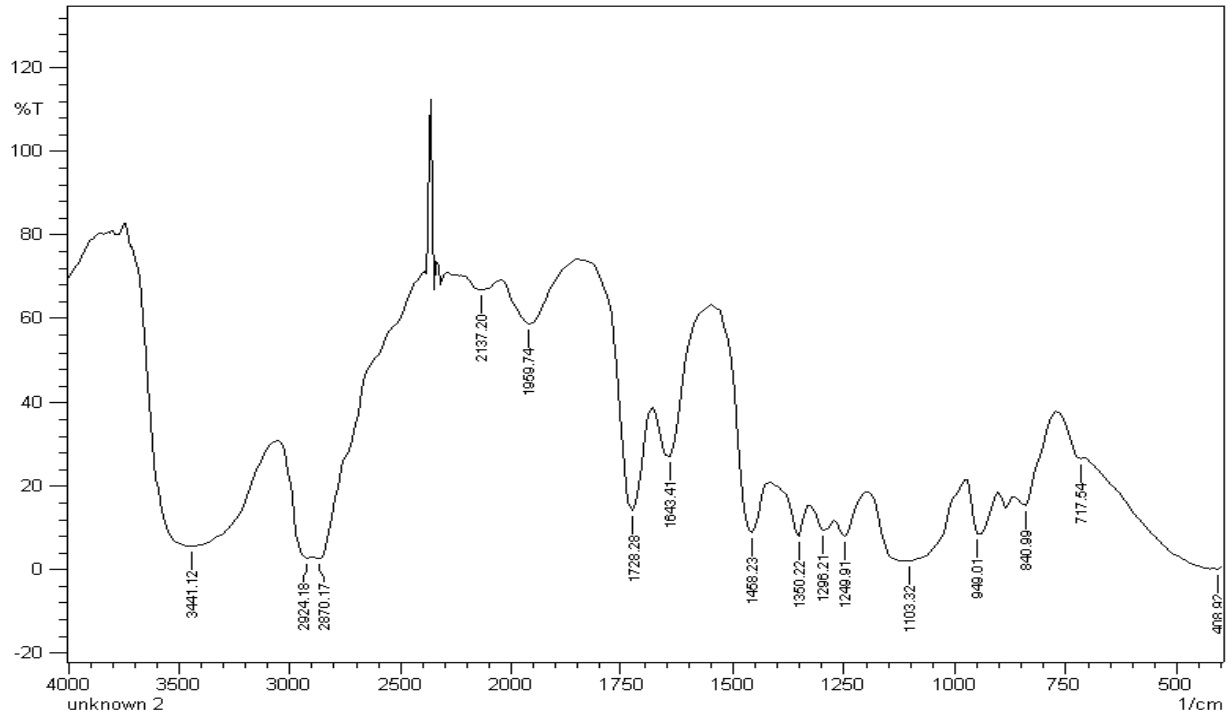


Fig 5: FT-IR Spectrum of OLM+Poloxamer188 (SD3).

