SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUG BY SOLID DISPERSION TECHNIQUE – FABRICATION AND EVALUATION

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

Chennai

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26101010

Under the guidance of

Dr. GRACE RATHNAM M. Pharm., Ph.D;

Department of pharmaceutics

DEPARTMENT OF PHARMACEUTICS

C.L.BAID MEHTA COLLEGE OF PHARMACY

(An ISO 9001-2000 certified institute)

THORAIPAKKAM, CHENNAI-600097

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that the dissertation work entitled **"SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUG BY SOLID DISPERSION TECHNIQUE – FABRICATION AND EVALUATION"** has been carried out by **Register No. 26101010** in partial fulfilment of the requirements for the award of degree **Master of Pharmacy in Pharmaceutics** under **The Tamilnadu Dr. M.G.R. Medical University, Chennai – 32** under my guidance in the **Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai – 97** during the academic year **2011-2012.**

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DECLARATION

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DECLARATION

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Date:

Reg. No. 26101010

Place:

Acknowledement

Considering the magnitude of the human, material and financial resources that have gone into this study, chances are that a listing of the people worth appreciating will be incomplete. I will therefore like to thank everyone who has contributed in any way to the success of this research including those whose names I might have amnestically missed out. The mention of the names is also more important to me than the order of appearance.

Firstly, I will like to acknowledge my director, principal, HOD and guide Dr. Grace Rathnam whose ideas and contributions made this study a success. Her availability for guidance and scrutiny will not go unappreciated. I admire her sense of responsibility, passion, and diligence I would like to acknowledge for giving me the opportunity to undergo my research work in Orchid Healthcare Pharma.

I sincerely acknowledge and appreciate the invaluable role of my supervisor, Md. Abdul Razack whose mentorship and guidance have been most inspiring and motivating. I cannot quantify the value of knowledge and skills he has impacted in me. I am impressed by his constructive criticism of this work, his attention to details and most especially his interest in the research which have all contributed to the success of this study. I am ever grateful.

My sincere gratitude goes to my parents, the apple of whose eye I am, thank you Mum and Dad for encouraging and supporting my academic excellence. I am grateful for the trust you have in me and all your efforts to ensure I succeed in the path I have chosen to tread.

My sincere acknowledgement to Shri K Raghavendra Rao, chairman and managing director, Orchid Chemicals & Pharmaceuticals Ltd. and the initial push given by Mr. Mani, president; Dr.J Suryakumar, senior vice president; Mr. Punit tandon, director; and my thankful for the members of staff, Orchid Healthcare Pharma, Irrungattukottai of the Witwatersrand for their professional assistance with my studies. I am particularly grateful to for their co-operation and assistance.

Some of my friends deserve a mention here. I appreciate you all – be honor and glory forever and ever for bearing the pain and loneliness of my long absence. This dissertation will not be complete without a sincere acknowledgement of my colleagues at and finally, immortal, invisible, the only wise God, be honor and glory forever and ever.

TABLE OF CONTENTS

ABBREVIATIONS

USP	United States Pharmacopeia
mg	Milligram
Gm	Gram
API	Active Pharmaceutical Ingredient
Rpm	Rotations per minute
Min	Minute
^{o}C	Degree Celsius
Ph Eur	European pharmacopeia
BP	British Pharmacopeia
λ_{max}	Absorption maximum
FDA	Food and Drug Administration
FT-IR	Fourier Transform Infra Red Spectroscopy
H.P.L.C	High Perfomance Liquid Chromatography
U.V	Ultra Violet Spectroscopy
I.P	Indian Pharmacopoeia
HCl	Hydrochloric acid

CHAPTER 1

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication.[1, 2] Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route.[3-5]

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. So, solid dispersion technologies is used to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability.[6]

Solubilization[7]

Solubility is defined as the concentration of the undissolved solid in a solvent under a given set of conditions. The solution becomes saturated and the dissolved solute is in equilibrium with the excess undissolved solute.

Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast enough dissolution at the site of administration, often gastrointestinal tract.[8]

Dissolution of solid dosage forms in gastrointestinal fluids is a prerequisite to the delivery of the drug to the systemic circulation following oral administration. Dissolution depends on the solubility of the drug substance in the surrounding medium. Surface area of drug particle is another parameter that influences drug dissolution and in turn drug absorption, particle size is a determinant of surface area.[9]

The dissolution of a substance may be described by the modified Noye's-Whitney equation;

$$\frac{dc}{dt} = (\mathrm{Cs} - \mathrm{C})\,\mathrm{KDS}/\,\mathrm{Vh} \qquad \ldots 1$$

Where dc/dt is the rate of increase in C, the concentration of drug in a bulk solution in which dissolution of the solid particles is taking place; K is a proportionality constant; D is the diffusion coefficient of the drug in the solvent; S is the surface area of un dissolved solid; V is the volume of the solution; h is the thickness of the diffusion layer around a particle; and C_s is the solubility of the drug in the solvent. If we consider a given drug under well-defined conditions (such as controlled liquid intake), we may assume that D, V and h are relatively constant values. Thus we can reduce equation (1) to:

$$\frac{dc}{dt} = \mathrm{KS}\,(\mathrm{Cs} - \mathrm{C}) \qquad \ldots 2$$

Equation (2) shows that the two variables, which may be controlled by the formulation, are the surface area and the solubility of the drug. These two variables can be altered by the following techniques:

1. Control the solubility of a weak acid or base by buffering the entire dissolution medium, the "microenvironment", or the diffusion layer surrounding a particle.
2. Control the solubility of the drug through choice of the physical state, such as crystal form, its hydrate and its amorphous form.
3. Determine the surface area of the drug through control of particle size.[10]

Terms of Appropriate Solubility[11]

The approximate solubilities of Pharmacopoeial and National Formulary substances are indicated by the descriptive terms in the accompanying table-1.

Table 1: Terms of solubility

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

BCS Classification[12]

According to the BCS, drug substances are classified as follows:

Class I - High Permeability, High Solubility.

Class II - High Permeability, Low Solubility.

Class III - Low Permeability, High Solubility.

Class IV - Low Permeability, Low Solubility.

Class boundaries

- A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Solubilization Techniques to Improve Bioavailability by Manufacturing Process[13]

The three major approaches in overcoming the bioavailability problem are:

- The Pharmaceutical approach, which involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.
- The chemical approach in which the pharmacokinetics of the drug is altered by modifying its chemical structure. This approach includes salt formation or incorporating polar or ionizable groups in the main drug structure resulting in the formation of prodrug.
- The biologic approach where by the route of drug administration may be changed such as changing from oral to parentral route.

The attempts, whether optimizing the formulation, manufacturing process or physicochemical properties of the drug, are mainly aimed at enhancement of dissolution rate, as it is the major rate-limiting step in the absorption of most drugs. Increasing the effective surface are of the drugs will be discussed briefly.

1. Solid dispersions:

Solid dispersion is drug dispersed in a biologically inert matrix. Drug in soluble hydrophilic carrier improves the dissolution rate by reducing particle size, higher porosity, drug is in amorphous state, improving wettability and hence possibly bioavailability for poorly water soluble drugs**.** Polymers used are polyethylene glycol, polyvinyl pyrollidone of low molecular weight material such as sugars. The mechanism of improving dissolution was not yet understood. Recently surfactants have been included to stabilize the formulations, this avoiding drug recrystallization and potentiating their solubility.[14]

2. Nanosizing:

Reducing drug particle size to below submicron level i.e., 100-200 nm. This reduction of particle size leads to significant increase in the dissolution rate of drug. Elans nanomilling technology is utilized, which works on two approaches ‘top

down' (Wet milling technology) and 'bottom up' (precipitation, crystallization). Stabilizers are used to stabilize the nanosupension against inter-particle forces between particles due to dispersion or vander walls forces. The inter-particle forces are needed to overcome by repulsive forces. There are two modes of imparting repulsive forces or energetic barriers to colloidal system. Steric stabilization and electrostatic stabilization. Steric stabilization is achieved by adsorbing polymers in to particle surface, electrostatic stablization is obtained by adsorbing changed molecules, which can be ionic surfactants or charged polymers, on to the particle surface. Nanosupension are typically converted to a solid dosage form by spray drying process.[15]

3. Micronization:

The process involves reducing the size of the solid drug particles to 1 to10 microns commonly by spray drying or by use of air attrition methods (fluid energy mill). Greater the surface area faster the dissolution. E.g. Griseofulvin, several steroidal and sulfa drugs.

4. Co-grinding of drug with Excipients:

Particle size reduction is performed by milling in jet miller for poorly soluble compound to increase the bioavailability after micronisation of drugs. In co-grinding method the large quantities of water soluble polymers are used as an excipient. Markus Vogt *et al.*[16] assesed the dissolution of poorly soluble drugs albendazole, felodipine was improved with various excipients like lactose monohydrate, cornstarch, poly vinyl pyrolidone, hydroxy propyl methyl cellulose and sodium lauryl sulphate.

5. Lyophilization:

The material to be dried is first frozen and then subjected under a high vacuum to heat and the frozen liquid sublimed leaving only the solid, dried components of the original liquid. The four components of freeze driers are vacuum chamber for drying, vacuum source, heat source and vapor removal system. Gole et al. and Lawrence *et al.*[17] described the inventive preparation of lyophilized matrix

with gelatin, pectin, soy fibre protein and monitor. The low soluble and bitter actives like risperidone and ibuprofen are coated by particulate coating with natural or synthetic polymer and organic solvents and dried by vapor removal system.[18]

6. Use of Surfactants:

The surface-active agents enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the dissolution fluid. Nonionic surfactants like polysorbates are widely used. Examples of drugs whose bioavailability have been increased by use of surfactants in the formulation include steroids like spironolactone.

7. Use of Salt forms:

Salts have improved solubility and dissolution characteristics in comparison to the original drug. Alkali metals salts of acidic drug like penicillin's and strong acid salts of basic drugs like atropine are more water-soluble than the parent drug.

8. Alteration of pH of the Drug Microenvironment:

This can be achieved in two ways – *in situ* salt formation, and addition of buffers too the formulation. E.g. Buffered aspirin tablets.

9. Use of more soluble metastable polymorphs:

Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important. In general, amorphs are more soluble than metastable polymorphs, anhydrates are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than solvates. The B form of chlorampheical palmitate is more water-soluble than the A and the C forms.

10. Solute-solvent complexation:

Solvates of drugs with organic solvents (also called as pseudopolymorphs) generally have higher aqueous solubility than their respective hydrates or the original drug.

11. Solvent deposition:

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.

12. Selective adsorption on insoluble carriers:

The weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media. Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisolone by maintaining the concentration gradient at its maximum.

13. Molecular encapsulation and cyclodextrins:

The beta and gamma cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusions complexes with hydrophobic drug having poor aqueous solubility. These cyclodextrin molecules are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guest; the outside of the host molecule is relatively hydrophilic. Thiazide diuretics, arbiturates, benzodiazepines.

Solid Dispersion Technology

Definition:

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

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and bioavailability. There are practical limitations for these techniques. The salt formation is not feasible for compounds that are neutral, weakly acidic or weakly basic. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formulations that are usually undesirable from the view points of patient acceptability and commercialization.

In 1961, Sekiguchi and Obi[19] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as "Solid Dispersion"[16].

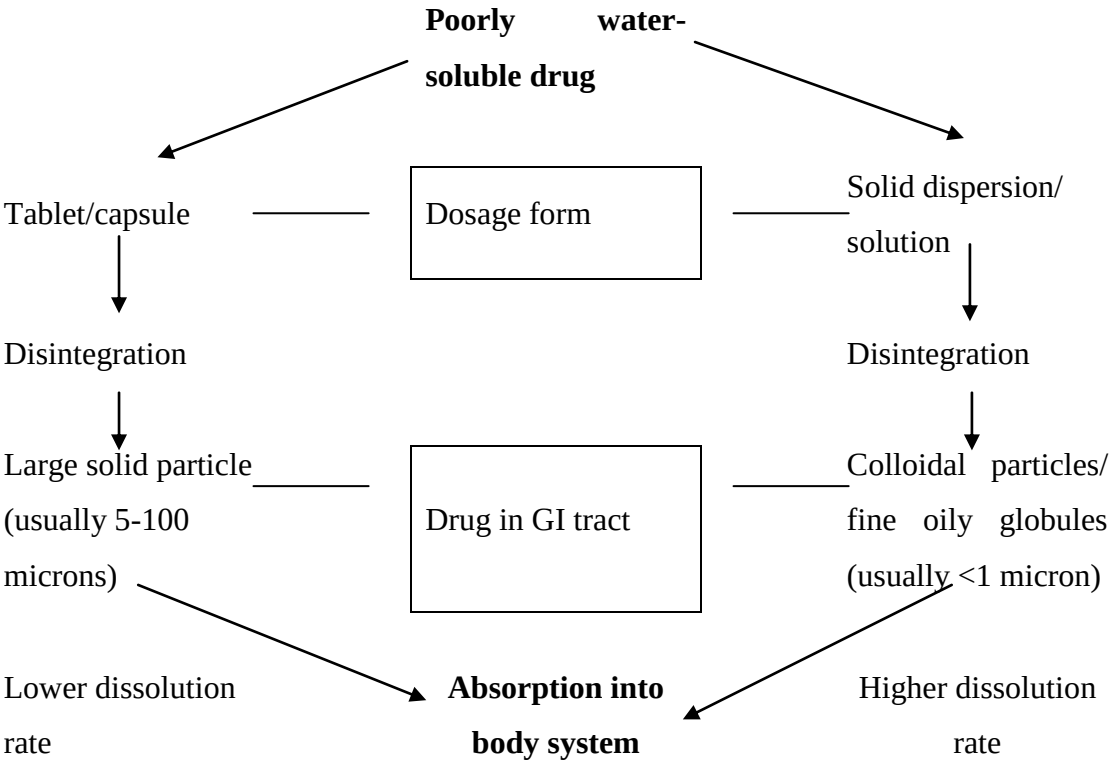


Fig. 1: A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion.[20]

From conventional capsules/tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5 μm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, the excess drug precipitates out as fine colloidal particle or oily globules of submicron size.

Complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction has been utilized to improve the dissolution rate but, there are substantial limitations with each of these techniques.

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs[21].

Historical Background

In 1961, a unique approach of solid dispersion to reduce the particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi and Obi.[19] They proposed the formation of a eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by a rapid solidification process. Upon exposure to aqueous fluids, the active drug was expected to be released into the fluids as fine, dispersed particles because of the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix.

Levy and Kanig[22] subsequently noted the possibility of using a solid solution approach in which a drug is dispersed molecularly in a soluble carrier. In a series of reports in 1965-66, Goldberg et al[23] presented a detailed experimental and theoretical discussion of advantages of solid solution over the eutectic mixture.

In 1965, Tachibana and Nakamaru[24] reported a novel method for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers such as polyvinyl pyrrolidone. They dissolved the drug and the polymer carrier in a common solvent and then evaporated the solvent completely. A colloidal dispersion was obtained when the coprecipitate was exposed to water.

In 1966, Mayersohn and Gibaldi[25] demonstrated that the dissolution rate of griseofulvin could be markedly enhanced when dispersed in polyvinyl pyrrolidone by the same solvent method.

Chiou and Riegelman[26] used PEG 6000 as a dispersion carrier. It is believed that this relatively new field of pharmaceutical technique and principles will play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms. Therefore, a thorough understanding of its fast release principles, methods of preparation, selection of suitable carriers, determination of physical properties, limitations and disadvantages will be essential in the practical and effective application of this approach.

