1.1. INTRODUCTION

An increased demand for more patient friendly dosage forms has been observed since from past few years. The oral route of drug administration is the most 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 (Singh, 2011) (Sugwara, 2005). Although 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 results in poor bioavailability is most common among the problems that can be encountered when delivering an active agent via oral route (Streubel, 2006) (Desai, 2006). Drug absorption from the gastro intestinal tract can be limited by various factors with the most common one being poor aqueous solubility and poor permeability of a drug molecule. When delivering an active ingredient orally, it must first dissolve in gastrointestinal fluids before it can then permeate the membranes of the gastro intestinal tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption (Direndra, 2009). Solubility behaviour of a drug plays a key role for its oral bioavailability. For some drugs solubility presents a challenge to the development of a suitable formulation for oral administration.

Consideration of modified Noyes-Whitney equation (Noyes and Whitney, 1897) (Nernst, 1904) provides some hints as how the dissolution rate of poorly soluble drugs might be improved to minimize the limitations to oral bioavailability. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of solid compound (Fincher, 1968) and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness to ensure sink conditions for dissolution and last to improve the apparent solubility of the drug under physiologically relavant conditions. Particle size reduction is
usually achieved by conventional trituration and grinding, ball milling, fluid energy micronization, controlled precipitation by change of solvents or temperature, application of ultra-sonic waves (Scheikh, 1966) (Hem, 1967) (Skauen, 1967) and spray drying, (Kornblum. and Hirschorn, 1970) administration of liquid solutions from which upon dissolution with gastric fluids, the dissolved drug may precipitate in very fine particles (Levy, 1963) and administration of water soluble salts of poorly soluble drugs from which the parent neutral forms may precipitate in ultrafine form in gastrointestinal fluids. The reduction of particle size can result in fine particles but may not produce expected faster dissolution and absorption. This results from the possible aggregation and agglomeration of fine particles due to their increased surface energy and the subsequent stronger vanderwaal’s attraction between non polar molecules. This lead to precipitate and precipitate effect is believed to be responsible for slower in vitro dissolution rates. Other methods such as salt formation, complex formation with cyclodextrins, and solubilisation of drugs in solvents have been utilized to improve the dissolution properties of poorly soluble drugs however there are some limitations with each of this techniques. The demand for developing new technologies has been increasing annually. As the development cost of a new drug molecule is high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and the production of more cost effective dosage forms. An unique approach of solid dispersion is to reduce the particle size and increase rate of dissolution and absorption (Sekiguchi and Obi, 1961). Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly soluble drugs. (Kanig, 1964) (Chiou and Riegelman, 1970).

Most 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 \textit{in vivo} will be concurrently accelerated with an increase in the rate of drug dissolution. In the biopharmaceutical classification system drugs with low aqueous solubility and high membrane permeability are categorized as class II drugs (Amidon, 1995). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs. Screening methods for identifying potential drug candidates identified a number of poorly soluble drugs as potential therapeutic agents. It has been estimated that 40\% of new chemical entities currently being discovered are poorly water soluble (Lipinski, 2001). Many of the potential drugs are abandoned in the early stages of development due to solubility problems. Therefore it is more important that methods for overcoming solubility limitations should be identified and applied commercially such that potential therapeutic benefits of these agents can be realized.

Solid dispersion technology is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting solvent method. Solid products consists of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix may be crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. (Chiou and Riegelman, 1971) Solid dispersions reduce the particle size 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 poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and improved bioavailability. (Leuner and Dressman, 2001) (Kang, 2004) Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of the drug and increase the drug dissolution by direct dissolution or cosolvents. (Pouton, 2006) Solid dispersions produce larger and more porous micro particles and
therefore results in a higher dissolution rate. (Ghaderi, 1999). In solid dispersions poorly water soluble crystalline drugs are presented as amorphous state having higher solubility (Pokharkar, 2006) Solid dispersion systems can also be used for sustained release of drugs. (Vasconelos and Sarmento, 2007) Solid dispersion systems can also be used for enhanced release of drug from ointment and suppository bases. Solid dispersion systems can be used for increasing the solubility and stability of drugs. The equipments used for preparation are available at small and large scale and methods of preparation are easy. Some of the limitations are they are hygroscopic in nature and may absorb moisture that may result in crystal growth. (Ghaderi, 1999) (Taylor and Zografi, 1997) (Arunachalam, 2010).