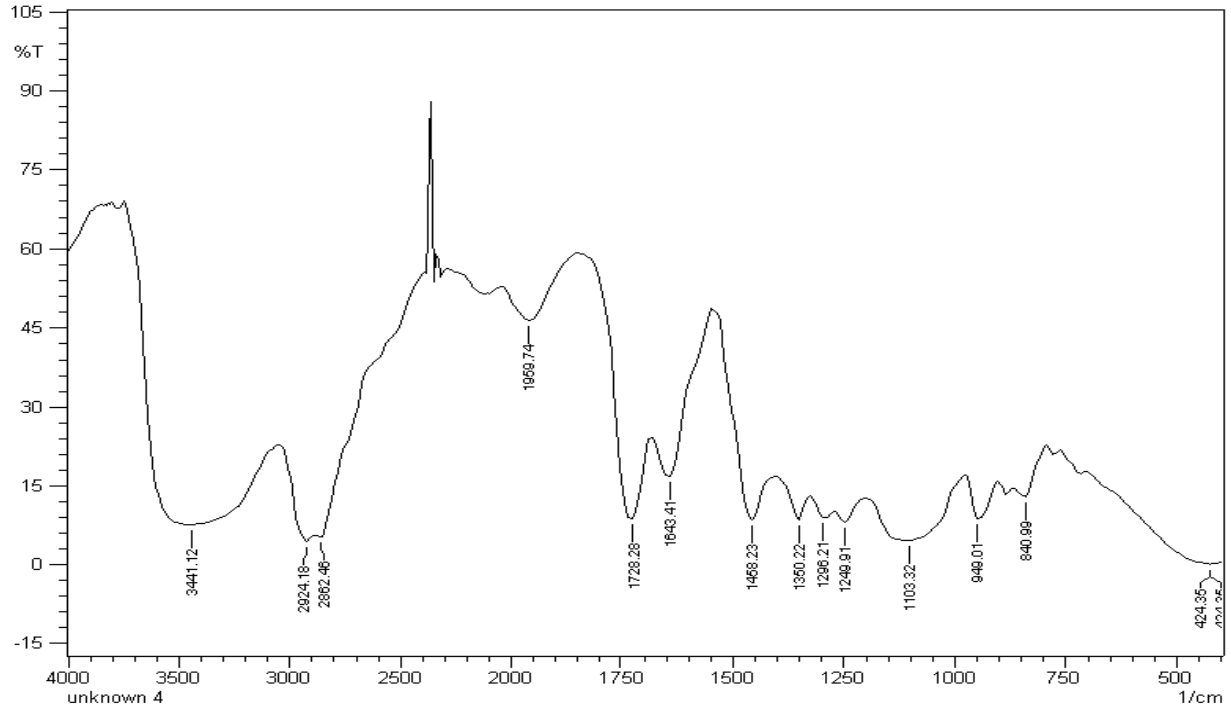


Fig 6: FT-IR spectrum of SEDDS (SE3)

5.5. Pseudo ternary phase diagram

SEDDS form fine oil-water emulsion with only gentle agitation, upon its introduction into aqueous media. Since the free energy required forming an emulsion is very low for the formation of emulsion spontaneous. Surfactant forms a layer around the emulsion droplets and reduces the interfacial energy as well as providing a mechanical barrier to coalescence. The visual test measures the apparent spontaneity of emulsion formation. The series of SEDDS were prepared and their self-emulsifying properties were observed visually. Pseudo ternary phase diagram was constructed to identify the self-emulsifying regions and optimized concentration of oil, surfactant, and co-surfactant was used for formulation. From this study surfactant: co-surfactant (Km) ratio 1:1 has been selected as the optimized concentration.

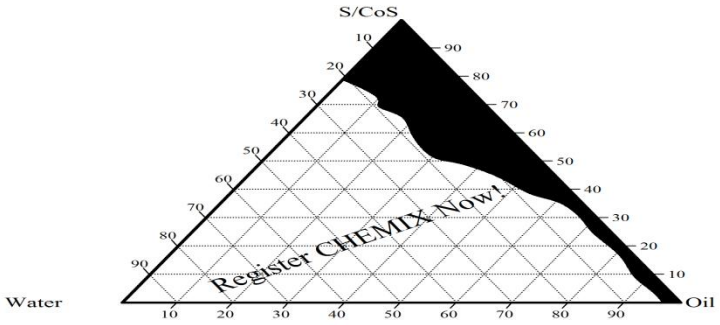


Fig 7: Ternary plot of Tween80 and PEG400 (1:1).

5.6. EVALUATION OF PREPARED FORMULATIONS

5.6.1. Drug content

Percentage drug content estimation of all formulations was done by UV spectrophotometer. The absorbances were measured and percentage drug content was calculated. Percentage drug content of all formulations were found in the range of 95.77%-98.26% which is within the pharmacopoeial limits and shown in **table no.17**.

Table 17: % Drug content of prepared formulations

Sl. No.	Formulation Code	% Drug Content
1	SD1	96.43
2	SD2	96.98
3	SD3	98.26
4	C1	95.77
5	C2	96.28
6	C3	96.91
7	SE1	96.43
8	SE2	97.12
9	SE3	97.57

5.6.2. Saturation solubility studies

Table 18: Saturation solubility data of OLM and prepared formulations

Formulation	Drug: polymer	Distilled water(mg/ml)
OLM	1:0	0.037
Solid dispersion (drug:poloxamer188)	1:1 (SD1)	0.041
	1:2 (SD2)	0.043
	1:4 (SD3)	0.048
Complexation (drug:β-CD)	1:1 (C1)	0.039
	1:2 (C2)	0.042
	1:4 (C3)	0.045

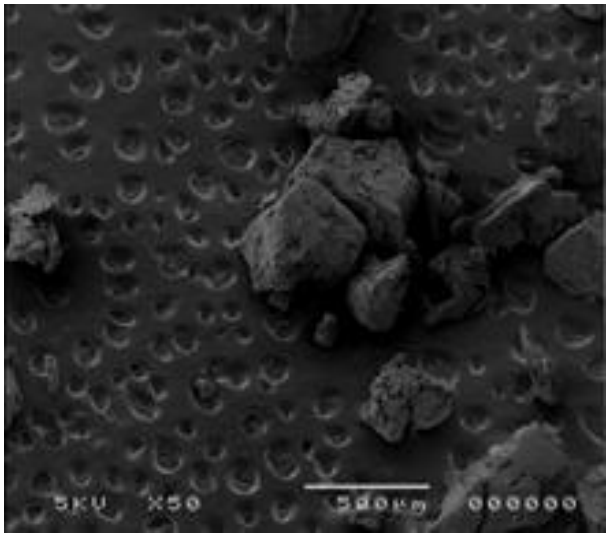
The solubility of OLM in distilled water was determined to be 0.037 mg/ml. While for solvent evaporation method with poloxamer188 and complexation with β-CD it was in the range of 0.041-0.048 mg/ml and 0.039-0.042 mg/ml respectively.