Advantages:

1. Solid dispersions are used for the improvement of the bioavailability of poorly water soluble drugs[27]by enhance the dissolution of the drug.[28]
2. Solid dispersions are better than other particle size reducing techniques to enhance the solubility, because the other size reduction techniques reduces the size to a limit approximately 2-5 microns which doesn't cause enough enhancement in drug solubility or drug release in the small intestine and to improve the bioavailability.[29]
3. Reduce pre-systemic metabolism, this may be due to carrier inhibit the enzyme responsible for biotransformation of the drug.
4. Liquid form of the drug can be transformed to solid form.
5. The problems of solid powder such as less size of particles shows poor mechanical properties (include high adhesion and poor flow properties) can be overcome by the use of solid dispersions.
6. Solid dispersions can be formulated as extended release dosage forms.[30]

Disadvantages:

1. Amorphous state of a drug may undergo crystallization.
2. Aging may decrease the dissolution rate and changes in crystallinity.
3. Solid dispersions may be deteriorated in presence of moisture and excessive temperature. The presence of moisture influences the crystallinity of the drug and stability issues are complicated.[31-34]Some polymers used in solid dispersion are hygroscopic in nature and may absorb moisture that may result in the crystal growth. Sometimes the metastable form of drug may be changed to stable form. Hence, there may be a decrease in solubility and dissolution rate.[35, 36]
4. It is also difficult to understand the relation between structure of drug and its release from solid dispersion.
5. Difficulty in understanding the physical structure of solid dispersions.
6. Problem of residual solvents.
7. Prediction of shelf life of amorphous materials is difficult.

Applications:

1. To obtain a homogeneous distribution of a small amount of drug.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released dosage form.
5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
6. To reduce pre systemic inactivation of drugs like morphine and progesterone.
7. Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.
8. Improve exposure (increase bioavailability, more rapid onset, decrease dose)
9. Reduce variability (Decreased Fed / Fasted effect).

Reasons for Improvement of Solubility

The enhancement in dissolution rate as a result of solid dispersion formulation, relative to pure drug varies from as high as 400 folds to less than two-fold. Corrigan[37] reviewed the current understanding of the mechanism of release from solid dispersion. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another.[38] The main reasons postulated for the observed improvements in dissolution of these systems are as follows.

1. Particles with reduced particle size: Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.[39] A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.[40]

2. P**articles with improved wettability:** A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement.[41] Carriers with surface activity, such as cholic acid and bile salts can significantly increase the wettability property of drug.[42]

3. **Particles with higher porosity:** Particles in solid dispersions have been found to have a higher degree of porosity.[43] The increase in porosity also depends on the carrier properties. For instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.[44]

4. Drugs in amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility.[45] The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.[46] In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.[47]

Types of Solid Dispersions

Based on their molecular arrangement, six different types of solid dispersions can be distinguished:

1. Simple eutectic mixtures
2. Amorphous precipitation in a crystalline carrier
3. Solid solutions
    I. According to their miscibility
    a) Continuous
    b) Discontinuous solid solutions
    II. According to distribution of solvate molecules in the solvendum
    a) Substitutional crystalline solid solutions
    b) Interstitial crystalline solid solutions
4. Glass solution and Glass suspension

1. Eutectics:

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.[48]

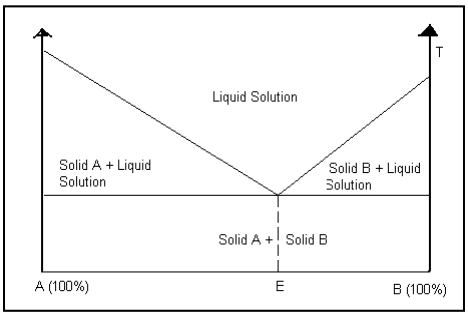


Fig. 2: **Phase diagram for a eutectic system**

2. Amorphous solid solution:

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve dissolution properties of drugs. Other carriers urea and sugars such as sucrose, dextrose and galactose, organic polymers such as PVP, PEG and various cellulose derivatives have been utilized for this purpose.

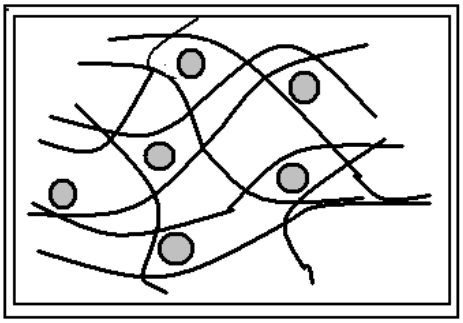


Fig.3: Amorphous Solid Solution

3. Solid solutions:

According to their miscibility two types of solid solution are:-

A. Continuous Solid Solutions:

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

B. Discontinuous solid solutions:

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease. According to Goldberg[48] the term solid solution should only be applied when the mutual solubility of the two components exceeds 5%.

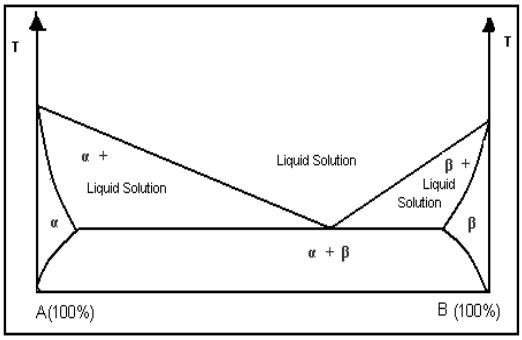


Fig.4: **Phase Diagram for Discontinuous Solid Solution**

According to the way in which the solvate molecules are distributed in the solvendum the two type of solid solution are:-

A. Substitutional Solid Solutions:

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.[49]

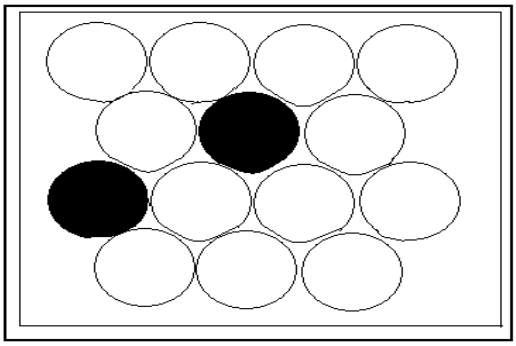


Fig.5: Substitutional Crystalline Solid Solution

B. Interstitial Crystalline Solid Solutions:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.[50]

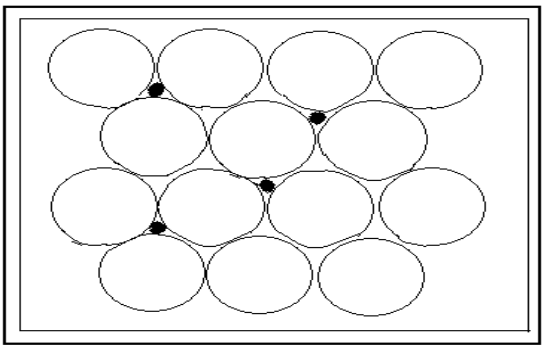
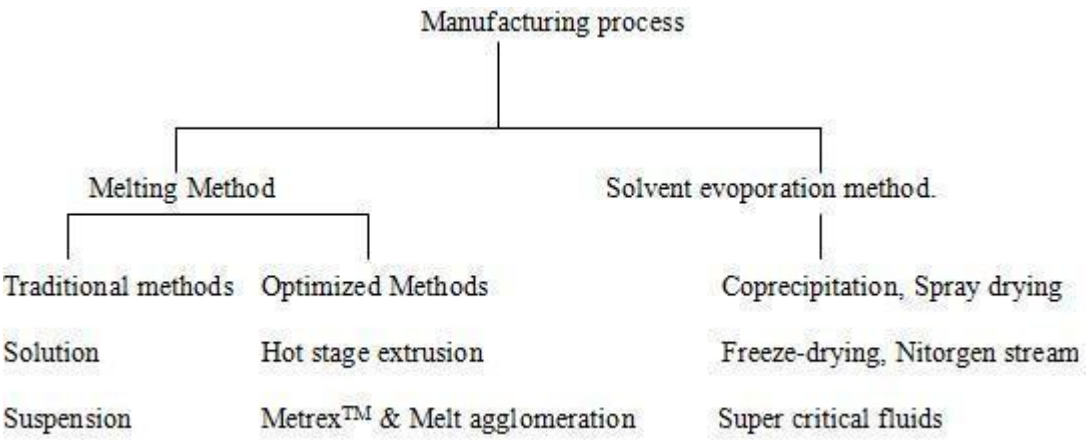


Fig.6: **Interstitial Crystalline Solid Solution**

4. Glass Solutions and Glass Suspensions:

Chiou and Riegelman[26] first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature T_g.

Methods of Preparation



1. Melting Method (Fusion Method):

The melting or fusion method, involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.[26]

2. Melt Extrusion Method:

Melt extrusion method is same as the melt method except that intense mixing of 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. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.[51, 52]

3. Solvent Evaporation Method:

In this method, the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involve the removal of solvent resulting the formation of solid dispersion. This enabled them to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier PVP. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 °C.[53]

4. Melting Solvent Method (Melt Evaporation):

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.[54]

5. Physical Mixture Method:

The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until used for further studies.[55]

6. Co-Grinding Method:

The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a sieve. The resultant granules were dispersed in petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies.

7. Co-precipitation method:

Solute and solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of solute in a crystalline carrier. E.g: amorphous sulfathiazole in crystalline urea. Such dispersions are often called as co-evaporates or co-precipitates.

Alternative Strategies:

1. Lyophilisation Technique/ Freeze-drying/ Cryodessication:

Freeze-drying involves transfer of heat and mass to and from the product under preparation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.[56] Lyophilization is carried out by sublimation in which the transition of a substance from the solid to the vapor state, without first passing through an intermediate liquid phase.

Freeze Drying Involves Four Steps:

- Pretreatment
- Freezing
- Primary Drying
- Secondary Drying

Pretreatment:

Pretreatment includes any method of treating the product prior to freezing. This may include concentrating the product, formulation revision (addition of components to increase stability and/or improve processing), decreasing a high vapor pressure solvent or increasing the surface area.

Freezing:

In this step, it is important to cool the material below its triple point, the lowest temperature at which the solid and liquid phases of the material can co-exist. This ensures that sublimation rather than melting will occur in the following steps.

Primary Drying:

During this drying phase, the pressure is lowered and enough heat is supplied to the material for the water to sublime. In the initial drying phase, about 95% of the water in the material is sublimated.

Secondary Drying:

The secondary drying phase aims to remove unfrozen water molecules, since the ice was removed in the primary drying phase. In this phase, the temperature is raised higher than in the primary drying phase, and can even be above 0 °C, to break

any physico-chemical interactions that have formed between the water molecules and the frozen material. At the end of the operation, the final residual water content in the product is extremely low, around 1% to 4%.

Advantages:

1. Product is dried without elevated temperatures.
2. Rapid reconstitution time.
3. Constituents of the dried material remain homogenously dispersed.
4. Sterility of product can be achieved and maintained.

Disadvantages:

1. Volatile compounds may be removed by high vacuum.
2. Most expensive unit operation.
3. Stability problems associated with individual drugs.

2. Electrostatic Spinning Method:

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology.[57] Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. They are collected on a screen to give a nonwoven fabric, or on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength.[58] Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble polymers in controllable dissolution properties.

3. Super Critical Fluid Technology:

This technology has been introduced in the late 1980s and early 1990s. SCFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). The spray drying, solvent evaporation and hot melt

method often result in low yield, high residual solvent content or thermal degradation of the active substance. In the supercritical fluid carbon dioxide is used as either a solvent for drug and matrix or as an anti-solvent.[59]

When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. However, the application of this technique is very limited, because the solubility in CO_2 of most pharmaceutical compounds is very low (<0.01 %wt) [60]and decreases with increasing polarity.

Selection of a Carrier[38]:

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Be freely water-soluble with intrinsic rapid dissolution properties.
2. Be non-toxic and pharmacologically inert.
3. Be heat stable with a low melting point for the melt method.
4. Be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Be able to preferably increase the aqueous solubility of the drug and
6. Be chemically compatible with the drug and not form a strongly bonded complex with the drug.

Table 2: Materials used as carrier for solid dispersion

Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose.
Acids	Citric acid, succinic acid
Polymeric materials	Povidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, hydroxy ethyl cellulose (HEC), cyclodextrin, hydroxy propyl cellulose (HPC), pectin, galactomannan.
Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate, eudragit L100, eudragit S100, Eudragit RL, Eudragit RS.
Surfactants	Polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans.
Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

Carriers

1. Polyethylene glycol (PEG)

General characteristics of PEGs Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200 – 3,00,000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500 - 20,000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW up to 600, PEGs are fluid, in the range 800-1500 they have a consistency that is best described as Vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents.

The melting point of the PEGs of interest lies under 65^{o}C in every case (e.g. the m.p.

of PEG 1000 is 30-40°C, the m.p. of PEG 4000 is 50-58°C and the m.p. of PEG 20 000 is 60-63ºC).[61] These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds[62] and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000.[63] PEGs of MW 4000-6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high.

The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dispersion. If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug.[64]

2. Polyvinylpyrrolidone (PVP)

General characteristics of PVP polymerization of vinylpyrrolidone lead to PVP of molecular weights ranging from 2500 to 3,00,0000. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid[65]. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration.[66] Similarly to PEG, solid dispersions prepared with high proportions of PVP tend to exhibit higher drug solubility and release rate than those with high proportions of drug.

3. Polyvinylalcohol (PVA), crospovidone (PVP-CL), polvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA):

All three polymers belong to the polyvinyl group. Whereas PVA and PVP-PVA copolymers are both water soluble, crospovidone swells when dispersed in water.[67]

4. Cellulose Derivatives:

General characteristics of cellulose derivatives - Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by b-1, 4-glycoside bonds.

5. Hydroxypropylmethylcellulose (HPMC):

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% are derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10,000 to 1,500,000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane.[68]

6. Hydroxypropylcellulose (HPC):

HPC exhibits good solubility in a range of solvents, including water (up till 40ºC), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37,000 (Type SSL) to 1,150,000 (Type H).[69] Several studies were carried on the influence of the chain length and proportion of HPC in the solid dispersion on the release behavior of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

7. Carboxymethylethylcellulose (CMEC):

CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8[70]. Likewise, the bioavailability of the test substance MFB-1041 could be substantially improved in beagles.[71]

8. Urea:

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than threefold by incorporating it in a co evaporate with urea.[72]

9. Sugar, Polyols and their Polymers:

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co evaporates.

10. Emulsifiers:

The release behavior of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are usually used in combination with another carrier.[73]

11. Organic acids and their derivatives:

Organic acids such as succinic acid and citric acid have been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin.[23, 26]

12. Cyclodextrins:

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.[38]

Advantages of cyclodextrins:

- Increasing the stability of the drug.
- Release profile during gastrointestinal transit through modification of drug release site and time profile.
- Decreasing local tissue irritation.
- Masking unpleasant taste.

Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drug and carriers in solvent and filling into hard gelatin capsules or compressed into tablets. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties, as a result the bioavailability of solid dispersions is not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization and lyophilization of drugs.

One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carrier, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or

prevent crystallization of drugs from super-saturated systems. Attention must be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipid in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP-3 based drug metabolism and p-glycoprotein-mediated drug efflux will require careful consideration.

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms.

Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, an exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability, possible drug-carrier interactions must also be investigated.[74]

CHAPTER 2

DISEASE PROFILE

Osteoporosis

Osteoporosis is a disease characterized by low bone mass and loss of bone tissue that may lead to weak and fragile bones. Osteoporosis, leads to increased risk for fractured bones (broken bones), particularly in the hip, spine, and wrist.
Osteoporosis is often considered to be a condition that frail elderly women develop. However, the damage from osteoporosis begins much earlier in life. Because peak bone density is reached at approximately 25 years of age, it is important to build strong bones by that age, so that the bones will remain strong later in life. Adequate calcium intake is an essential part of building strong bones.

According to the World Health Organization, the prevalence of osteoporosis among U.S. white women post menopause is estimated to be 14% in those 50-59 years of age, 22% in those 60-69 years of age, 39% in those 70-79 years of age and 70% in those 80 years of age and older. Significant risk has been reported in people of all ethnic backgrounds. White and Asian racial groups, however, are at greatest risk.[75]

Causes:

Osteoporosis occurs when there is an imbalance between new bone formation and old bone resorption. The body may fail to form enough new bone, or too much old bone may be reabsorbed, or both. Two essential minerals for normal bone formation are calcium and phosphate.