Solid dispersions are of six types based on the molecular arrangement.

1. Simple eutectic mixtures

2. Amorphous precipitation in crystalline matrix

3. Solid solutions
   
   Continuous solid solutions

   Discontinuous solid solutions

   Substitutional solid solutions

   Interstitial solid solutions

4. Glass suspension

5. Glass solution

6. Complex formation between the drug and carrier
**Simple Eutectic Mixtures:**

A eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its crystalline components. These components are assumed to crystallize simultaneously in very small particle sizes. The increase in specific surface area is responsible for increased rate of dissolution. (Goldberg, 1966).

![Phase Diagram for a Eutectic System](image)

**Fig 1.1: Phase Diagram for a Eutectic System**

**Amorphous Precipitation:**

Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces greater dissolution rate. (Sekikana, 1979) (Breitenbach, 2002).
Fig 1.2: Diagrammatic Representation of Amorphous Precipitation

**Solid Solutions:**

Solid solutions are solid solute dissolved in a solid solvent. Particle size is reduced in solid solution to a molecular level i.e., the dissolution of the drug occurs in the solid state matrix. Hence this system yields much higher rates of dissolution than simple eutectic mixtures. (Chiou and Riegelman, 1971) (Goldberg, 1965).

Based on the miscibility solid solutions are of two types

**Continuous Solid Solutions:**

Components in continuous solid solutions are miscible in all proportions. Bonding strength between the components is stronger than the strength between the molecules of each of the individual components.

**Discontinuous Solid Solutions:**

In these systems the solubility of each of the component in the other component is limited. In this one of the solid components is completely dissolved in the other solid component.
Fig 1.3: Phase Diagram for Discontinuous Solid Solution

According to the way in which solvate molecules are distributed in the solvendum they are two types.

**Substitutional Crystalline Solutions:**

In this type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystalline lattice. Substitution is only possible when the size of the solute molecule differs by less than 15% or so from that of the solvent molecules. (Humerotherly and Paynor, 1954) (Rastogi and Ramavarma, 1956) (Wilcox, 1964).

Fig 1.4: Diagrammatic Representation of Substitutional Crystalline Solid Solution
**Interstitial Crystalline Solid Solutions:**

In this type of solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In these solid solutions, the solute molecules should have a molecular diameter that is not greater than 0.59 of the solvent molecule molecular diameter. The volume of the solute molecules should be less than 20% of the solvent. (Reedhill, 1964).

![Diagrammatic Representation of Interstitial crystalline Solid Solution](image)

Fig 1.5: Diagrammatic Representation of Interstitial crystalline Solid Solution

**Glass Suspension:**

In glass suspension particle size of the dispersed phase is dependent on cooling / evaporation rate. Glass suspension is obtained after crystallization of drug in amorphous matrix. (Simonelli, 1969).

**Glass Solution:**

A glass solution is a homogenous system in which a glassy or a vitreous form of the carrier solubilises drug molecules in its matrix. It is a homogenous glassy system in which a solute dissolves in a glassy solvent. Poly vinyl pyrrolidone dissolved in organic solvent under
goes a transition to a glassy state upon evaporation of solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. (Sarkari, 2002).

**Compound or Complex Formation:**

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of a drug from a complex depends on the solubility, dissociation constant and intrinsic absorption rate of the complex. (Geneidi, 1978).

**Solid Dispersions can be prepared by various methods:**

**Physical Mixing:**

Physical mixtures are prepared by weighing the calculated amount of drug and carrier and then mixing in a glass mortar by trituration. The resultant physical mixtures are passed through sieve No. 100 and stored in a desiccator until used for further studies. (Jafar, 2010).

**Co-grinding (Kneading) Method:**

In this method calculated amount of drug and carrier are weighed and mixed together with few ml of water. The damp mass obtained was passed through a sieve and the resultant powdered mass was dried at 60°C under vacuum, until a constant weight is obtained. The powdered mass was stored in a desiccator until used for further studies.