All the formulations showed an increase in drug solubility compared to pure drug among which solid dispersion having drug-carrier ratio 1:4 (SD3) showed maximum solubility (0.048

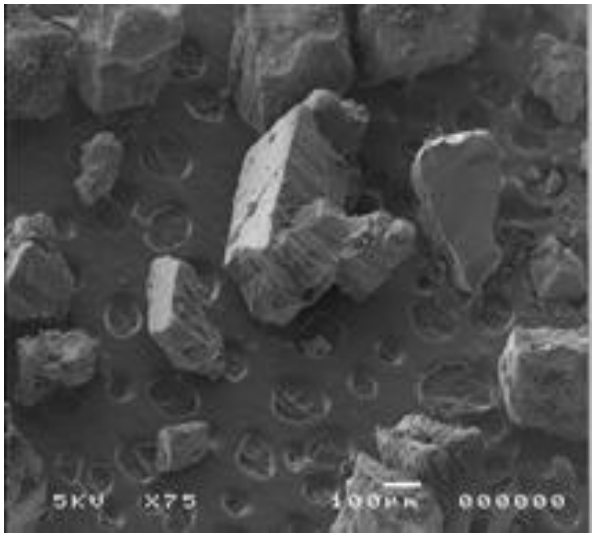
mg/ml). Furthermore, enhancement in solubility of OLM was influenced by the concentration of polymers in solid dispersion as well as in inclusion complexes. With increase in polymers concentration, a predominant increase effect on solubility was observed.

5.6.3. Scanning electron microscopy (SEM)

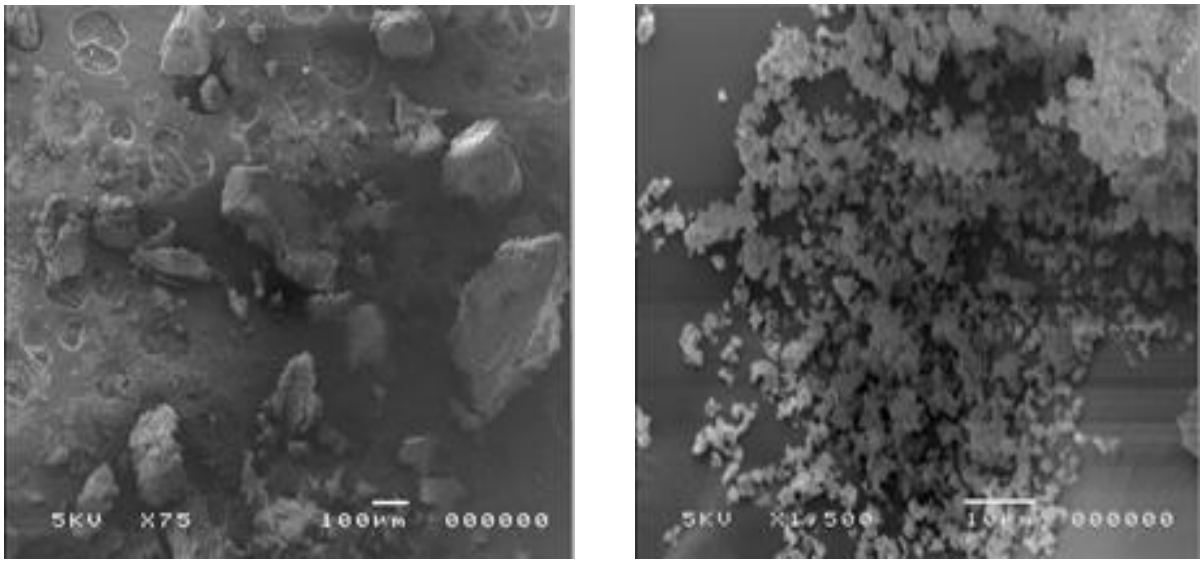
To study about the shape and surface characteristics, SEM studies were performed for the individual components. OLM, poloxamer188, β-CD and SD3 inclusion complexes of drug showed significant difference in the microscopic structure. The reduction in the crystallinity was observed in SD3 formulation. Reduced size of the formulations is due to the method of preparation used, solvent evaporation method for preparing SD. Comparative SEM photographs for OLM, poloxamer 188, β-CD and SD3 were given in **figure no.7**. Except the SDs prepared in 1:4ratio (SD3), the SEM images of remaining showed the presence of minute amounts of drug (irregular shaped particles) which confirms the formation of the true SD in 1:4 ratio which supports the result obtained from FT-IR.