The leading cause of osteoporosis is a lack of certain hormones, particularly estrogen in women and androgen in men. Women, especially those older than 60 years of age, are frequently diagnosed with the disease. Menopause is accompanied by lower estrogen levels and increases a woman's risk for osteoporosis. Other factors that may contribute to bone loss in this age group include inadequate intake of calcium and vitamin D, lack of weight-bearing exercise, and other age-related changes in endocrine functions (in addition to lack of estrogen).

Other conditions that may lead to osteoporosis include overuse of corticosteroids (Cushing syndrome), thyroid problems, lack of muscle use, bone cancer, certain genetic disorders, use of certain medications, and problems such as low calcium in the diet.

The following are risk factors for osteoporosis:

- Women are at a greater risk than men, especially women who are thin or have a small frame, as are those of advanced age.
- Women those with a family history of osteoporosis, have a greater risk of developing osteoporosis than other women.
- Postmenopausal women including those who have had early or surgically induced menopause, or abnormal or absence of menstrual periods are at greater risk.
- Cigarette smoking, eating disorders such as anorexia nervosa or bulimia, low amounts of calcium in the diet, heavy alcohol consumption, inactive lifestyle, and use of certain medications, such as corticosteroids and anticonvulsants, are also risk factors.
- Rheumatoid arthritis itself is a risk factor for osteoporosis.
- Having a parent that has/had osteoporosis is a risk factor for the offspring.

Symptoms:

Early in the course of the disease, osteoporosis may cause no symptoms. Later, it may cause dull pain in the bones or muscles, particularly low back pain or neck pain. Later in the course of the disease, sharp pains may come on suddenly. The pain may not radiate (spread to other areas); it may be made worse by activity that puts weight on the area, may be accompanied by tenderness, and generally begins to subside in one week. Pain may linger more than three months.

People with osteoporosis may not even recall a fall or other trauma that might cause a broken bone, such as in the spine or foot. Spinal compression fractures may result in loss of height with a stooped posture (called adowager's).Fractures at other sites, commonly the hip or bones of the wrist, usually result from a fall.

Treatment:

Treatment for osteoporosis focuses on slowing down or stopping the mineral loss, increasing bone density, preventing bone fractures, and controlling the pain associated with the disease.

CHAPTER 3

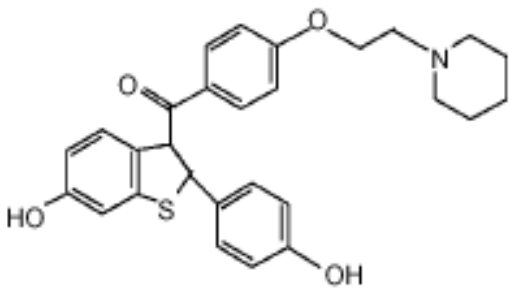
DRUG AND EXCIPIENT

PROFILE

Raloxifene Hydrochloride

Chemical Nomenclature:
2-(4-hydroxyphenyl)-3-({4-[2-(piperidin-1-yl)ethoxy]phenyl}carbonyl)-1-benzothiophen-6-ol.

Chemical Formula: $C_{28}H_{27}NO_4S$
Structure:



Molecular weight: 473.583

Description

A second generation selective estrogen receptor modulator (SERM) used to prevent osteoporosis in postmenopausal women. It has estrogen agonist effects on bone and cholesterol metabolism but behaves as a complete estrogen antagonist on mammary gland and uterine tissue

Physical Properties **:** Off white to pale yellow crystals.

Solubility **:** Very sparingly soluble in water (0.25mg/ml)

Melting Point **:** 143-147ºC

Indication

For prevention and treatment of osteoporosis in post-menopausal women, as well as prevention and treatment of corticosteroid-induced bone loss. Also for the reduction in the incidence of invasive breast cancer in postmenopausal women with osteoporosis or have a high risk for developing breast cancer.

Mechanism of action

Raloxifene binds to estrogen receptors, resulting in differential expression of multiple estrogen-regulated genes in different tissues. Raloxifene produces estrogen-like effects on bone, reducing resorption of bone and increasing bone mineral density in postmenopausal women, thus slowing the rate of bone loss. The maintenance of bone mass by raloxifene and estrogens is, in part, through the regulation of the gene-encoding transforming growth factor-β3 (TGF-β3), which is a bone matrix protein with antiosteoclastic properties. Raloxifene activates TGF-β3 through pathways that are estrogen receptor-mediated but involve DNA sequences distinct from the estrogen response element. The drug also binds to the estrogen receptor and acts as an estrogen agonist in preosteoclastic cells, which results in the inhibtion of their proliferative capacity. This inhibition is thought to contribute to the drug's effect on bone resorption. Other mechanisms include the suppression of activity of the bone-resorbing cytokine interleukin-6 promoter activity. Raloxifene also antagonizes the effects of estrogen on mammary tissue and blocks uterotrophic responses to estrogen. By competing with estrogens for the estrogen receptors in reproductive tissue, raloxifene prevents the transcriptional activation of genes containing the estrogen response element. As well, raloxifene inhibits the estradiol-dependent proliferation of MCF-7 human mammary tumor cells in vitro. The mechansim of action of raloxifene has not been fully determined, but evidence suggests that the drug's tissue-specific estrogen agonist or antagonist activity is related to the structural differences between the raloxifene-estrogen receptor complex (specifically the surface topography of AF-2) and the estrogen-estrogen receptor complex. Also, the existence of at least 2 estrogen receptors (ERα, ERβ) may contribute to the tissue specificity of raloxifene.[76]

Pharmacokinetics[77]

Absorption

Raloxifene is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass glucuronidation. Approximately 60% of an oral dose is absorbed; however, because of extensive presystemic glucuronide conjugation, absolute bioavailability is only 2%. Significant interpatient differences in

bioavailability may result from alterations in the rate of glucuronide formation and enterohepatic recycling.

Distribution

Raloxifene is widely distributed into tissues; the volume of distribution (V) is 2348 L/kg after administration of a single oral dose of 30-150 mg. V is not dose dependent. Studies with radioactively labeled raloxifene indicate extensive distribution into the liver, serum, lungs, and kidneys. Conversion of the drug to an active metabolite appears to occur in several tissues, including the liver, lungs, spleen, bone, uterus, and kidneys. Raloxifene and its conjugates are 95% bound to albumin and a 1-acid glycoprotein *invitro*. Raloxifene does not bind to sex steroid-binding globulin. Although it is unknown whether raloxifene is distributed into breast milk, its high protein-binding profile should theoretically limit such distribution. Nevertheless, lactating women should not use raloxifene. Raloxifene is a pregnancy category X drug and is therefore contraindicated in pregnant women.

Metabolism:

Raloxifene undergoes extensive first-pass metabolism. Conjugate formation includes Raloxifene 4'-glucuronide, 6-glucuronide and 6, 4'-diglucuronide. Very small amounts of free raloxifene (<1% of a dose) are detected in the circulation. The absence of other metabolites suggests that raloxifene is not metabolized by the cytochrome P-450 isoenzyme system. Although raloxifene may be converted back within certain tissues, reconversion to the parent compound does not appear to occur in major target organs, such as the uterus and skeleton. Therefore, it appears that the tissue selectivity of raloxifene is not explained by deconjugation of metabolites to the parent compound in different tissues. The terminal log linear portions of plasma concentration curves for raloxifene and its conjugates are parallel.

The clearance of raloxifene hydrochloride 400 mg/day given for five days to healthy premenopausal women was 51.5-128.3 L/hr/kg, depending on the phase of the menstrual cycle. A mean steady-state V of 4135 L/kg was observed for the women. There is no evidence to date to suggest significant influences of sex, race and age (42-84 years) on the clearance of raloxifene. The half-life ($t_{1/2}$) of raloxifene at steady state ranges from 15.8 to 86.6 hours and averages 32.5 hours. One study

evaluated the $t_{1/2}$ of raloxifene in 14 healthy postmenopausal women and 14 healthy men. The $t_{1/2}$ ranged from 11 to 27 hours. The oral clearance of a single dose of raloxifene is 44.1 L/ hr/kg. The $t_{1/2}$of raloxifene may be prolonged to 27.7 hours, secondary to reverse systemic metabolism and enterohepatic recycling, when the drug is given on a long-term basis.

Excretion:

Raloxifene is excreted primarily in the feces. Glucuronide metabolites are eliminated in the biliary tract, and are subsequently broken down by bacteria to the parent drug. Less than 0.2% of raloxifene is excreted unchanged in the urine; less than 6% is excreted in the urine as glucuronide conjugates.

Pharmacodynamics

Raloxifene, a selective estrogen receptor modulator (SERM) of the benzothiophene class, is similar to tamoxifen in that it produces estrogen-like effects on bone and lipid metabolism, while antagonizing the effects of estrogen on breast and uterine tissue. Raloxifene differs chemically and pharmacologically from naturally occuring estrogens, synthetic steroidal and nonsteroidal compounds with estrogenic activity, and antiestrogens. Estrogens play an important role in the reproductive, skeletal, cardiovascular, and central nervous systems in women, and act principally by regulating gene expression. When estrogen binds to a ligand - binding domain of the estrogen receptor, biologic response is initiated as a result of a conformational change of the estrogen receptor, which leads to gene transcription through specific estrogen response elements of target gene promoters. The subsequent activation or repression of the target gene is mediated through two distinct trans activation domains of the receptor: AF-1 and AF-2. The estrogen receptor also mediates gene transcription using different response elements and other signaling pathways. The role of estrogen as a regulator of bone mass is well established. In postmenopausal women, the progressive loss of bone mass is related to decreased ovarian function and a reduction in the level of circulation estrogens. Estrogen also has favorable effects on blood cholesterol.

Current Therapy Options

Selective estrogen receptor modulators (SERMs). SERMs demonstrate tissue-selective activities that produce estrogenic actions in certain organs (e.g bone, brain, and liver) during postmenopausal HRT. The 3 SERMs that are approved by FDA include tamoxifen, raloxifene, and toremifene. Although these drugs have demonstrated numerous benefits, they are also associated with very serious side effects, such as an increased risk of endometrial cancer, which limit their utility.[78, 79]

Tamoxifen and toremifene are approved for the treatment of various types of breast cancer, whereas raloxifene is the only SERM currently approved by FDA for the treatment and prevention of postmenopausal osteoporosis, as well as for the reduction in risk of invasive breast cancer.[80] Raloxifene slows bone thinning and causes a slight increase in bone thickness. It also decreases resorption of bone and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone are manifested as reductions in serum and urine levels of bone turnover markers, decreases in bone resorption based on radiocalcium kinetics studies, increases in BMD, and decreases in incidence of fractures. Several clinical studies have demonstrated that administration of raloxifene 60 mg/d is effective in treating postmenopausal osteoporosis. Postmenopausal women either with or without prevalent vertebral fractures who were evaluated in the Multiple Outcomes of Raloxifene Evaluation (MORE) study demonstrated a reduction of 30% to 50% in the occurrence of incident vertebral fractures.[81] The Continuing Outcomes Relevant to Evista (CORE) trial analyzed the long-term skeletal effects of raloxifene. The study reported a 30% to 40% reduction in markers of bone turnover after 1 year. Investigators observed a 2% to 3% increase in lumbar spine and femoral neck BMD after 3 years.[82]

Role in Therapy:

Raloxifene carries FDA-approved labeling for use in the prevention and treatment of osteoporosis in post-menopausal women. Clinical evidence suggests that raloxifene increases bone mineral density, decreases the risk of vertebral fractures, potentially prevents breast cancer, and has no significant effect on endometrial tissue growth. In addition, raloxifene has positive effects on LDL cholesterol and total cholesterol, although data on effects on cardiovascular

morbidity and mortality are not yet available. Raloxifene may be used as an alternative to traditional hormone replacement therapy for osteoporosis, especially in women with a high risk of breast cancer. Raloxifene is an appropriate choice for women who cannot tolerate the adverse effects of estrogen or in women who decline estrogen therapy. However, raloxifene should not be used in women experiencing hot flashes as a primary symptom of estrogen deficiency or in those with a history of venous thromboembolism.

Each treatment decision should be based on the individual patient. Other agents (such as bisphosphonates and calcitonin) are available for women with osteoporosis who are primarily interested in bone-related benefits.

Ultimately, it will be information on cardiovascular or breast cancer benefits that will determine the future role of raloxifene. Trials assessing these possibilities are ongoing and should provide health care providers with more complete information on the advantages of raloxifene, if any, over standard hormone replacement therapy.

Excipients

Polyethylene Glycol

1. Non-proprietary Names

BP: Macrogols

2. Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.

3. Empirical Formula and Molecular Weight

$HOCH_2$ $(CH_2OCH_2)_m$ CH_2OH where m represents the average number of oxyethylene groups, molecular weight 6000.

4. Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

5. Applications

- Pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.
- Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.
- Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

6. Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are

liquids; grades 1000 and above are solids at ambient temperatures.

Grades of PEG 6000 and above are available as free flowing milled powders.

7. Typical Properties

Type of PEG 6000 -- Density (g/cm^3) --1.080

Freezing point (8 ^{0}C) -- 55–61

Viscosity (kinematic) [mm2/s (CST)] -- 250–390

Melting point -- 55–638 ^{0}C

Moisture content -- hygroscopicity decreases with increasing molecular weight. Solid grades e.g. PEG 4000 and above are not hygroscopic.

Solubility: All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular- weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerine and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

8. Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

9. Incompatibilities

- The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterifies or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.
- Liquid and solid polyethylene glycol grades may be incompatible with some colouring agents.

Poly Vinyl Alcohol

1. Nonproprietary Names

Ph Eur: Poly (Vinyl Alcohol); USP: Polyvinyl Alcohol

2. Synonyms

Airvol; Alcotex; Celvol; Elvanol; Gelvatol; Gohsenol; Lemol; Mowiol; poly(alcohol vinylicus); Polyvinol; PVA; vinyl alcohol polymer.

3. Empirical Formula and Molecular Weight

$(C_2H_4O)_n$ 20,000–200,000, polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20,000–200,000.

4. Functional Category

Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

5. Applications

Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations.

- It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products.
- It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration, and in transdermal patches.

6. Description

Polyvinyl alcohol occurs as an odourless, white to cream-colored granular powder.

7. Typical Properties

Solubility: Soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 908 ^{0}C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature**.**

8. Stability and Storage Conditions

Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 1008 ^{0}C and rapid degradation at 2008 ºC; it is stable on exposure to light.

9. Incompatibilities

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxyl groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulphates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present

Cyclodextrins

1. Nonproprietary Names

BP, USP-NF & PhEur: Alfadex betadex; Gamma Cyclodextrin

2. Synonyms

β-Cyclodextrin beta-cycloamylose; beta-dextrin; betadexum; cavamax W7 pharma; cycloheptaamylose; cycloheptaglucan; cyclomaltoheptose**; ß-cyclodextrin** .

3. Empirical Formula and Molecular Weight: $C_{42}H_{70}O_{35}$, molecular weight 1135

4. Functional Category

Solubilizing agent; stabilizing agent.

5. Applications

- Cyclodextrins are crystalline, no hygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are α -, β -, γ cyclodextrin, which have respectively 6, 7, and 8 glucose units.
- Cyclodextrins may be 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.

- In oral tablet formulations, β-cyclodextrin may be used in both wet-granulation and direct-compression processes. The physical properties of b-cyclodextrin vary depending on the manufacturer. However, β-cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1% w/w magnesium stearate, when it is directly compressed.

6. Description

Cyclodextrins are cyclic oligosaccharides containing at least six D- (þ)-glucopyranose units attached by a glucoside bonds. The three natural cyclodextrins, α , β, γ, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively. Cyclodextrins occur as white, practically odourless, fine crystalline powder, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

7. Typical Properties of β-cyclodextrin

- Compressibility 21.0–44.0%.
- Density (bulk): 0.523 g/cm^3.
- Density (tapped): 0.754 g/cm^3.
- Melting point: 255–2658 ^{0}C;
- Moisture content: 13.0–15.0% w/w.
- Particle size distribution β-cyclodextrin: 7.0–45.0 mm
- Solubility: Soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 208 ^{0}C, 1 in 20 at 508 ^{0}C; practically insoluble in acetone, ethanol (95%), and methylene chloride.