**Solvent Method:**

In the solvent method of preparation, the carrier and the active ingredient are dissolved in a suitable organic solvent and the solvent is evaporated at elevated temperature under vacuum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The co-precipitate is then dried.
under vacuum to remove any solvent freely adhering to the particle surface. (Cilurzo, 2002) (Wamian, 2002).

**Fusion Method (Melting Method):**

In fusion method, the carrier is heated to a temperature above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogenously disperse the drug through the matrix. An important limitation of fusion method is the exposure of drugs to elevated temperatures, particularly if the carrier is high melting solid and the drug is heat sensitive. (Froemming, 1978).

**Fusion-Solvent Method:**

In this method carrier is melted and drug is incorporated in the form of solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties and if the liquid is innocuous, the need for solvent removal is eliminated. This method is particularly useful for drugs having high melting point or that are thermolabile (Singla and Vijan, 1990) (Fernandez, 1992).

**Melt Extrusion Method:**

This method is same as fusion method except that intense mixing of the components is induced by the extruder. The drug carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, implants, ophthalmic inserts. The intermediates can then be further processed into conventional tablets. Advantages of this method are that the drug carrier mix is only subjected to an elevated temperature for about one minute which enables the drugs that are thermolabile can be processed. (Breitenbach, 2002) (Forster, 2001).
Lyophilization Technique / Freeze Drying:

It is the promising and suitable technique to incorporate drug substances in stabilizing matrices (Errikson, 2002). It is an alternative technique to solvent evaporation technique. Lyophilization technique is 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. (Perissuti, 2002).

Freeze drying involves four steps:

- Pre-treatment
- Freezing
- Primary Drying
- Secondary Drying

Pre-treatment:

Pre-treatment includes any method of treating the product prior to freezing. Methods of pre-treatment include freeze concentration, solution phase concentration, formulation to preserve product appearance, formulation to stabilize reactive products, formulation to increase the surface area and decreasing high vapour pressure solvents.

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. Larger crystals are easier to freeze-dry. To produce larger crystals, the product should be frozen slowly or can be
cycled up and down in temperature. This cycling process is called annealing. Usually, the freezing temperatures are between -50°C and -80°C.

**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.

In this phase, pressure is controlled through the application of partial vacuum. The vacuum speeds sublimation, making it useful as a deliberate drying process. Furthermore, a cold condenser chamber provides a surface for the water vapour to re-solidify on. This condenser plays no role in keeping the material frozen, rather, it prevents water vapor from reaching the vacuum pump, which could degrade the pump's performance. Condenser temperatures are typically below −50 °C (−60 °F). It is important to note that, in this range of pressure, the heat is brought mainly by conduction or radiation; the convection effect is negligible, due to low air density.

**Secondary Drying:**

The secondary drying phase aims to remove unfrozen water molecules, since the ice was removed in the primary drying phase. This part of the freeze-drying process is governed by the material’s adsorption isotherms. 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. Usually the pressure is also lowered in this stage to encourage desorption (typically in the range of microbars, or fractions of a Pascal). However, there are products that benefit from increased pressure as well.
After the freeze-drying process is complete, the vacuum is usually broken with an inert gas, such as nitrogen, before the material is sealed. At the end of the operation, the final residual water content in the product is extremely low, around 1% to 4%.

**Desired Characteristics of Freeze-Dried Products:**

They shall be sufficiently dry, sufficiently porous, sterile, free of pyrogens, free of particulates, chemically stable.

**Advantages:**

- Lyophilization has many advantages compared to other drying and preserving techniques.
- Lyophilization maintains quality of the product because they remain at a temperature that is below the freezing-point during the process of sublimation.
- Lyophilized products can usually be stored without refrigeration, which results in a significant reduction of storage and transportation costs.
- Lyophilization greatly reduces weight, and this makes the products easier to transport.
- They are porous; most freeze-dried products can be easily rehydrated. Lyophilization does not significantly reduce volume; therefore water quickly regains its place in the molecular structure of the product.