OLM powder



Poloxamer 188



β-CD **SD3**

Fig 8: SEM images of OLM, Poloxamer188, β-CD and SD3 formulation

5.6.4. *In- vitro* Dissolution Studies

Table 19: *In- vitro* drug release profile

Time (min)	% Cumulative Drug Release									
	OLM	**SD1**	**SD2**	**SD3**	**C1**	**C2**	**C3**	**SE1**	**SE2**	**SE3**
0	0	0	0	0	0	0	0	0	0	0
5	11.24	13.56	19.56	22.12	15.43	16.25	16.89	12.69	14.63	18.91
10	14.56	16.44	27.82	34.76	18.56	20.21	22.53	15.91	17.24	21.38
15	16.33	23.20	43.43	48.51	22.74	24.89	31.21	21.31	22.83	28.12
20	19.21	27.43	55.31	62.37	25.36	37.91	42.78	23.87	33.51	39.49
30	23.89	35.98	69.65	75.26	32.25	54.68	59.34	29.77	41.61	53.28
45	27.28	57.88	82.34	88.36	53.33	66.53	76.74	48.38	56.72	69.53

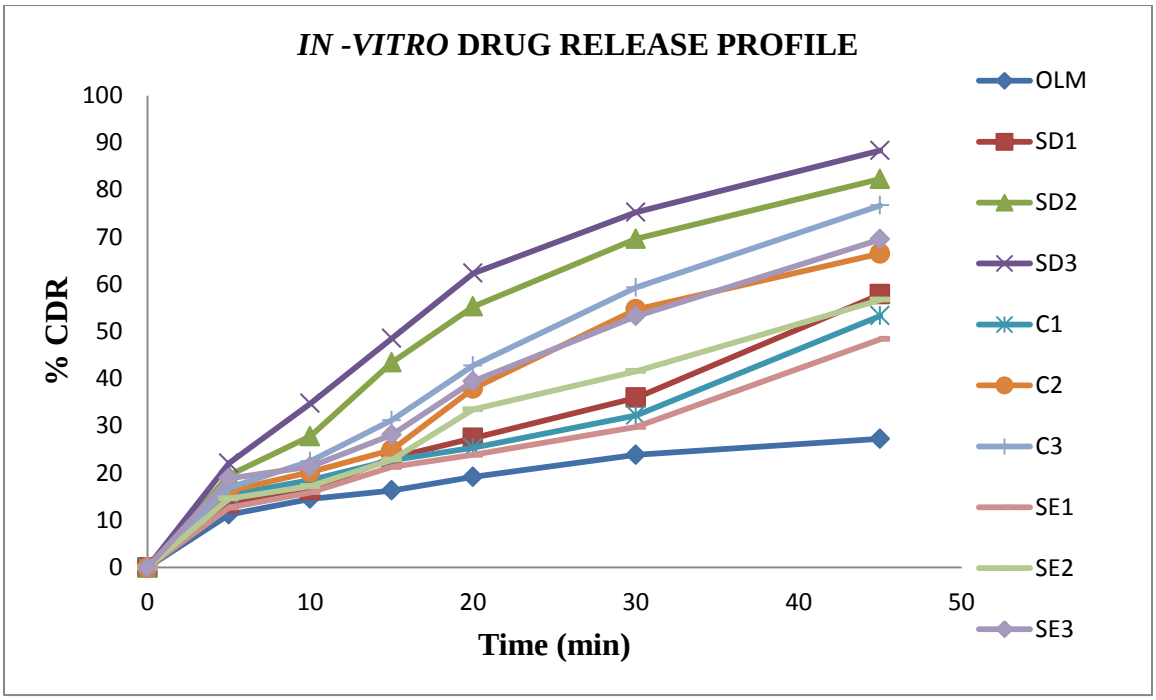


Fig 9: Comparative *in- vitro* drug release profile of pure drug and all formulations.

In-vitro drug release of different SD, complexation and SEDDS formulations were compared with pure drug **(figure no.9)**. Dissolution studies were performed in 6.8 pH phosphate buffer. As compare to drug release of pure drug **(27.28%),** drug release of all prepared formulations were in the range of **48.38%-88.36%** within 45 minutes of dissolution studies. Among all, the formulations prepared by using solid dispersion with poloxamer188 in the ratio of 1:4 (SD3) showed maximum drug release **(88.36%)** within 45 min. This showed that with increase in concentration of carrier (poloxamer188) the dissolution rate of OLM also increased significantly.

The increase in dissolution rate of OLM from solid dispersion of poloxamer188 might be due to the reduction of crystal size of the drug, conversion of drug to amorphous or microcrystalline state and decrease in wettability leading to formation of film surrounding the drug particle and hence decreasing the hydrophobicity of the drug.