8. Stability and Storage Conditions

β-Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

9. Incompatibilities

The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl- β-cyclodextrin. β-cyclodextrin is nephrotoxic and should not be used in parenteral formulations;

Povidone

1. Non-proprietary Names

BP: Povidone; JP: Povidone; PhEur: Povidone; USP: Povidone

2. Synonyms

E1201; Kollidon; Plasdone; Poly[1-(2-oxo-1-pyrrolidinyl)ethylene];Polyvidone; Polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

3. Functional Category

Disintegrant; dissolution enhancer; suspending agent; tablet binder

4. Molecular weights: K 17 - 10,000; K 30 - 50,000

5. Applications

- Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.
- Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms
- Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions

6. Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

6. Typical Properties

Density (bulk) 0.29–0.39 g/cm^3

Density (tapped) 0.39–0.54 g/cm^3

Melting point Softens at 1508 ºC.

Dynamic viscosity (m Pascals)- 5.5-8.5 (K 28/32)

K-value Approximate molecular weight—50,000

7. Stability and Storage Conditions

- Povidone darkens to some extent on heating at 1508 ^{0}C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–1308 ^{0}C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.
- Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

8. Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

Crospovidone

1. Nonproprietary Names

BP: Crospovidone; PhEur: Crospovidone; USP-NF: Crospovidone

2. Synonyms

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; **Polyplasdone XL; Polyplasdone XL-10**; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3. Empirical Formula and Molecular Weight

$(C_6H_9NO)n$ >1 000,000 The USP32–NF27 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

4. Functional Category

Tablet disintegrant.

5. Applications in Pharmaceutical Formulation or Technology

- Crospovidone is a water-insoluble tablet disintegrate and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.
- Larger particles provide a faster disintegration than smaller particles. crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.
- The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

6. Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

7. Typical Properties

- Acidity/alkalinity pH = 5.0–8.0 (1% w/v aqueous slurry)
- Polyplasdone XL-10 -- Density (bulk) (g/cm^3) -- 0.323
  Density (tapped) (g/cm^3) -- 0.461
  Surface area (m^2/g) -- 1.2–1.4
- Polyplasdone XL -- Density (bulk) (g/cm^3) -- 0.213
  Density (tapped) (g/cm^3) -- 0.273
  Surface area (m^2/g) -- 0.6–0.8
- Moisture content -- Approximately 60%.
- Particle size distribution less than 400 mm for polyplasdone XL; less than 74 mm for polyplasdone XL-10. Approximately 50% greater than 50 mm and maximum of 3% greater than 250 mm in size for kollidon CL. Minimum of 90% of particles are below 15 mm for kollidon CL-M. The average particle size for crospopharm type A is 100 mm and for crospopharm type B it is 30 mm.

- Solubility practically insoluble in water and most common organic solvents

8. Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

9. Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Poloxamer

1. Nonproprietary Names

BP: Poloxamers; PhEur: Poloxamers ; USP-NF: Poloxamer.

2. Synonyms

Lutrol; monolan; pluronic; poloxalkol; poloxamera; polyethylene– propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; supronic; synperonic.

3. Typical poloxamer grade

Poloxamer	Physical form	a	b	Average molecular weight
407	Solid	101	56	9840–1460

3. Functional Category

Dispersing agent; emulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

4. Applications in Pharmaceutical Formulation or Technology

- Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents.
- The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical

and surface-active properties vary over a wide range and a number of different types are commercially available.

- Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings.
- Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes, and in the preparation of solid-dispersion systems.
- More recently, poloxamers have found use 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. They may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers. Poloxamer 338 and 407 are used in solutions for contact lens.

5. Description

Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

6 Typical Properties

- Acidity/alkalinity pH = 5.0–7.4 for a 2.5% w/v aqueous solution.
- Cloud point >1008 ^{0}C for a 1% w/v aqueous solution, and a 10% w/v aqueous solution of poloxamer 188.
- Density 1.06 g/cm3 at 258 ºC.
- Flash point 2608 ^{0}C.
- Flowability: solid poloxamers are free flowing.
- HLB value 0.5–30; 29 for poloxamer 188.
- Melting point 52–578 ºC for poloxamer 407.
- Moisture content: Poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at relative humidity greater than 80%.

7. Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mould growth. The bulk material should be stored in a well-closed container in a cool, dry place.

8. Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

Lactose, Spray-Dried

1. Synonyms

FlowLac 90; FlowLac 100; Lacto press Spray-Dried; Lacto press Spray-Dried 250; NF Lactose–315; NF Lactose–316 Fast Flo; **SuperTab 11SD**; SuperTab 14SD.

2. Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$-342.30 (for amorphous); $C_{12}H_{22}O_{11}\,H_2O$-360.31 (for monohydrate)

3. Functional Category

Directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler.

4. Applications in Pharmaceutical Formulation or Technology

Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

5. Description

Lactose occurs as white to off-white crystalline particles or powder. It is odourless and slightly sweet-tasting. Spray-dried direct compression grades of lactose are generally composed of 80–90% specially prepared pure a-lactose monohydrate along with 10–20% of amorphous lactose.

6. Typical Properties

Super tab 11SD -- Density (bulk) (g/cm^3) -- 0.60.

Density (tapped) (g/cm^3) -- 0.71

7. Stability and Storage Conditions

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

8. Incompatibilities

Lactose is a reducing sugar. The amorphous lactose, which is the most reactive form of lactose present in spray-dried lactose, will interact more readily than conventional crystalline grades) Typical reactions include the millard reaction with either primary or secondary amines.

Lactose, Anhydrous

1. Synonyms

Anhydrous 60M; Anhydrous Direct Tableting (DT); Anhydrous DT High Velocity; Anhydrous Impalpable; Lactopress Anhydrous; Lactopress Anhydrous 250; lactosum anhydricum; lattosio; milk sugar; **SuperTab 21AN**; SuperTab 22AN; saccharum lactis.

2. Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$- 342.30

3. Functional Category

Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

4. Applications in Pharmaceutical Formulation or Technology

- Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder.
- Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

5. Description

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

6. Typical Properties

- Brittle fracture index 0.0362
- Bonding index 0.0049 (at compression pressure 177.8 MPa)(1)
- Density (true) 1.589 g/cm3 for anhydrous b-lactose

- Density (bulk) 0.71 g/cm3 for Super Tab 21AN.
- Density (tapped) 0.88 g/cm3 for Super Tab 21AN.

7. Stability and Storage Conditions

Mould growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; stored in a well-closed container in a cool, dry place.

8. Incompatibilities

Lactose anhydrous is incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 408C and 75% RH, the mixture containing anhydrous Lactose showed greater moisture uptake and drug degradation. Lactose anhydrous is a reducing sugar with the potential to interact with primary and secondary amines (Millard reaction) when stored under conditions of high humidity for extended periods.

Magnesium Stearate

1. Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

3. Functional Category

Tablet and capsule lubricant.

4. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

5. Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

6 .Typical Properties

Crystalline forms High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk) -- 0.159 g/cm3

Density (tapped) -- 0.286 g/cm3

Density (true) -- 1.092 g/cm3

Flash point -- 2508 ^{0}C

Flowability: Poorly flowing, cohesive powder.

Melting range --117–1508 ^{0}C

7. Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

8. Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.[83]

CHAPTER 4

LITERATURE

REVIEW

Jha RK *et al.* (2011)[84] described two simultaneous approaches to improve its bioavailability, complexation of raloxifene with cyclodextrin(s), and formulation of mucoadhesive microspheres of the complex using different proportions of carbopol and HPMC. Significant improvement in the solubility of raloxifene was observed, and it differed with the combination of excipients used, Microspheres possessed remarkable mucoadhesion and offered controlled drug release, lasting up to 24 hours. FT-IR studies evidenced no interaction among drug and excipients.

Balasubramaniam Jagadish *et al.* (2011)[85] enhanced dissolution and bioavailability of raloxifene hydrochloride by co-grinding with different super disintegrants namely crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG), using a ballmill, Significant enhancement in dissolution rate was observed with coground mixture of raloxifene with CP (1 : 5). The extent of the mean plasma exposures of raloxifene was 7-fold higher in animals treated with co-ground mixture of raloxifene, CP (1: 5) compared to animals treated with milled raloxifene. Co-grinding of raloxifene with CP, reduced drug crystallinity, increased the rate and extent of dissolution, and improved bioavailability.

V. K. Rai *et al.* (2011)[86] enhanced dissolution of a poorly soluble drug, raloxifene by hydrophilic binders like PVP, HPMC, HPC and comparison was made with hydrophobic binder, ethyl cellulose, dissolution behaviour of different formulation and pure drug was studied in different relevant media, which reveals significant improvement in dissolution behavior of drug was observed using hydrophilic binder.

Rahmat Talukder *et al.* (2011)[87] enhanced the dissolution rates of raloxifene HCl by solid dispersion using polyethylene glycols (PEG). Higher the PEG level in dispersions, higher is the drug release rates. Mechanistically it appears that PEG molecules form conjugates with raloxifene through hydrogen bonding, which increases the dissolution rates of raloxifene. Additionally solvent method promotes the formation of metastable form of the drug in the dispersion, which further enhances the dissolution rates.

N. L. Prasanthi *et al.* (2011)[88] fast dissolving tablets were direct compressed by incorporating super disintegrants like crosscarmellose sodium and sodium starch glycolate. The study was performed by incorporating the super disintegrants in 2 % and 4 % concentration for each and 2 % - 2 % in combination of both super disintegrants. The tablets containing super disintegrants in combination showed excellent *in vitro* dispersion time and drug release as compared to other formulations.

M.D.Dhanaraju *et al.* (2011)[89] prepared solid dispersions by hot melt method by employing 6 different carriers and mixing ratios (1:1, 1:2, and 1:3). 10 batches of raloxifene formulation were conducted to select prototype formula, batch containing polaxomer and glycerol was selected as optimized formulation. The formulation obtained was investigated by preliminary stability studies.

Vyas Jigar *et al.* (2011)[90] prepared rofecoxib solid dispersions by different method using urea, PEG 6000 and PVP K30 as carriers. Solid dispersions prepared by fusion and solvent evaporation showing maximum solubility were selected and formulated into tablet. Solid dispersion prepared by fusion method using PEG 6000 at 1:9 drug carrier ratio has shown highest improvement in the dissolution profile of rofecoxib.

Muralidhar.S *et al.* (2011)[91] formulated solid dispersions of etoricoxib using PEG 6000 as carrier at various proportions by using different techniques like physical mixtures, kneading method and solvent evaporation method. It was observed that solvent evaporation method exhibited higher dissolution rate than the corresponding solid dispersion.

Bobe.K.R *et al.* (2011)[92] prepared atorvastatin solid dispersion by solvent evaporation and fusion methods by using mannitol, PEG 4000 and PVP K30. Solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. The study also shows that dissolution rate of atorvastatin can be enhanced to considerable extent by solid dispersion technique with PEG.

Niranjan Kumar.M *et al.* (2011)[93] prepared alprazolam solid dispersions by solvent evaporation method by using PEG 6000 and PVP k-30 as carriers at different ratios. Dissolution rates and drug releases of solid dispersions with PVP-K30 was most effective to enhance the dissolution rate of the drug.

Dan Liua *et al.* (2006)[94] were aimed to increase dissolution rate of a poorly water-soluble drug as solid dispersions itraconazole. Cooling curve method was used to determine the eutectic point of drug-poloxamer 188 mixture and the phase diagram of the binary system was constructed. Solid dispersions of itraconazole were prepared by the hot melt method and characterized by differential scanning calorimetry (DSC). Solubility and dissolution studies in various media were conducted with pure itraconazole, a physical mixture and solid dispersions. The eutectic mixture showed increase in drug dissolution rate.

Muralidhar S *et.al.* (2011)[95] formulated solid dispersions using PEG 6000 as carrier at various proportions. The solid dispersions were prepared with different techniques like physical mixtures, kneading method and solvent evaporation method. The drug release profile was studied in water containing 2% SLS. All the solid dispersions exhibited superior dissolution than pure drug. Solvent evaporation method was found to be superior to other method.

Sachin Kumar Singh *et al.* (2011)[96] prepared solid dispersions by the solvent evaporation method at different drug: polymer ratios. The dissolution rate of prednisone from solid dispersions was markedly enhanced by increasing the polymer concentration. The tablets were prepared from solid dispersion systems using polyethylene glycol PEG 6000 as a carrier at low and high concentration. The results showed that PEG 6000-based tablets exhibited significantly higher prednisone dissolution (80% within 30 minutes) than did conventional tablets prepared without PEG 6000 (G25% within 30 minutes).

Chin Sung Cho *et al.* (2010)[97] developed a stabilized formulation of amorphous raloxifene hydrochloride, solid dispersion granules of amorphous

raloxifene were prepared by fluidized bed granulation with non-pareil beads, compressed and filmcoated to produce solid dispersion tablets. Dissolution profile of solid dispersion granules revealed that the they meets the acceptance criteria, and the content of RXF was maintained over 95% for 5 months at accelerated conditions of 40^0 C and 75% R.H. Therefore, we suggest the usefulness of SDT for the development of generic pharmaceuticals containing amorphous raloxifene

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Dehghan M.H.G *et al.* (2010)[98] prepared solid dispersions of glipizide by using water soluble carriers such as PEG and mannitol by fusion method and PVP K 30 by solvent evaporation method in different ratios. It was found that the optimum weight ratio 1.5 for PEG-6000 shows higher solubility and dissolution rate. Finally it was concluded that PEG-6000 shows greater dissolution enhancing capacity than mannitol and PVP K 30.

Arun Prasad.K *et al.* (2010)[99] studied solid dispersion tablet of terbinafine hydrochloride by using carriers PEG 6000 (by melting method) and polyvinyl pyrrolidone K 30 (by solvent method) at different ratio. The solid dispersion showing better release profile was chosen to formulate into a tablet using croscaramellose sodium as super disintegrant. The solid dispersions prepared by solvent evaporation method using PVP K30 showed increased dissolution rate of terbinafine when compared to other formulations.

S-H. Kim *et al.* (2009)[100] characterized and Improved Dissolution Rate of raloxifene solid Dispersions with various ratios of PVP K-30 and poloxamer 407 in different concentration using spray drying technique. Their physicochemical characterizations were evaluated by SEM, FT-IR. The *in vitro* release behavior of solid dispersion presented at simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) and the dissolution rate of hydrochloride was dramatically higher than commercial drug.

Jani Rupal *et al.* (2009)[101] used aceclofenac, a non steroidal anti-inflammatory drug for post traumatic pain have been prepared solid dispersions

using PEG-6000 and PVP at different ratios by solvent evaporation method and physical mixture method. It is found that PEG 6000 based solid dispersions were more effective in enhancing the dissolution rate of aceclofenac .

Bhole P *et al.* (2009)[102] studied the solid dispersion of felodipine was prepared by using PEG 6000 and PVA as a carrier with different drug polymer ratios using different techniques (physical mixing and solvent evaporation). Solid dispersions with both polymers increased drug release, particularly greater in the case of PVA than PEG 6000.

Michael F *et al.* (2008)[103] evaluated the pharmacokinetics of raloxifene in oral and intravenous formulations with HBenBCD in male Wistar–Hannover rats. analytical methodology to measure raloxifene and its metaboliteswas developed by measuring raloxifene metabolism *in vitro*. Formulation with HBenBCD significantly increased raloxifene oral bioavailability these studies demonstrate that raloxifene formulations containing HBenBCD significantly increased the oral bioavailability in rats relative to formulations that did not contain HBenBCD.

Van den Mooter *et al.* (2006)[104] increased the dissolution of temazepam by solid dispersions using PEG 6000 and PVP K30. Dispersions with PEG 6000 were prepared by fusion-cooling and co-evaporation, while dispersions containing PVP K30 were prepared by co-evaporation. In contrast to the very slow dissolution rate of pure temazepam, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. The aqueous solubility of temazepam was favored by the presence of PEG 6000.