**Electrostatic Spinning Process:**

In this process drug matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro or nano scale. This process is restricted to limited amount of matrices, because only a few high molecular weight materials are fibre forming materials. (Sethia and Squillante, 2002).
**Super Critical Fluid Technique:**

Super critical fluid methods are mostly applied with carbon dioxide which is used as either a solvent for drug and matrix or as an anti-solvent (Kompella and Koushik, 2001) When super critical carbon dioxide 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 process does not require organic solvent; hence this technique is referred to as ‘solvent free’. The technique is known as rapid expansion of super critical solution (RESS). All other super critical techniques are precipitation methods. These techniques are alternative methods to remove solvents from a solution containing a drug and a polymer. First type of precipitation technique is gas anti-solvent technique (GAS) or precipitation from gas saturated solution (PCGS). The solution is brought into contact with compressed carbon dioxide. The conditions are chosen so that carbon dioxide is miscible with the solution under super critical conditions, whereas drug and matrix will precipitate upon expansion of the solution. When the volume of solution expands the solvent strength decreases. This results in precipitation of drug and matrix. This technique is applied with poly ethylene glycol as matrix. This method results in the formation of solid dispersion with a crystalline matrix. The second type of precipitation technique involves the spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or super critical anti solvent. The super critical anti-solvent rapidly penetrates into droplets in which drug and matrix becomes super saturated, crystallize and form particles. This process is precipitation with compressed anti-solvent (PCA) (Subramaniam, 1997).
Spraying on Sugar Beads using a Fluidized Bed Coating System:

In this method drug carrier solution is sprayed onto granular surface of excipient on sugar spheres to produce either granules ready for tableting or drug coated pellets for capsulation in one step. This method can be applied for both controlled and immediate release solid dispersions. (Ho Ho, 1996).

Direct Capsule Filling:

Direct filling of hard gelatin capsules with liquid melt of solid dispersion avoids grinding induced changes in the crystallinity of drug. The filling of hard gelatin capsules with molten dispersions of triamterene-poly ethylene glycol 500 using a Zanasi LZ 64 capsule filling machine. A surfactant must be mixed with carrier to avoid formation of drug rich surface layer. (Serajuddin, 1990) (Law, 1922).

1.1.1 Mechanism of Dissolution:

The dissolution of a drug from various solid dispersion systems consists of:

- In simple eutectic mixture components are crystallized simultaneously into very small particulate sizes. The increase in specific surface area therefore is mainly responsible for the increased rate of dissolution of poorly soluble drug.

- Amorphous precipitation occurs when the drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the crystallize form of the drug.

- In solid solutions particle size is reduced to a molecular level i.e. the dissolution of drug occurs in the solid state matrix. Hence the system would yield much higher rates of dissolution.
• In glass solution glassy or vitreous form of the carrier solubilises drug molecules in the matrix.

• Increased dissolution rate occurs by complex formation between drug and carrier.

• Co-precipitate interacts with water in its vicinity.

• Finely dispersed drug in the matrix is released and the solubilised drug is super saturated in the diffusion layer.

1.1.2 Polymers Used in Solid Dispersions:

Polyethylene Glycols:

Polyethylene glycols are obtained by reacting ethylene glycol with ethylene oxide. Their molecular weight ranges from 200 to 300,000. Polyethylene glycols of molecular weight between 200-600 are viscous liquids at room temperature where as those between 900 to 8,000 are white, waxy solids. As the molecular weight increases the water solubility decreases. In preparation of solid dispersions low molecular weight polymers are used. Polymers of molecular weight 200 to 20,000 are used extensively. (Ford, 1980).