On the other hand complexation of OLM with β-CD also showed an increase in drug release from the inclusion complex formed compared to pure drug. With increase in concentration of β-CD, the amount of drug release was also significantly increased. This might be due to the fact that β-CD exhibited high solubility in water which resulted in better wettability and solubility of drug particles, which in turn enhanced its dissolution.

Drug release from the SEDDS formulation of OLM was significantly higher than pure drug but lower than formulation prepared by solid dispersion and complexation technique. Higher drug release of SEDDS of OLM compared to pure drug might be due to the formation of microemulsions with small droplet size, which allowed of faster rate of drug release into the aqueous phase.

The increase in dissolution rate of OLM was found in the order of **SD3>SD2>SD1>C3>C2>C1>SE3>SE2>SE1>pure drug**. Thus from the above results it was found that solid dispersion technique improved the better solubility of OLM as compared to the complexation and selfemulsification techniques. Based on the drug release profile, formulation SD3 was found to be best formulation and selected for three months of stability study.

5.6.5. Drug release kinetics

More often, kinetics of drug release studies allows the measurement of some important physical parameters, such as the drug diffusion coefficient and resorting to model fitting on experimental release data. Thus, mathematical modeling has very important value in the process optimization of all the phenomena affecting drug release kinetics from the formulation. The pattern of the drug release from the solid dispersion, inclusion complexes and SEDDS of OLM was investigated by different kinetic equations (Zero order, First order, and Higuchi's equation). The release mechanism was understood by fitting the obtained data to Korsmeyer-Peppas model.

The **figure no.9 to 12** shows the different release kinetics pattern and release mechanism from the different formulations as well as the best fit release pattern **(table no.20).**