CHAPTER 5

AIM AND PLAN OF WORK

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. The most commonly used techniques to increase dissolution rate are particle size reduction, salt formation and lyophilization, but all these methods have practical limitations like improper enhancement of solubility and all the drugs are not suitable for these techniques.

To overcome all these, solid dispersion technique by solvent evaporation approach is successfully applied to improve the solubility and dissolution rate, there by bioavailability.

The aim of this present investigation is to enhance solubility of raloxifene hydrochloride by formulating as solid dispersions.

To effectuate this formulation, solubility trials are performed with different carriers to enhance the solubility, dissolution rate and consequently bioavailability of the drug. Carriers like polyethylene glycol, polyvinyl pyrrolidine, polyvinyl alcohol, polaxamer, polyplasdone, sugars, cellulose polymers and cyclodextrins. Further various molecular weight grades of these polymers are used to prepare the solid dispersion.

The main objectives of this study are as follows:

- To prepare the solid dispersion of raloxifene hydrochloride using different carriers by solvent evaporation technique.
- To analyse the drug and carrier interactions by FTIR study.
- To evaluate the solubility and *invitro* drug release of solid dispersions.
- To prepare the immediate release tablets.
- To evaluate the drug release from the tablets prepared with solid dispersion by *invitro* dissolution studies.

CHAPTER 6

MATERIALS AND METHODS

6.1 Materials

Table 3: List of Ingredients and Suppliers

S. No.	Ingredients	Manufacturer / Supplier
1	API	Orchid Health Care Pharmaceuticals
2	Cyclodextrin	Roquette Pharma
3	PVP K17	ISP Pharmaceuticals
4	PVP K30	ISP Pharmaceuticals
5	Crospovidone XL	ISP Pharmaceuticals
6	Crospovidone XL 10	ISP Pharmaceuticals
7	Polaxomer 407	Sigma Aldrich
8	Poly Vinyl Alcohol 4-88	Merck Chemicals
9	Poly Ethylene Glycol 6000	Sigma Aldrich
10	Hydroxy Propyl Cellulose	Shin-etsu
11	Hydroxy Propyl Methyl Cellulose	Shin-etsu
12	Lactose monohydrate NF	DMV Int.
13	Lactose anhydrous NF	DMV Int.
14	Lactose monohydrate 200M	DMV Int.
15	Mannitol	Roquette Pharma
16	Magnesium Stearate	Mallinckrodt
17	Opadry White	Colorcon

Table 4: List of equipments

S.NO	EQUIPMENT	MAKE
1.	Electronic Balance	Mettler Tolido & Sartorius
2.	Mechanical sifter	Sams Techno Mumbai
3.	Optical microscopy	KAY Enterprises
4.	Double Cone Blender	Sams Techno Mumbai
5.	Compression Machine	Cadmach(16 Stations), Ahmadabad
6.	Tap Density Tester	Electrolab, Mumbai
7.	Disintegration Tester	Electrolab, Mumbai
8.	Hardness, Thickness Tester	Erweka & Varian, Mumbai
9.	Friabilator	Electrolab, Mumbai
10.	Mechanical Stirrer	Remi Motors
11.	Conventional Coating Pan	Sams Techno, Mumbai
12.	Dissolution Apparatus USP XXIV	Labindia, Disso2000
13.	HPLC	Shimadzu
14.	UV spectroscopy	Shimadzu

6.2 Methods

6.2.1 Pharmaceutical buffer preparations

6.2.1.1 0.1 N Hydrochloric acid - 0.85 ml of concentrated hydrochloric acid was dissolved in 100 ml of distilled water.

6.2.1.2 Glycine buffer pH 3.0 - 25 ml 0.2 M glycine and 5.7 ml HCl were diluted to 100 ml with distilled water.

6.2.1.3 Acetate buffer pH 4.5 - Dissolve 2.99 gm of sodium acetate and 1.66 ml of glacial acetic acid in water, dilute to 1000 ml and mix, pH adjusted with glacial

acetic acid or sodium hydroxide to 4.5.

6.2.1.4 Phosphate buffer pH 6.8 - 100 ml of 0.1 M potassium dihydrogen phosphate and 44.8 ml of 0.1 M sodium hydroxide were diluted to 200 ml with distilled water.

6.2.1.5 Phosphate buffer pH 7.2 - 100 ml of 0.1 M potassium dihydrogen phosphate and 69.4 ml of 0.1 M sodium hydroxide, dilute to 200 ml with water.

6.2.1.6 pH 2.5 buffer - 16.8 ml of dibutylamine in 70 ml of water. pH is adjusted to 2.5 with phosphoric acid, dilute to 100 ml with purified water.

6.2.2 Solubility Studies

500 mg of Raloxifene hydrochloride (RLX) was weighed and transferred into different conical flask. 50 ml of different dissolution media were transferred into individual conical flask and were closed appropriately. All the flasks were sonicated for 1 hr and the samples were filtered by using 0.45 µ PTFE filter. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 280 nm by HPLC. Solubility of RLX in different dissolution media and results are mentioned in table 9.

6.2.3 Preformulation Studies

The drug and carrier were mixed in 1:1 ratios as per procedure 6.2.5 and interaction studies were evaluated by physical appearance, drug content and by FTIR.

6.2.4 Calibration Curve of RLX

6.2.4.1 Preparation of RLX Stock Solution:

100 mg of RLX was weighed and dissolved in 100 ml of methanol.

6.2.4.2 Preparation of RLX Standard Dilutions:

Aliquots of RLX stock solution was transferred into 5 volumetric flasks and were further diluted with Purified water so as to get 2,4,6,8, & 10 ppm of standard dilutions of RLX. The absorbance of the above dilutions was measured at 285 nm using purified water as blank in UV spectroscopy.

6.2.5 Preparation of RLX Solid Dispersions

Solvent Evaporation Method

2 gm of RLX was taken in a china dish and was dissolved in 5 ml of methanol. To the methanol solution, 2 gm of carrier was added and the mixture was evaporated at room temperature for 24 hrs. Then the mixture was collected and packed in an amber colored glass containers and was hermetically sealed, stored at ambient conditions. Compositions of various solid dispersions of RLX are given in table 5.

Table 5: Composition of Various Solid Dispersions of RLX

S. No	Composition	Ratio
1	RLX + PEG-6000	1 : 1
2	RLX + PVA 4-88	1 : 1
3	RLX + ß-cyclodextrin	1 : 1
4	RLX + PVP K17	1 : 1
5	RLX + PVP K30	1 : 1
6	RLX + Polyplasone XL10	1 : 1
7	RLX + Polaxomer 407	1 : 1
8	RLX + HPC L.S	1 : 1
9	RLX + HPMC K4MCR	1 : 1
10	RLX + Pharmatose 200M	1 : 1
11	RLX + Supertab 11SD	1 : 1
12	RLX + Supertab 21AN	1 : 1
13	RLX + Mannitol	1 : 1

6.2.6 Evaluation of Solid Dispersions

6.2.6.1 Angle of repose: [105]

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\tan \theta = h/r$$

Where; θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

6.2.6.2 Compressibility index[106]

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials, because all of these can influence the observed compressibility index. It is determined by measuring both the bulk volume and tapped volume of a powder.

Basic methods for the determination of compressibility index: There are some variations in the method of determining the compressibility index, the basic procedure is to measure the unsettled apparent volume (V_O), and the final tapped volume (V_f), of the powder after tapping the material until no further volume changes occur.

The compressibility index is calculated as follows:

$$\text{Compressibility index} = 100 \times V_0\text{-}V_f / V_0$$

Alternatively, the compressibility index may be calculated using measured values of

bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping.

Flow properties and corresponding angle of repose, compressibility index are shown in table 6.

Table 6: Flow properties determination

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)
1	Excellent	25-30	<10
2	Good	31-35	11-15
3	Fair	36-40	16-20
4	Passable	41-45	21-25
5	Poor	46-55	26-31
6	Very poor	56-65	32-37
7	Very very poor	> 66	>38

6.2.6.3 Particle Size Determination

The average particle sizes of the prepared solid dispersions were analyzed by optical microscopy.

6.2.6.4 Determination of Drug Content of Solid Dispersions

Preparation of mobile phase for HPLC

- pH 2.5 buffer and acetonitrile was mixed in the ratio 67:33 (v/v) respectively.
- It was filtered through 0.45 µm membrane filter and degassed.

Preparation of diluents for HPLC

pH 2.5 and acetonitrile was mixed in ratio 40 : 60 (v/v) respectively.

Weigh 360 mg of solid dispersion and transferred into a 250 ml volumetric flask and diluents were added and kept in sonicator for about 30 minutes with intermediate shaking.

A portion of the above solution was centrifuged at 2500 rpm for 10 minutes by using centrifuge tubes with caps.

- 5 ml of above supernatant solution was pipette into a 50 ml volumetric flask; volume was diluted with diluents and mixed.
- 2 ml was filtered through 0.45 µm PTFE filter.

Chromatographic Parameters

- The liquid chromatography is equipped with a 280 nm UV detector.
- Column**:** 150 mm × 4.6 mm column that contains 5 µm packing of octyl silane chemically bonded to porous silica.
- Column temperature : 35 ºC
- Flow rate : 1.5 mL/min
- Injection volume : 10 µL
- Run time : 8 minutes

System Suitability

- 10 µL portions of blank (diluents) & standard solution (five replicate injections) were injected into chromatography, chromatograms were recorded and responses of the major peak were measured.
- The USP tailing factor for RLX peak should be not more than 2.
- The USP plate count for RLX peak should be not less than 2000.
- The %RSD for the area of RLX peak obtained from the five injections of standard solution should be not more than 2.0.

6.2.6.5 Saturated Solubility studies

Saturated solubility studies of RLX solid dispersions were performed in purified water. Excess amount of 500 mg RLX dispersions were weighed and transferred into different conical flask. 50 ml of purified water transferred into

individual volumetric flask and were closed appropriately. All the flasks were placed in the sonicator and sonicated for 1 hr. Then the flasks were removed and the samples were filtered by using 0.45 µ PTFE filter. The clear solution obtained by filtration was suitably diluted with diluents and the absorbance values were noted at 280 nm by using purified water as blank.

6.2.6.6 Dissolution Studies

Dissolution studies of solubility enhanced dispersions were performed in a calibrated 8 station dissolution test apparatus equipped with paddles (USP apparatus II method) employing 1000 ml of purified water as a medium. The paddles were operated at 50 rpm and temperature was maintained at 37 ± 0.5 ºC throughout the experiment. 5 ml samples were withdrawn at 10, 20, 30 & 45 min of time periods as given by FDA dissolution data base. Equal volume of dissolution medium was replaced to maintain the constant volume throughout the experiment. Samples withdrawn and diluted with same medium and the amount of the drug dissolved was estimated UV spectrophotometer at 285 nm. Dissolution profiles of solid dispersions are shown in table 14 and fig. 16.

6.2.7 Preparation of Tablets

Based upon the solubility studies performed, seven solubility enhanced dispersions were selected for further preparation as tablets. The tablets were prepared by direct compression process. The ratio of drug and disintegrant were maintained constant while the diluents concentration was adjusted according to assay. The compositions of various tablet formulations are given in table 7.

The materials were individually weighed, passed through sieve #40 and blended for 15 minutes by using double cone blender. The powder mixture was then lubricated with magnesium stearate and blended for 5 min. Blend was compressed as tablets using cadmach 16 stations mini press. To minimize the processing variables all batches of tablets were compressed, under identical condition. The powder blends were evaluated for flow properties such as angle of repose and compressibility index.

The compressed tablets were further evaluated for their physical parameters such as weight uniformity, hardness, friability, disintegration time and drug content and the values are shown in table 15.

Table 7: Composition of RLX Solid Dispersion tablets

Ingredient (mg/tablet)	Formulations						
	RLX_1	**RLX_2**	**RLX_3**	**RLX_4**	**RLX_5**	**RLX_6**	**RLX_7**
Solid dispersions*	120.4	113.6	121.5	129.1	127.7	123.4	120.9
Supertab DCL 21 AN*	83.0	80.0	82.0	74.0	76.0	80.0	83.0
Supertab DCL 11 SD	20.88	20.88	20.88	20.88	20.88	20.88	20.88
Polyplasdone XL	14.4	14.4	14.4	14.4	14.4	14.4	14.4
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Opadry white	7.2	7.2	7.2	7.2	7.2	7.2	7.2
weight of tablet (mg)	247.2	247.2	247.2	247.2	247.2	247.2	247.2

✷ Corrected according to assay value

6.2.8 Evaluation of tablets

6.2.8.1 Weight Uniformity

20 tablets from each batch at random were taken and weighted. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight. The deviation if any in the weight of individual tablets from the average weight was checked. This test highly describes that all tablets of a particular batch should be uniform in weight. If any weight variation is there, that should be within the I.P limits. The test was considered correct if not more than two tablets fall outside the I.P limits out of twenty tablets taken for the test[124].

Table 8: Limits for the Average Weight of Tablets

Average Weight	Percentage Deviation
80 mg or less	10
More than 80mg but less than 250mg	7.5
250 mg or more	5

6.2.8.2 Hardness

Hardness of the tablets was determined by using erweka hardness tester. The tablet to be tested is placed on the surface of the hardness tester and the reading were noted from the display which indicates the pressure required in kp to break the tablet. The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression.

6.2.8.3 Friability

Friability test was performed by using friabilator. 6.5 mg of tablets from each batch were weighed and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated friability. The acceptance limits of weight loss should not be more than 1%. This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting.

6.2.8.4 Disintegration Time

Six tablets were placed in six tubes of basket and 800 ml of water is taken, maintained at 37 ± 2 ^{0}C. Time was noted for all the tablets to disintegrate completely.

6.2.8.5 Estimation of Drug Content

20 tablets were crushed and the weight equivalent to 180 mg of RLX were transferred into a 250 ml volumetric flask and diluents were added and kept in sonicator for about 30 minutes with intermediate shaking. A portion of the above solution was centrifuged at 2500 rpm for 10 minutes by using centrifuge tubes with caps. 5 ml of above supernatant solution was pipette into a 50 ml volumetric flask,

volume was diluted with diluents and mixed. 2 ml was filtered through 0.45 µm PTFE filter and injected in HPLC.

6.2.8.6 Dissolution Studies

Dissolution studies of solubility enhanced dispersions were performed in a calibrated 8 station dissolution test apparatus equipped with paddles (USP apparatus II method) employing 1000 ml of purified water as a medium. The paddles were operated at 50 rpm and temperature was maintained at 37 ºC ± 1 ºC throughout the experiment. 5 ml samples were withdrawn at 10, 20, 30 & 45 min of time periods as given by FDA dissolution data base. Equal volume of dissolution medium was replaced to maintain the constant volume throughout the experiment. Samples withdrawn and diluted with same medium and the amount of the drug dissolved was estimated U.V spectrophotometer at 285 nm. Dissolution profiles of solid dispersion tablets were shown in table 16 and fig. 17.

CHAPTER 7

RESULTS AND DISCUSSION

Table 9: Solubility Studies of RLX in Different Dissolution Media

S.NO	Dissolution Media	Amount of Drug Soluble (mg/ml)
1	Purified water	0.44
2	0.1 N Hydrochloride	0.24
3	0.1% Polysorbate	0.61
4	pH 3.0 Glycine buffer	0.12
5	pH 4.5 acetate buffer	0.19
6	pH 6.8 phosphate buffer	0.18
7	pH 7.2 phosphate buffer	0.32

Table 10: Calibration curve for the estimation of RLX in purified water.