Effect of Polyethylene Glycol Molecular Weight:

The dissolution rate of pure Polyethylene glycol decreases with increasing molecular weight. (Corrigan, 1979) When the polymer is combined with a drug to prepare solid dispersion one of the three dissolution characteristics are observed. The dissolution rate of the drug in the solid dispersion can be decreased with an increase in the molecular weight of Polyethylene glycol. This phenomenon is observed for tolbutamide and indomethacin. (Miralles, 1982).
In some drug Polyethylene glycol solid dispersion systems the rate of dissolution decreases with molecular weight up to certain composition of drug above which the trend becomes irregular. (Ford, 1984) The dissolution rate of the drug in solid dispersion can be increased by increasing the molecular weight of Polyethylene glycol in furosemide and papaverine solid dispersions. (Nogami, 1970) It is due to high molecular weight of polyethylene glycol which forms more viscous solutions which further reduces rate of crystallization of drug. Increasingly favour the incorporation of drug as solid solutions.

**Polyvinyl Pyrrolidone:**

Polyvinyl pyrrolidone has a mean molecular weight ranging from 10,000 to 700,000. It is soluble in various solvents including water, ethanol, chloroform and isopropyl alcohol. It melts at a very high temperature, above 275°C, where it becomes decomposed. Polyvinyl pyrrolidone is therefore not suitable for the preparation of solid dispersion by melt method. Molecular weight of polyvinyl pyrrolidone used for preparation of solid dispersions are in the range of 10,000 to 700,000.

**Effect of Polyvinyl Pyrrolidone Molecular Weight:**

An increase in the molecular weight of polyvinyl pyrrolidone will decrease the dissolution rate of most drugs. Low molecular weight polyvinyl pyrrolidone under goes short swelling time prior to dissolution resulting in an increase in dissolution rate of polymer and drug. Polyvinyl pyrrolidone is an effective carrier and retards crystallization of many drugs. It is not an effective carrier for drugs such as caffeine or nalidixic acid probably due to its inability to effectively reduce crystallization. (Sekikawa, 1978).
Polymers and Surface Active Agents Combinations:

Surfactants lower the interfacial tension between a drug and dissolution medium, thereby promoting the wetting of the drug. The addition of surfactants to the dissolution medium enhances the solubility and dissolution of drugs. (Tripathi, 1992) It is also common to add surfactant to the dissolution media to achieve consistent results during the dissolution of drugs that are poorly soluble in water. Another alternative is incorporation of surfactants in solid dispersion to form ternary system. (Sheen, 1998) Examples of surfactants used are sodium lauryl sulphate, sodium dodecyl sulphate, dodecyltrimethyl ammonium poly ethylene dodecyl ether (Brij 35) are anionic, cationic and non-ionic. The amount of crystalline drug decreased with increasing concentration of anionic or cationic surfactants except for non-ionic surfactants. (Porter, 1996).

Phospholipids:

Improved bioavailability of griseofulvin in rats was observed after oral administration of a griseofulvin suspension containing 0.5% of lecithin. The improved dissolution, release characteristics and bioavailability of griseofulvin from griseofulvin- phospholipid co-precipitates as a result of decrease in crystallinity of griseofulvin and possible aggregation of phospholipid with griseofulvin. Initial dissolution rate after 60 minutes are for all co-precipitates than obtained for pure drugs. The release of drug decreases with increase in chain length of fatty ester of the phospholipid. (Fujji, 1987).

Polyvinylalcohol (PVA), Crospovidone (PVP-CL), Polvinylpyrrolidone-polyvinylacetate copolymer (PVPPVA):

All three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone/ vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone
swells when dispersed in water. (Suzuki and Sunada, 1998) The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increase in the drug release rate.

**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 β-1, 4-glycoside bonds.

**Hydroxypropylmethylcellulose (HPMC):**

HPMC is mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% is derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10,000 to 15,000,000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane. (Harwood and Johnson, 1994).

**Hydroxypropylcellulose (HPC):**

Hydroxypropylcellulose (HPC) exhibits good solubility in a range of solvents, including water, ethanol, methanol and chloroform. The average molecular weight of the HPCs ranges from 37,000 to 1,150,000. (Yuasa, 1993) The use of Hydroxypropylcellulose as carrier in solid dispersions has been shown to lead to enormous increase in the drug release rate.

**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. CMEC also dissolve
readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. (Hasegawa.K et.al, 1985) Solid dispersions of nifedipine and spironolactone show enormous increase in the dissolution rate of the drug with CMEC as carrier. (Kai, 1996).