Zero order kinetics

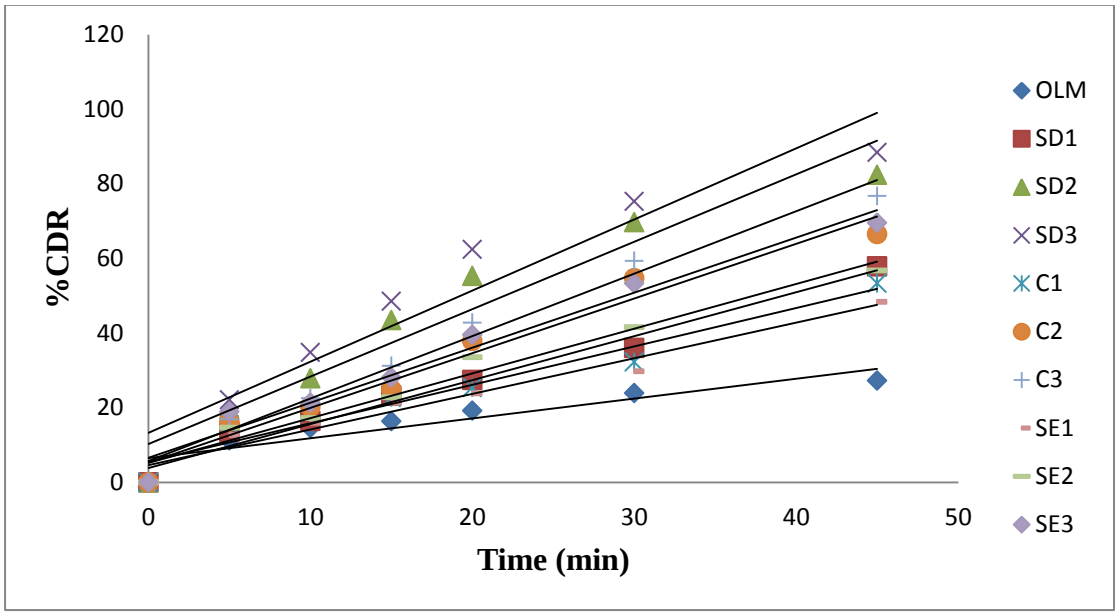


Fig 10: Comparative Zero order release profile of formulations

First order kinetics

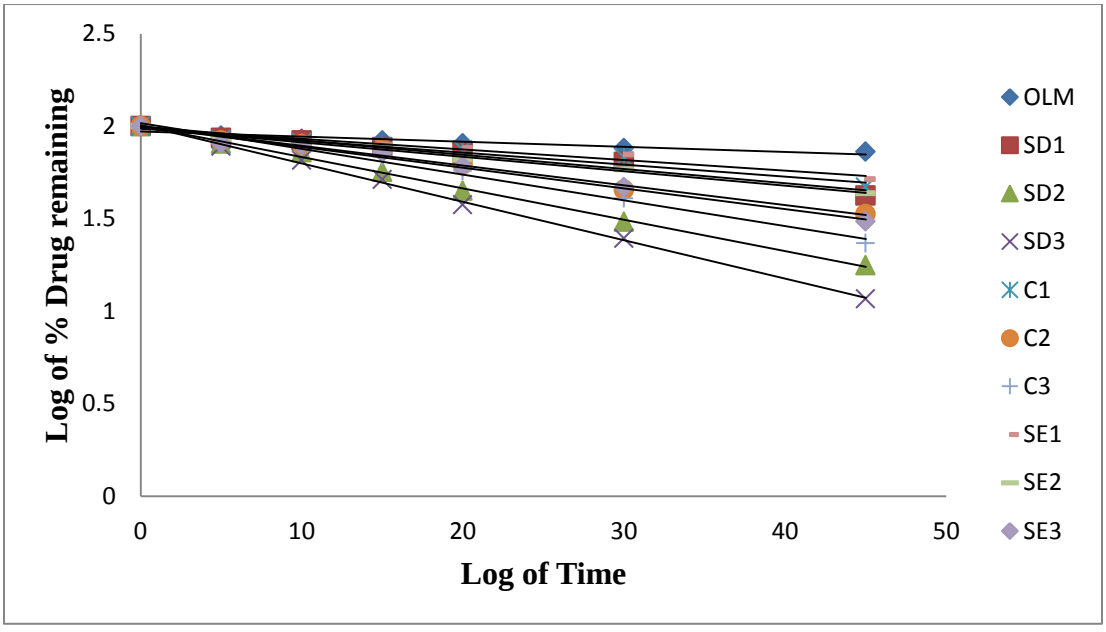


Fig 11: Comparative First order release profile of formulations

Higuchi release kinetic

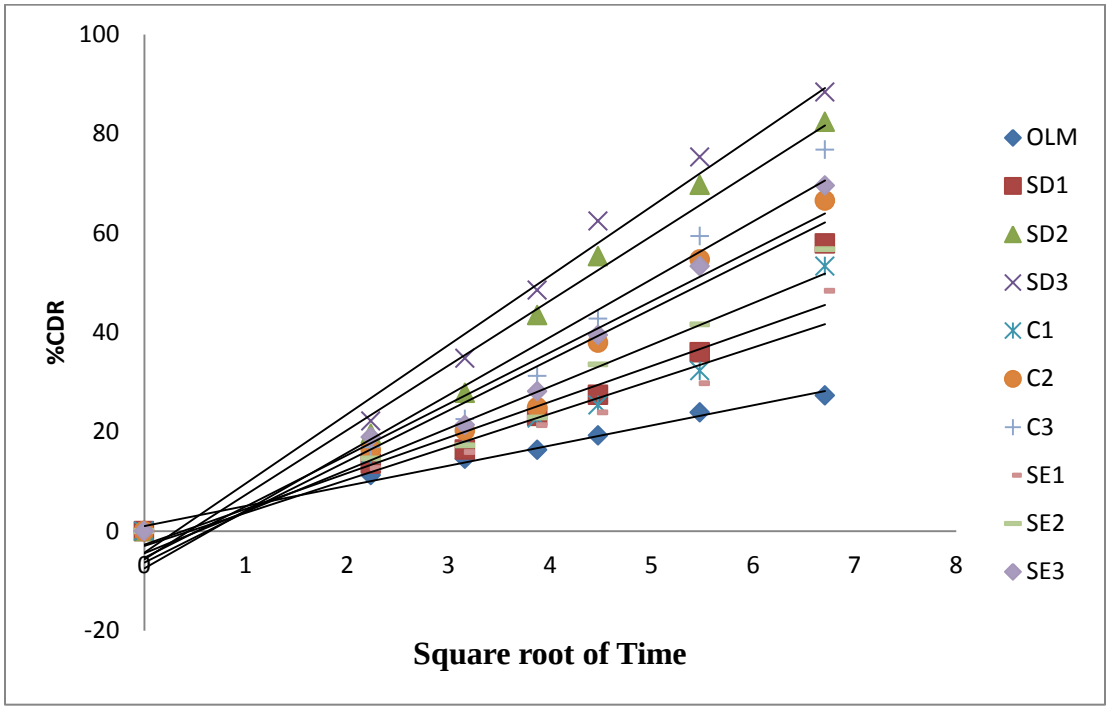


Fig 12: Comparative Higuchi release profile of formulations

Korsemeyer-peppas release Kinetics

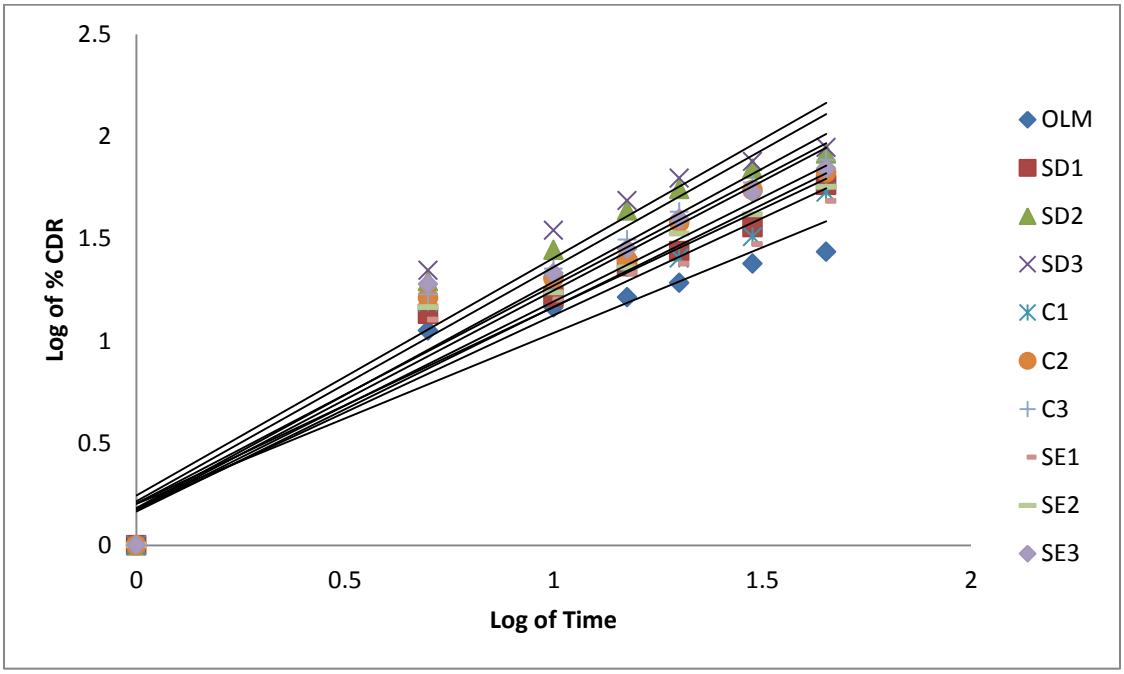


Fig 13: Comparative Korsmeyer-Peppas release profile of formulations

Table 20: Release exponent and rate constant values for all formulations

Formulation Code	KINETICS MODELS				
	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	N
SD1	0.9483	0.9653	0.9257	0.9424	1.0013
SD2	0.9337	0.9971	0.9738	0.9319	1.1454
SD3	0.9151	0.9883	0.9831	0.9181	1.1618
C1	0.9179	0.9461	0.9276	0.9094	0.9614
C2	0.9658	0.9849	0.9408	0.9406	1.0686
C3	0.9797	0.9891	0.9524	0.9461	1.1074
SE1	0.9607	0.9625	0.9388	0.9314	0.9511
SE2	0.9701	0.9891	0.9556	0.9387	1.0181
SE3	0.9698	0.9885	0.9551	0.925	1.0657

The cumulative release data were subjected to various kinetics models and results obtained from release kinetics studies were depicted in **Table no 20**. The *in-vitro* release profile of the drug from all formulations could be expressed by first order equation, as the plots shows high linearity **(R^2 = 0.9461-0.997)** in comparison to zero order **(R^2 = 0.9151-0.979)** and Higuchi **(R^2 = 0.925-0.983)**. The first order release model fitting of the release data **(R^2 =0.9461-0.997)** showed that the release rate was concentration-dependent. To confirm release mechanism the data were fitted into Korsmeyer- Peppas model.

All formulations showed high linearity **(R^2 = 0.9181-0.9461)** with slope (n) ranging from **0.951 to 1.168**, indicating that the drug was released from all formulations followed **Super case II** mechanism, as their **'n'** values are higher than **0.89**. So it was seen that all the formulations showed **First order** kinetics model following **Super case II** drug release mechanism.

5.6.6. Stability studies:

Stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a period of 3 month. The optimized formulation SD3 was selected for stability studies in order to study the effect of temperature and humidity on formulation. The formulation SD3was analyzed for visual appearance, drug content and *in-vitro* release studies. First month of stability studies revealed that there was no change in the physiochemical characteristics of formulation. In between 2 to 3 month SD3 formulation has shown slight changes in drug content and *in vitro* release which was in acceptable limits (±0.5). No significant changes were observed in formulation during study period, thus it can be concluded that the formulation was stable.