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.108
3	4	0.225
4	6	0.345
5	8	0.466
6	10	0.608

Fig 7: Calibration curve for the estimation of RLX in purified water

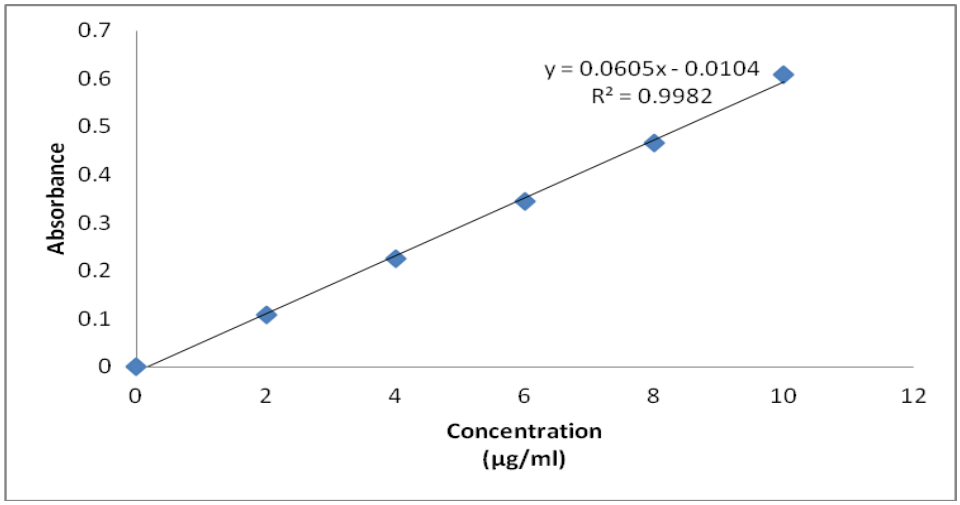

Table 11: Preformulation Studies on RLX

S. No	Description	Method Evaluated			
		Physical		Assay	
		0 Day	1 Month	0 Day	1 Month
1	RLX	Dark yellow	Complied	Complied	Complied
2	RLX + PEG-6000	Light yellow	Complied	Complied	Complied
3	RLX + PVA 4-88	Light yellow	Complied	Complied	Complied
4	RLX + ß-cyclodextrin std	Light yellow	Complied	Complied	Complied
5	RLX + PVA K 17	Intense yellow	Complied	Complied	Complied
6	RLX + PVP K30	Intense yellow	Complied	Complied	Complied
7	RLX + Polyplasdone Xl 10	Intense yellow	Complied	Complied	Complied
8	RLX + Polaxomer 408	Light yellow	Complied	Complied	Complied

Table 12: Flow Properties and Drug Content of RLX Solid Dispersions

S.NO	Solid Dispersions	Angle of Repose	Carr's Index (%)	Particle Size (microns)	Drug Content (%)
1	RLX 1	20	14	82±4.1	94±0.21
2	RLX 2	32	18	102±7.6	97±0.34
3	RLX3	30	18	87±6.9	97±0.31
4	RLX4	23	16	72±6.5	99±0.23
5	RLX5	22	15	75±2.9	93±0.37
6	RLX6	24	16	97±6.5	99±0.28
7	RLX7	26	14	92±2.8	105±0.33