Table 21: Stability studies of optimized formulation SD3 at 25ºC/60% RH

Storing Period	Visual Appearance	Drug Content (%)	Drug Release (%)
Initial	White amorphous powder	98.26	88.36
After 1 month	No change in appearance	97.89	88.02
After 2 months	No change in appearance	97.63	87.69
After 3 months	No change in appearance	97.46	86.92

Table 22: Stability studies of optimized formulation SD3 at 45ºC/75% RH

Storing Period	Visual Appearance	Drug Content (%)	Drug Release (%)
Initial	White amorphous powder	98.26	88.36
After 1 month	No change in appearance	97.83	87.83
After 2 months	No change in appearance	97.58	86.74
After 3 months	No change in appearance	97.38	85.88

Chapter 6

Conclusion

6. CONCLUSION

In this present study an attempt has been made to increase the solubility and dissolution rate of poorly water soluble drug OLM by three approaches; Solid dispersion, complexation and self-emulsification. Poloxamer188 and β-CD were used as carrier for preparation of solid dispersion and inclusion complex of OLM respectively. Whereas for formulation of SEDDS soyabean oil, tween80 and PEG600 were used as oil, surfactant and co-surfactant

Since all the formulations procedure were simple, inexpensive and less time consuming and from the results obtained, following conclusion can be made;

- Preformulation parameters such as melting point and solubility of the drug were evaluated. The results found to be satisfactory and all the values obtained comply within pharmacopoeial limits.
- Results obtained from FT-IR studies confirmed that there were no any possible interactions between OLM and other excipients.
- For preparation of SEDDS the best fit ratio of surfactant: co-surfactant (1:1) was selected by constructing pseudo ternary phase diagram.
- All the formulations prepared by SD and complexation techniques were evaluated for saturation solubility and result obtained were found to be satisfactory and complies with standard range.
- Drug content estimation for all formulations was performed and obtained result complies within the standard range.
- For surface morphology SEM study was performed for pure drug OLM, β-CD, poloxamer188 and optimized formulation SD3. Results of SEM study revealed that the

optimized formulation SD3 showed regular and reduced particle size of drug when compared to pure OLM, β-CD and poloxamer188 (irregular shape).

- *In-vitro* release study of all nine formulations and pure drug was conducted in USP-I (basket type) dissolution apparatus for the period of 45 min and drug release profile of all formulations were compared with that of pure drug. From the result obtained it can be concluded that all the prepared formulation have shown increase in percentage drug release than that of pure drug. Among the nine formulations, SD3 formulation prepared by SD technique following solvent evaporation method showed higher % drug release.
- The drug release kinetics showed that all formulations follow first order release kinetics and mechanism was found to be Super case II.
- Optimized formulation SD3 was subjected to 3 months stability studies at specific temperature and relative humidity. There was no significant change in physical appearance, drug content and *in-vitro* release profile. Thus, we can conclude that there was no any drug degradation during study period and prepared formulations were stable.

From the above experimental data it can be concluded that the solid dispersion technique can be the superior over complexation and self-emulsification techniques in order to increase the solubility and dissolution of OLM. In future solid oral dosage form (tablets, capsules) of OLM can be formulated by using the prepared solid dispersion of OLM with poloxamer188, which not only increases the solubility but also increases the oral bioavailability of OLM.

Chapter 7

Summary

7. SUMMARY

Olmesartan Medoxomil is a prodrug of Olmesartan which is potent and selective angiotensin-II type1 receptor antagonist used for treatment of hypertension. Due to poor aqueous solubility, oral bioavailability of OLM is less than 26%. In order to improve its solubility different approaches have been made such as solid dispersion, complexation and self-emulsification.

The scheme of work has been divided into different parts. Initially collection of theoretical and technical data by extensive literature survey, review literature and drug profile. This was followed by procurement of materials and standardization of all materials used in the formulation and they met pharmacopoeial and other established standards.

The solid dispersion and complexation formulations were prepared by using poloxamer188 and β-CD as a carrier respectively. While for preparation of SEDDS of OLM soyabean oil, tween80 and PEG400 were used as oil, surfactant and co-surfactant respectively.

The prepared formulations were evaluated for different parameters like solubility, drug content, SEM and *in-vitro* release behaviour.

The release data was fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas, Zero order and first order to evaluate the kinetics of drug release. The drug release follows first order kinetics following super case II mechanism.

From the obtained results it was summarized that formulation SD3 prepared by solid dispersion showed greater extent of drug release when compared to other formulations prepared by complexation and self-emulsification techniques.

The best formulation SD3 was subjected for stability studies at 25ºC/60% and 40ºC/75% RH for a period of 3 month. After analysing results showed there was no significant change in physical appearance, drug content and *in-vitro* release.

From this study it can be concluded that it is possible to enhance the solubility of OLM by solid dispersion, complexation and self-emulsification techniques among which solid dispersion was found to be the best technique. Furthermore, solid oral dosage forms (tablets, capsules) of OLM can be formulated by using the prepared solid dispersion of OLM with poloxamer188, which not only increases the solubility but also increases the oral bioavailability of OLM

Chapter 8

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