All values are expressed as mean ± SD, n=3

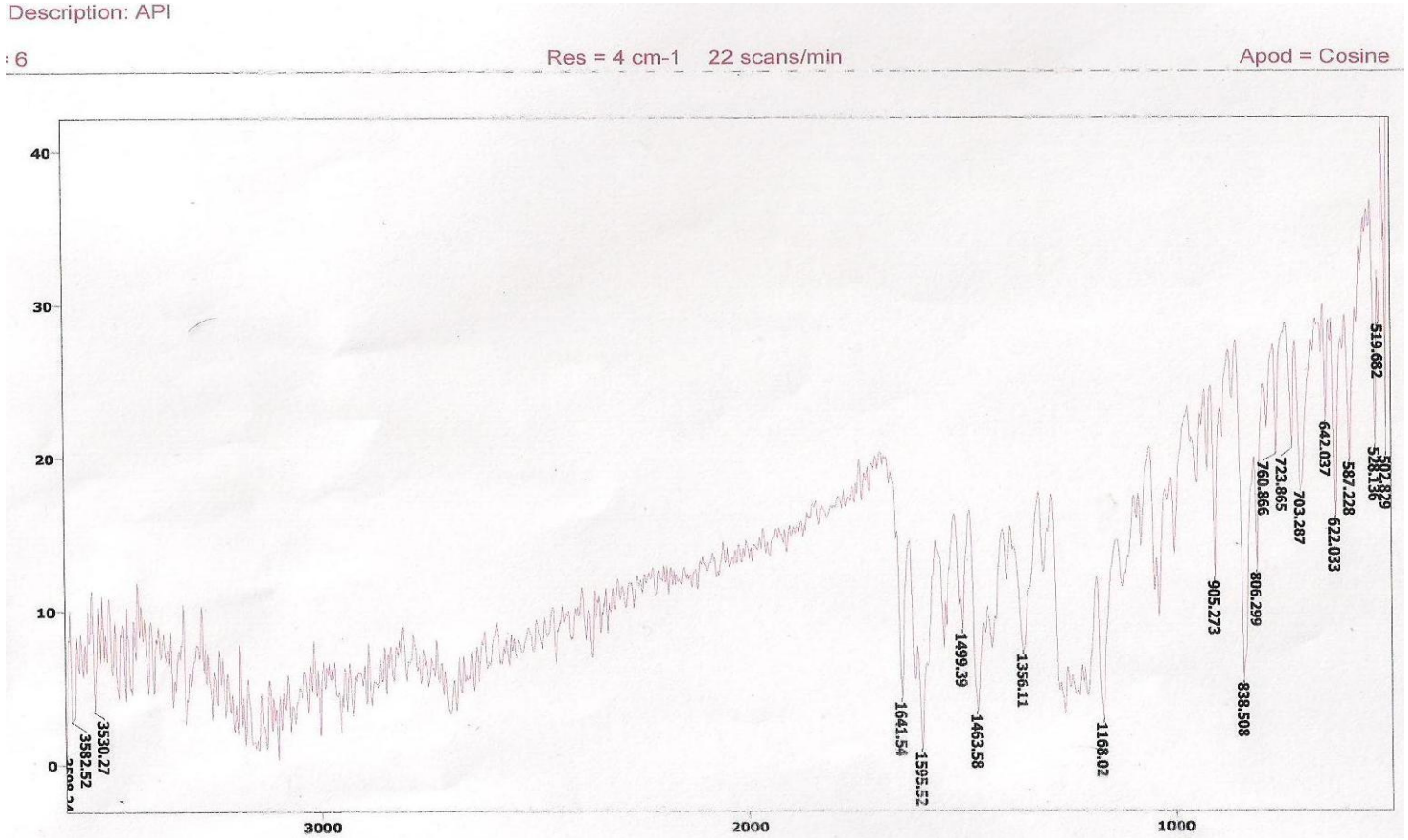

Fig. 8: FTIR spectra of RLX

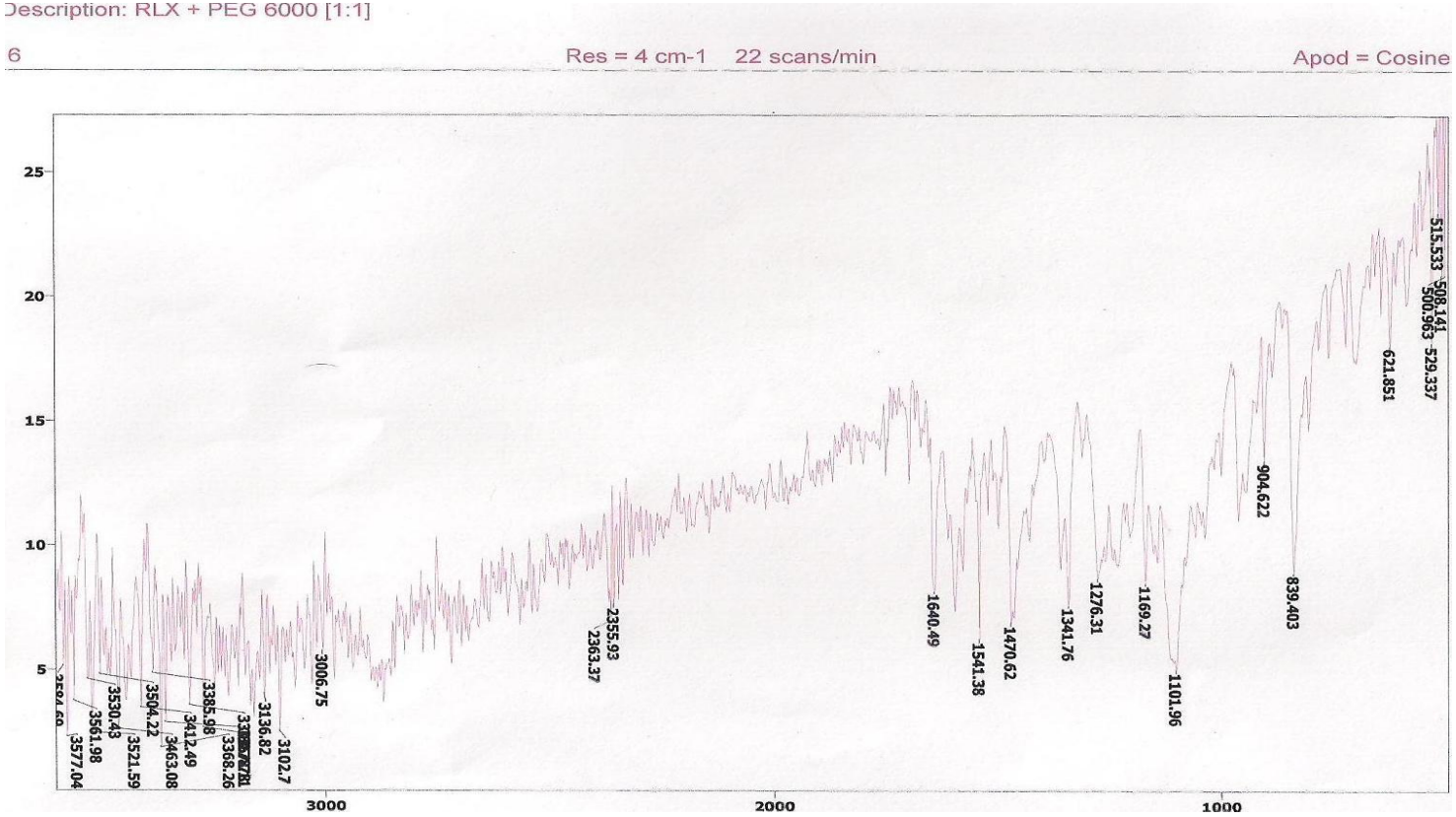

Fig. 9: FTIR spectra of RLX-PEG 6000

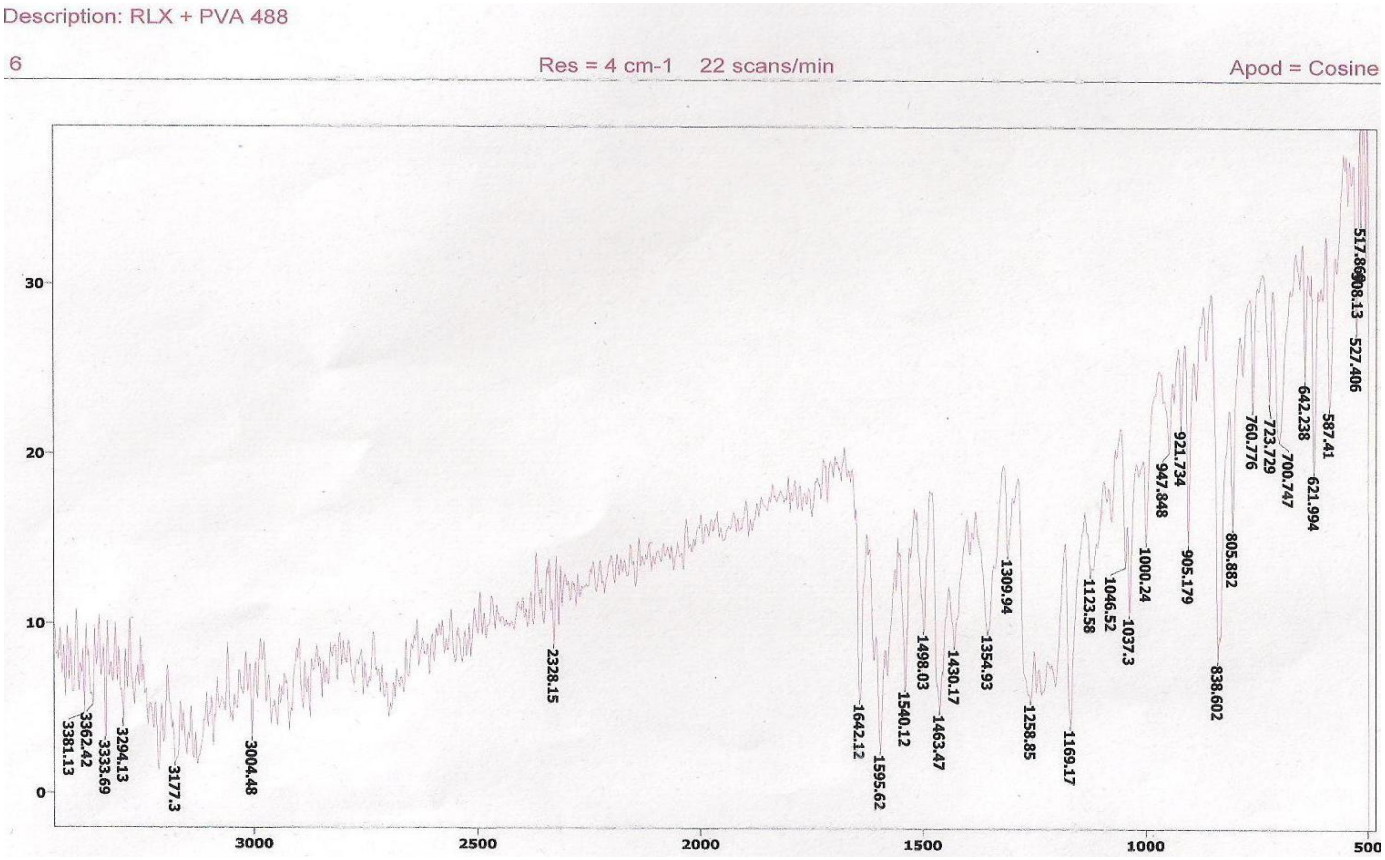

Fig. 10: FTIR spectra of RLX-PVA 4-88

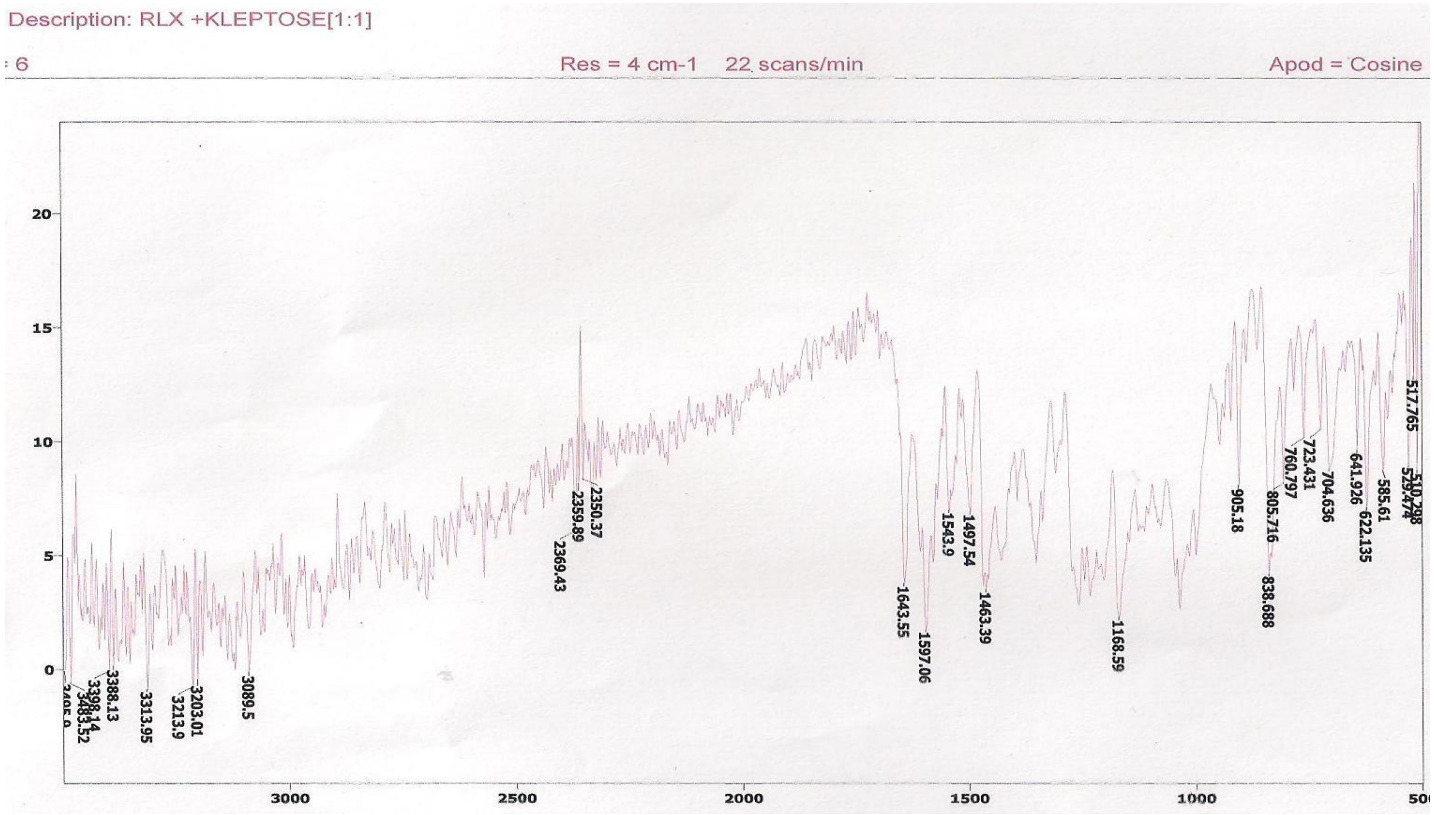

Fig. 11: FTIR spectra of RLX-ß CD

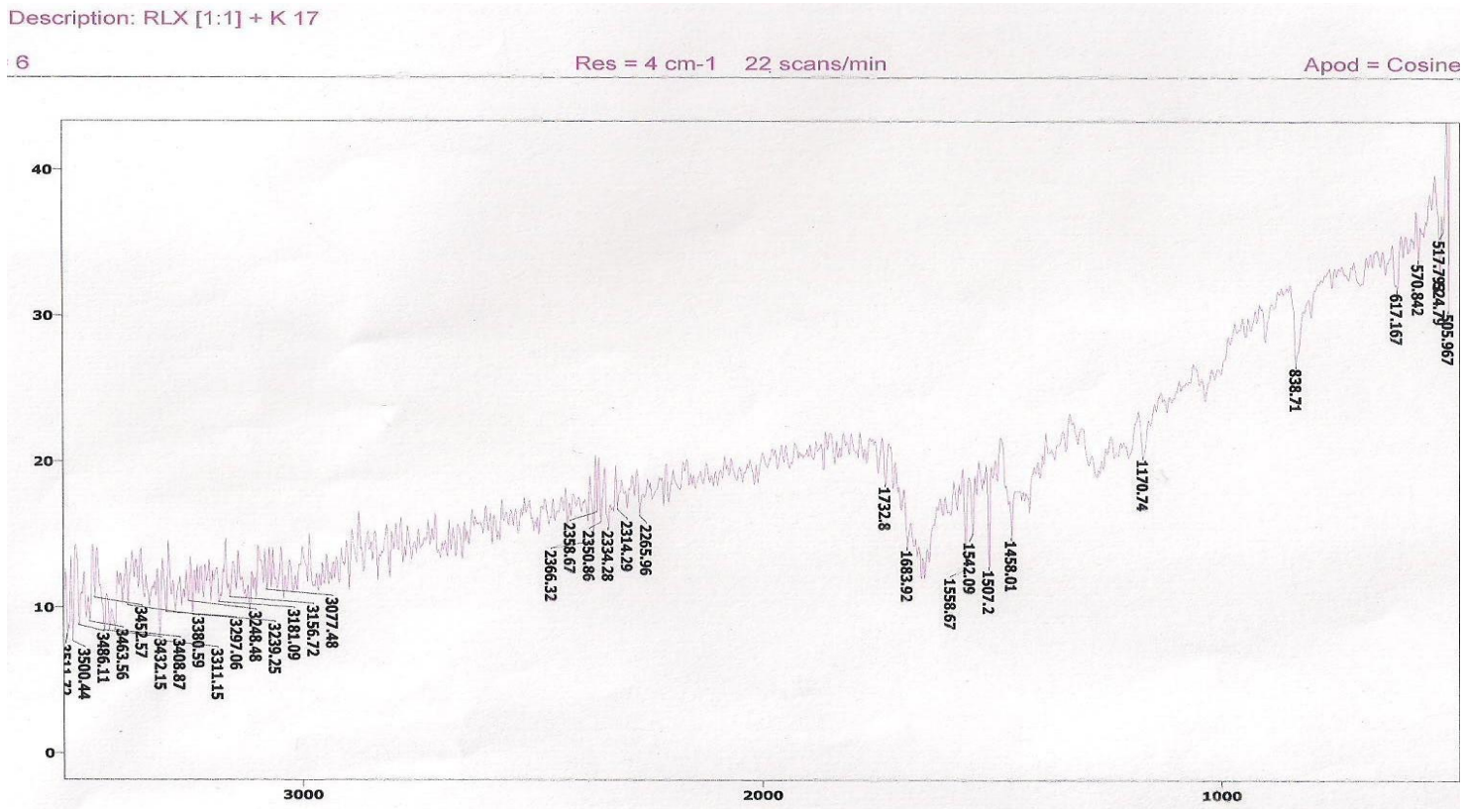

Fig. 12: FTIR spectra of RLX-K 17

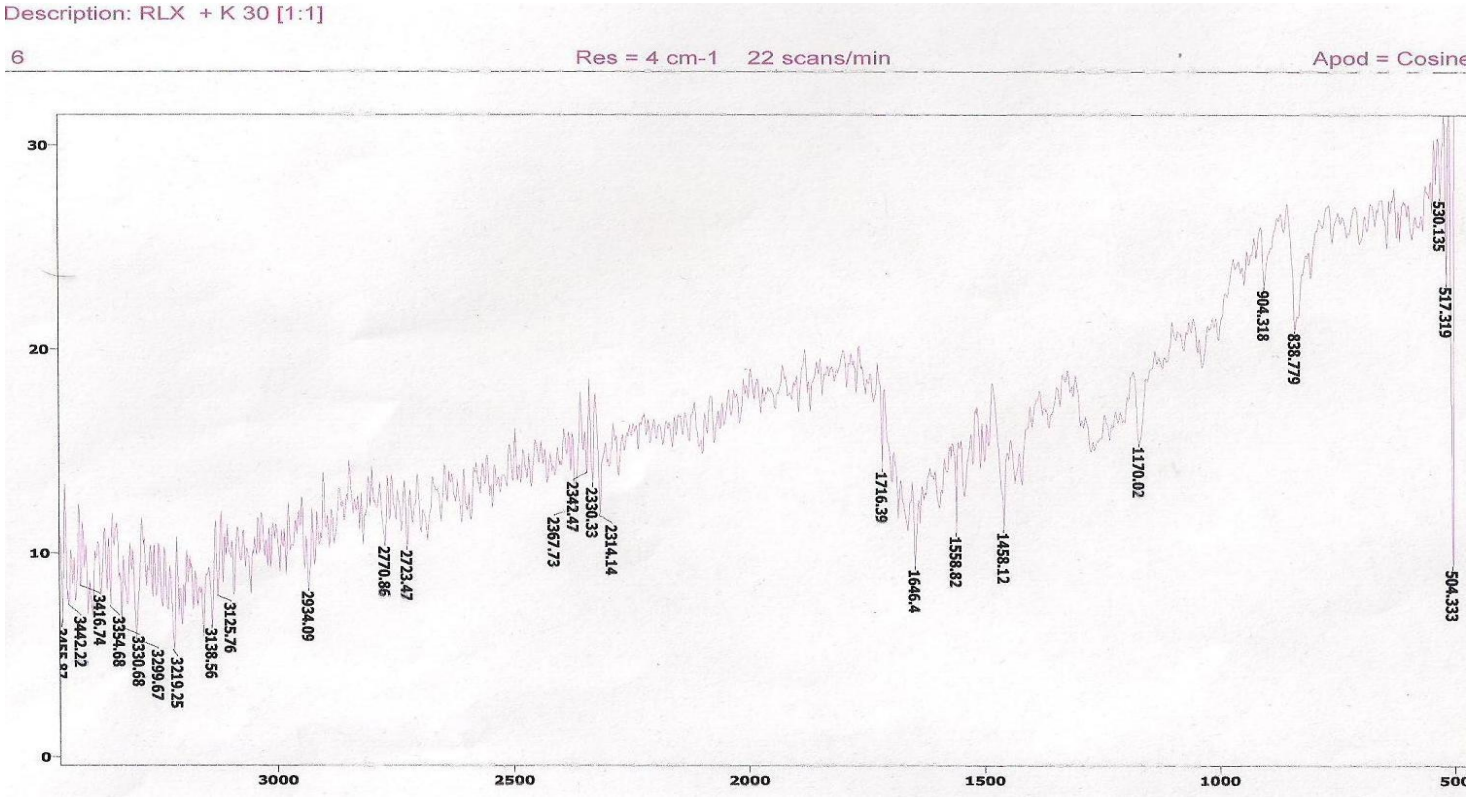

Fig. 13: FTIR spectra of RLX-K 30

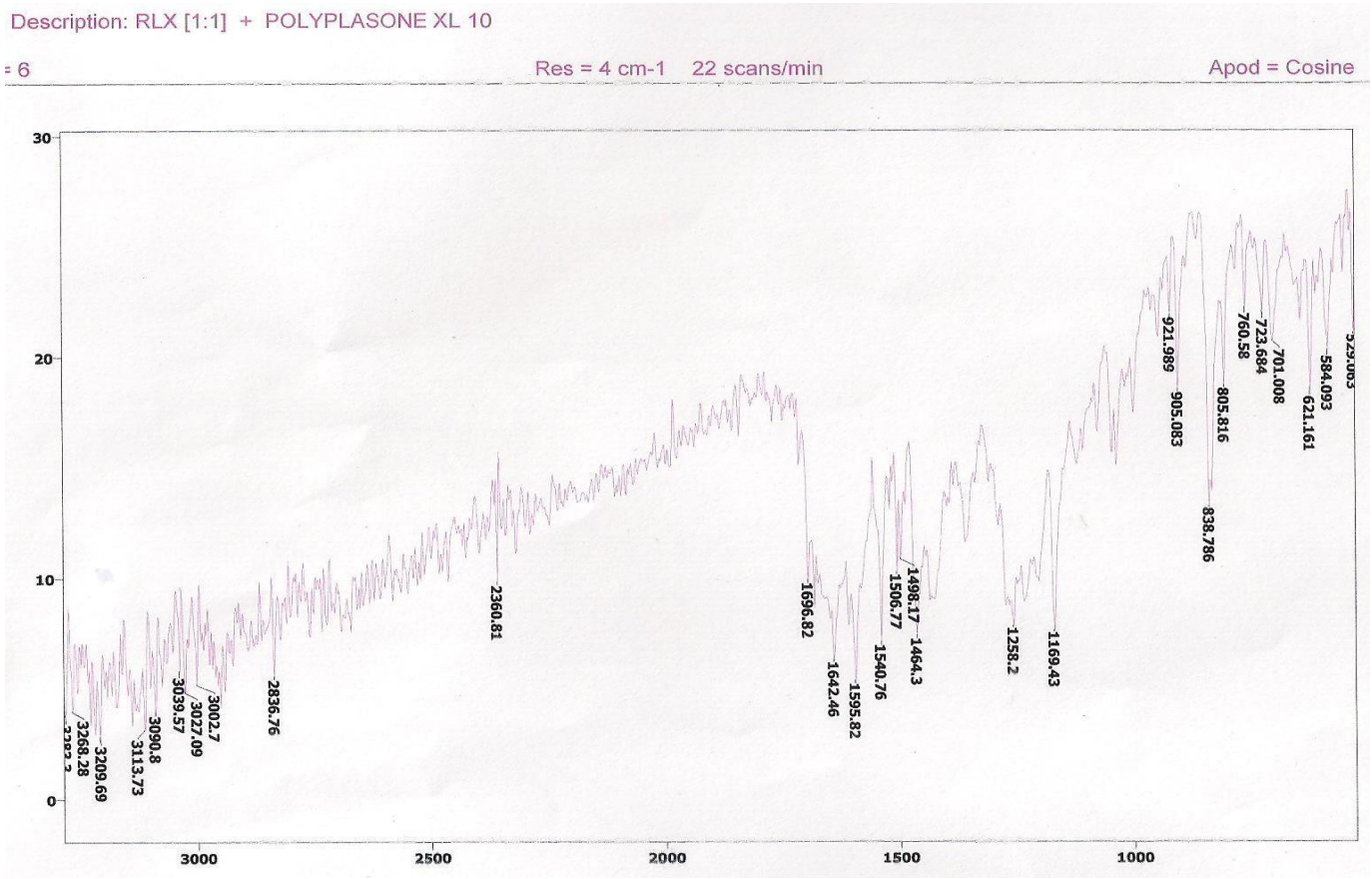

Fig. 14: FTIR spectra of RLX-POLY XL 10

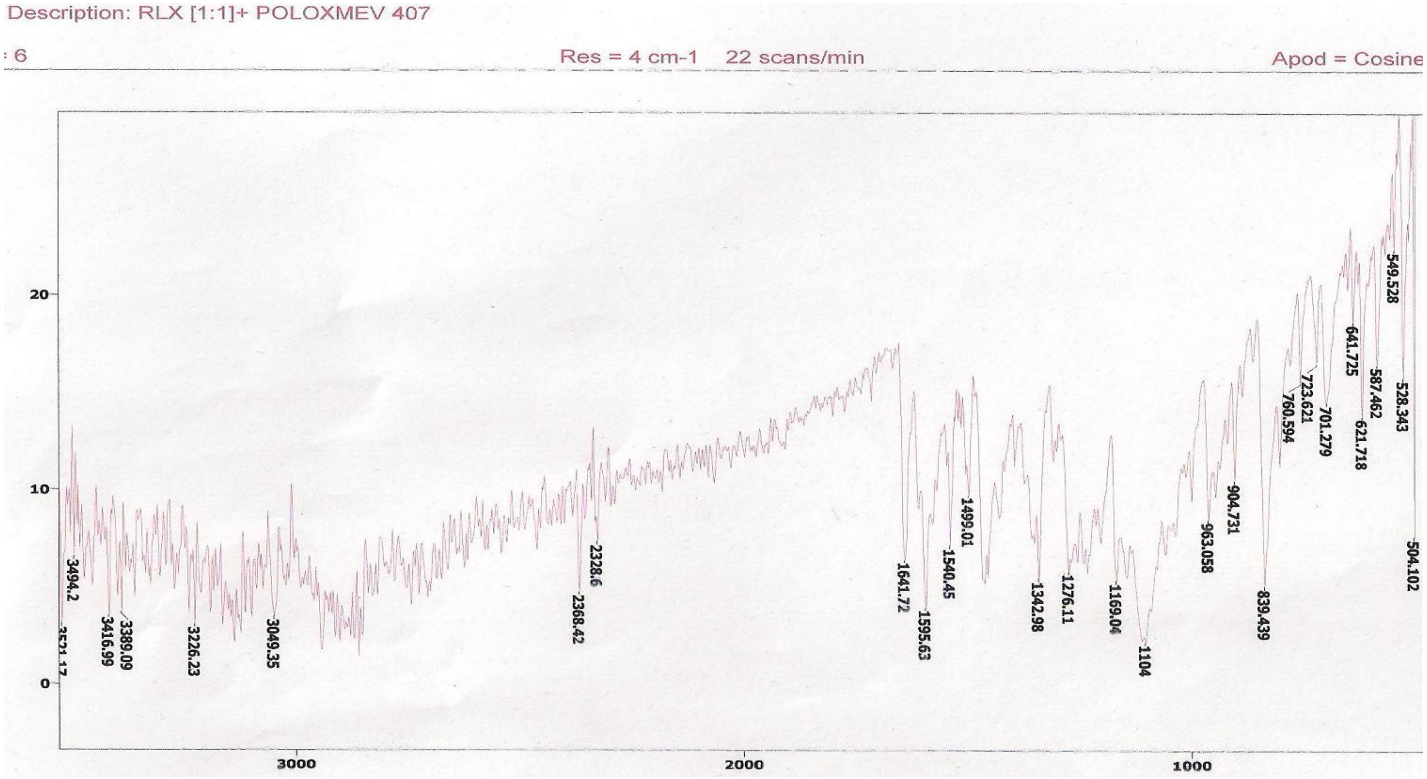

Fig. 15: FTIR spectra of RLX-POLAXOMER 407

Table 13: Composition of Various Solid Dispersions of RLX

S.NO	Composition		Ratio	Amount of Drug Soluble (mg/ml)
1	RLX + PEG- 6000	RLX_1	1 : 1	0.64
2	RLX + PVA 4-88	RLX_2	1 : 1	0.90
3	RLX + ß-cyclodextrin	RLX_3	1 : 1	2.18
4	RLX + PVP K 17	RLX_4	1 : 1	1.97
5	RLX + PVP K 30	RLX_5	1 : 1	1.48
6	RLX + Polyplasone XL 10	RLX_6	1 : 1	1.19
7	RLX + Polaxomer 407	RLX_7	1 : 1	1.07
8	RLX + HPC L.S	RLX_8	1 : 1	0.41
9	RLX + HPMC K4 MCR	RLX_9	1 : 1	0.46
10	RLX + Pharmatose 200 M	RLX_{10}	1 : 1	0.48
11	RLX + Supertab 11SD	RLX_{11}	1 : 1	0.48
12	RLX + Supertab 21AN	RLX_{12}	1 : 1	0.49
13	RLX + Mannitol	RLX_{13}	1 : 1	0.47

Table 14: Drug Release Profile of RLX Solid Dispersions

Time (min)	Cumulative % drug release							
	RLX	**RLX_1**	**RLX_2**	**RLX_3**	**RLX_4**	**RLX_5**	**RLX_6**	**RLX_7**
10	2±1.8	8±4.1	18±1.5	5±2.2	9±2.8	6±2.1	6±2.4	20±4.1
20	7±2.1	20±1.7	76±0.9	16±1.6	25±1.7	20±2.2	28±1.8	52±4.1
30	12±1.7	22±1.8	87±0.8	29±1.7	41±2.6	25±2.4	41±2.1.	54±4.1
45	19±0.6	29±2.1	95±4.1	70±1.6	43±1.4	32±1.3	53±2.5	62±4.1
Infinity	32±1.9	40±1.1	96±1.7	100±2.4	65±0.8	36±2.1	55±1.6	78±4.1

All values are expressed as mean ± SD, n=3

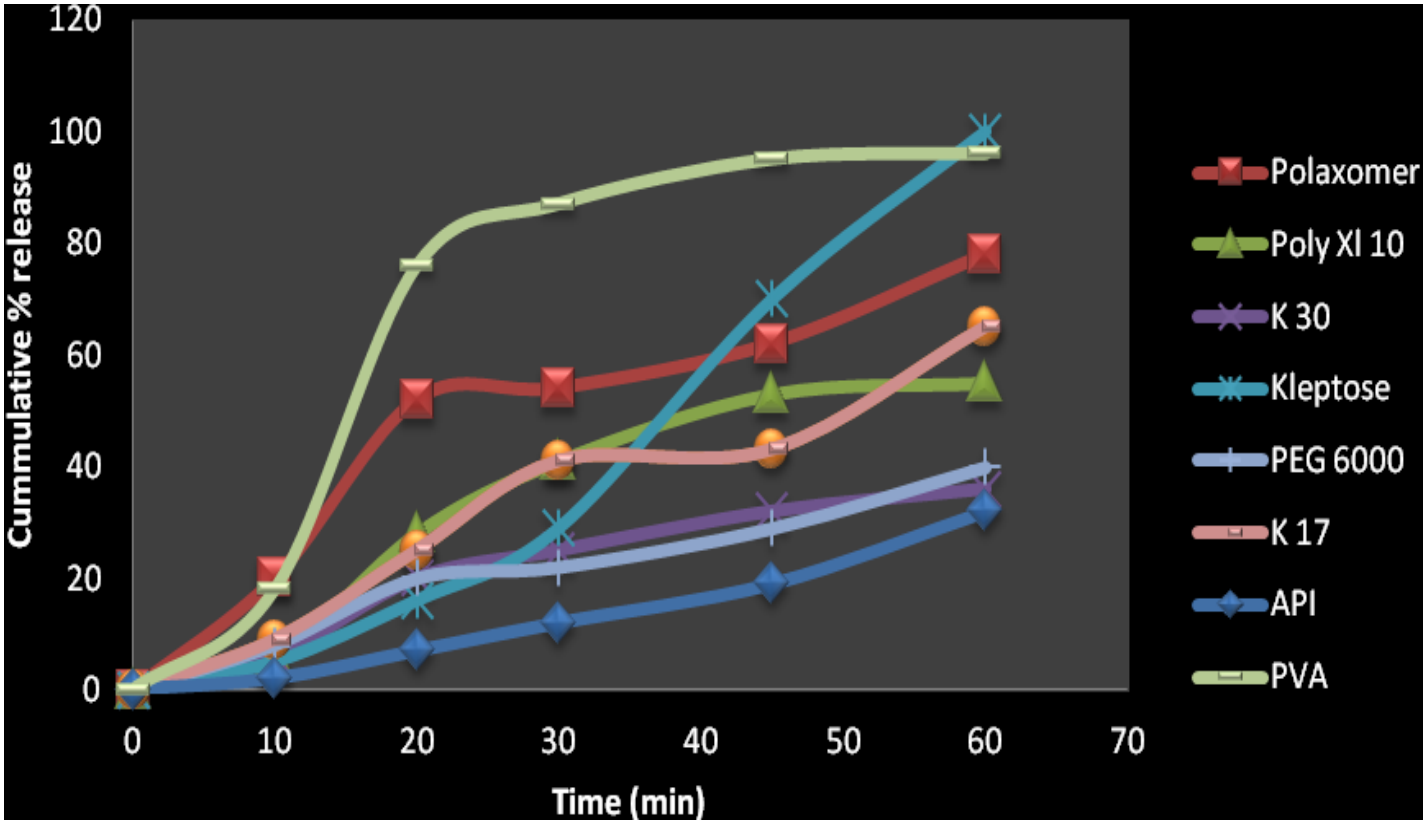

Fig. 16: Dissolution Profiles of RLX Tablet Formulations Using Solid Dispersions

Table.15: Evaluation of RLX Tablet Formulations

Tablet	Weight uniformity (mg/tablet)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	D.T (min)	Drug content (%)
RLX_1	241±0.62	4.2±0.21	6.0±0.46	0.21	5-6	101.1
RLX_2	240±0.92	4.2±0.16	5.0±0.39	0.23	2-3	99.4
RLX_3	241±0.61	4.2±0.11	9.0±0.53	0.46	2-3	98.6
RLX_4	240±0.51	4.6±0.12	6.0±0.85	0.15	3-4	102.3
RLX_5	240±0.71	3.0±0.12	5.0±0.86	0.20	8-9	101.4
RLX_6	240±0.62	4.4±0.11	10.0±0.24	0.79	1-2	102.1
RLX_7	238±0.91	4.5±0.12	3.0±0.43	0.17	9-10	103.4

All values are expressed as mean ± SD, n=10

Table 16: Drug Release Profiles of RLX Tablet Formulations Prepared by Solid dispersion technique.

Time (min)	Cumulative % drug release						
	RLX_1	**RLX_2**	**RLX_3**	**RLX_4**	**RLX_5**	**RLX_6**	**RLX_7**
10	3±2.2	10±1.7	14±0.5	5±0.3	9±1.5	12±2.3	12±1.6
20	18±2.4	25±0.5	35±0.9	27±1.6	17±2.5	25±1.6	44±1.8
30	23±2.6	34±1.6	63±2.3	36±0.6	28±2.0	32±1.5	64±0.7
45	35±0.6	46±1.1	74±1.2	47±1.8	40±2.5	46±1.5	89±0.7

All values are expressed as mean ± SD, n=3

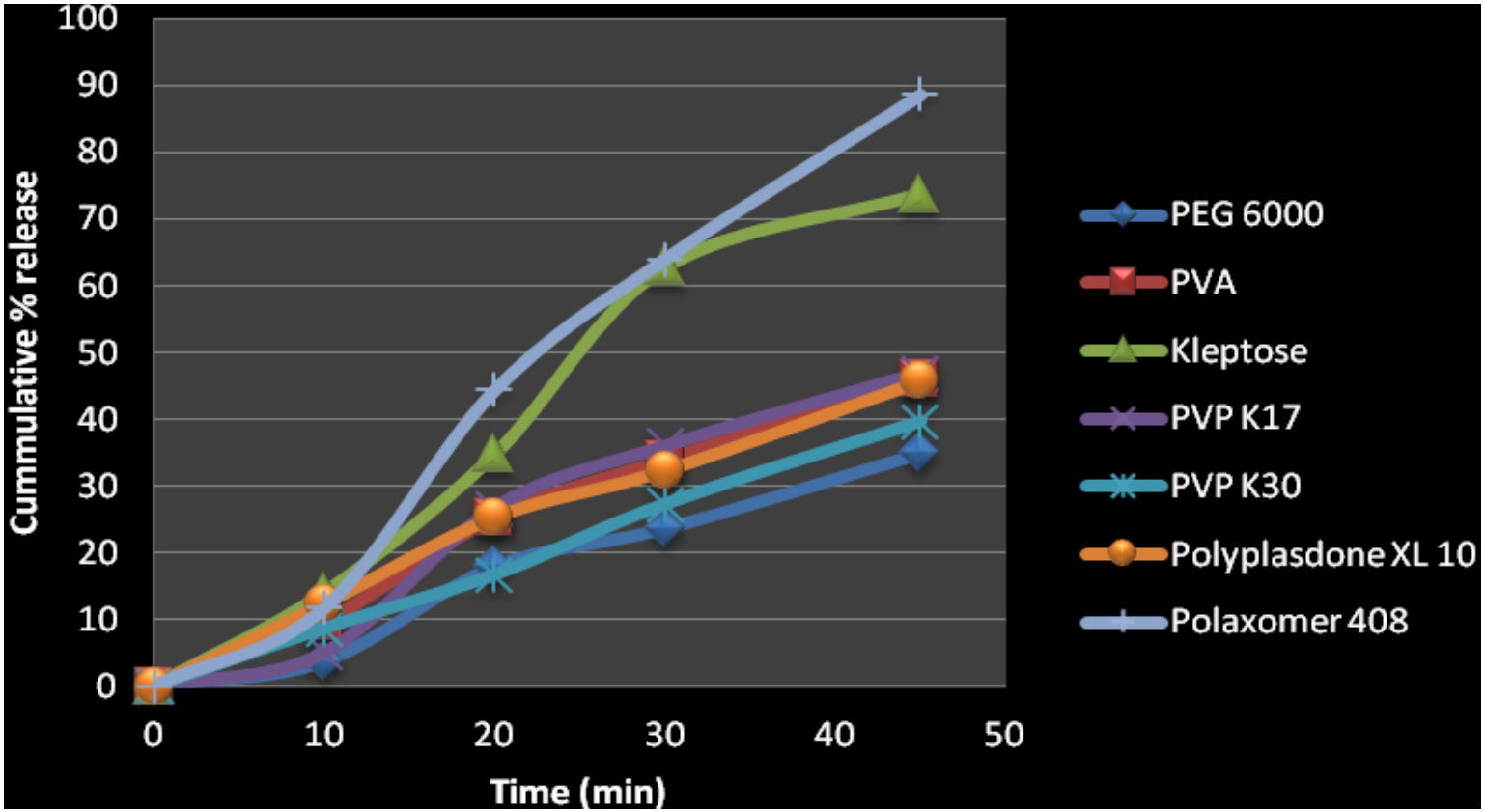

Fig. 17: Dissolution Profiles of RLX Tablet Formulations Using Solid Dispersions

Solubility studies were performed in wide range of pH, it is observed that RLX shows very poor solubility.

Preformulation studies were carried with 1:1 ratios of RLX and carriers for 1 month and evaluated for physical appearance showed no change in colour and assay values are satisfactory. FTIR of RLX showed its characteristic peaks at 3530 due to phenol -OH group, 1641 due to C=O stretching, 1595 due to C=C stretching, , 806 due to thiophene C-H, and 1158 due to C-O stretching. FTIR spectras of RLX and carriers showed that there was no significant change in the absorption spectrum. This indicates that there was no drug and carriers incompatibility.

Saturated solubility studies of solid dispersions in the purified water were performed which showed ß-cyclodextrin and polaxomer has maximum solubility, of all the carriers used seven were found to be satisfactory.

ß-cyclodextrin being hydrophilic in nature it undergoes complexation with hydrophobic drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The forces driving complexation were attributed to (i) the exclusion of high energy water from the cavity, (ii) Vander walls interactions, and (iii) hydrogen and hydrophobic bindings.

Polaxomer being a surfactant, when dispersion comes in contact with water, the polymer particles might have hydrated rapidly into the polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium.

Flow properties: All the solid dispersions prepared were evaluated for angle of repose, Carr's index, avg. particle size and drug content. It was found that all the dispersions exhibited excellent flow properties and fair compressibility index. The average particle size was in the range of 72±5 - 102±4 microns. The drug content for all dispersions were in the range of 93 – 105 %. Thus all the solid dispersions are suitable for compression as immediate release tablets.

Dissolution studies were performed for all the solid dispersions by using USP apparatus II (paddle). The drug from various dispersions were released at a faster rate compared to pure drug . The drug release from solid dispersions were in the order of PVA >Polaxomer> XL10 >PVP K17> ß-cyclodextrin> PVP K30 >PEG 6000.

Tablets: Solid dispersions were compressed into tablets and were evaluated for hardness, friability, disintegration time and assay. All the batches were found to be in specified limits.

Dissolution studies were performed for all the tablet formulations. The drug release of tablet formulations in the presence of various carriers were in the order of Polaxomer > ß-cyclodextrin > PVP K17 > PVA > Polyplasdone XL10 > PVP K30 > PEG 6000.

SUMMARY

AND

CONCLUSION

The objective of this study was to prepare Raloxifene hydrochloride solid dispersions with an aim to improve the solubility and dissolution rate by using different carriers. Raloxifene hydrochloride is a selective estrogen receptor modulator used as anti osteoporotic agent in post menopausal. It is available as pale yellow crystalline and is practically not soluble in water. Based on the biopharmaceutical properties RLX was selected as a drug candidate for improving its solubility and dissolution rate. Solid Dispersions were prepared using various carriers by solvent evaporation method. They were evaluated for flow properties and drug release studies.

Preformulation studies were performed on RLX and carriers used in the formulations and they found to be compatible. Characterization was done by FTIR study and interpreted that they were compatible without interactions. Solid dispersions prepared by solvent evaporation method using different carriers at 1:1 ratio and they showed enhanced solubility as compared to API. Carriers, ß-cyclodextrin, polaxomer and polyplasdone showed enhanced dissolution rate. The flow properties such as angle of repose and carr's index were evaluated and found to be excellent flow characteristics and fair compressibility index. The direct compression process was found to be suitable for compressing solid dispersions as tablets. Evaluation of tablets was performed and they were in specified limits. Based on the dissolution profiles of solid dispersions and their tablets it is concluded that solubility of raloxifene hydrochloride is enhanced using inclusion complex (ß-cyclodextrin), hydrophilic polymer (PVA) and surfactant (polaxomer).

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