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 poorly soluble compound ofloxacin can be improved by more than threefold by incorporating it in an co evaporate with urea. (Okonogi, 1997).

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 is problematic and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates. (Mura., 1999).

Organic acids and their derivatives:

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin. (Chiou and Riegelman, 1969) (Goldberg, 1966).
1.1.3 Methods of Preparation of Fast Dissolving tablets (FDTs)

Various technologies used in the manufacture of fast dissolving tablets are Freeze-Drying or Lyophilization, Sublimation, Direct Compression.

Freeze-Drying or Lyophilization:

It is the promising and suitable technique to incorporate drug substances in stabilizing matrices. It is an alternative technique to solvent evaporation technique. Lyophilization technique is 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. This technique creates an amorphous porous structure that can dissolve rapidly.

Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of fast dissolving tablets because of the availability of improved excipients especially super disintegrants and sugar based excipients. In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Super Disintegrants

Super disintegrants which are effective at low concentration have greater disintegrating efficiency and they are more effective intra granularly but have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. Super disintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction; it causes tablet to burst or the accelerated absorption of water leading to an enormous increase
in the volume of granules to promote disintegration. Because of the increased demands for faster dissolution requirements, there are now available a new generation of “Super disintegrants” in addition to the disintegrants. (Debjit, 2010).

**Mechanism of Addition of Super Disintegrants:**

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:

- Internal Addition (Intra granular)
- External Addition (Extra granular)
- Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles.

**Mechanism of Tablet Disintegration with Super Disintegrants:**

The tablets are broken into small pieces and then produce a homogeneous suspension which is based on the following mechanisms:

- Capillary action/ Water wicking
- By Swelling
- Air expansion /Heat of wetting
- Due to disintegrating particle/particle repulsive forces
• Due to deformation
• Due to release of gases
• By enzymatic reaction

Types of Superdisintegrants:

1. Starch:

   Starch is the first disintegrating agent widely used in tablet manufacturing. The mechanism of action of starch is wicking and restoration of deformed starch particles on contact with aqueous fluid and in doing so release of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression. The concentration of starch used is also very crucial. If it is below the optimum concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet. (Narmada, 2009).

2. Pregelatinised Starch:

   Pregelatinised starch is produced by hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrant and its optimum concentration is 5-10%. The main mechanism of action of Pregelatinised starch is through swelling. Pregelatinised starch is a modified starch prepared from potato starch and is used in fast-disintegrating aceclofenac tablets. (Garala Kevin, 2008)

3. Crospovidone (Kollidone):

   It is white, free flowing and compressible powder. It is a synthetic homo polymer of cross-linked N-vinyl-2-pyrrolidone. It is completely insoluble in water, acids, alkalis, and all organic solvents and swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure. It is chemically inert and has a high adsorptive capacity,
forms reversible physical complexes with many molecules without the formation of covalent chemical bonds. It is used as a super disintegrant and dissolution agent in granules, hard gelatin capsules and in tablets prepared by direct compression method. It has a greatest rate of swelling compared to other disintegrants. It has been reported that the cross linked polyvinyl pyrrolidone is used in the development of fast dissolving tablets. (Jeevana Jyothi, 2010).

4. Croscarmellose Sodium (Ac-di-sol):

Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities. Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for Capsules, Tablets and Granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Concentrations of up to 5% w/w of croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. (BiY, 1999)

5. Modified Starch:

To have high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross linking, which is available in market as cross linked starch. Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling and its optimum concentration is 4-6 %. If it goes beyond its limit, then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentration because of their greater swelling capacity.
6. Microcrystalline Cellulose (Avicel 102):

Microcrystalline cellulose is partially depolymerised cellulose prepared from alpha cellulose. Microcrystalline cellulose for direct compression tabletting comes in a number of grades like pH 101 (original product) and pH 102 (more agglomerated, large particle size with better fluidity). Avicel pH 102 used as diluent cum disintegrant. The mechanism of Avicel pH 102 is interlocking. The particle size of Avicel pH 102 is small. The decrease in particle size increases binding strength and decreases disintegration time so here we used Avicel pH 102. MCC is found in the concentration of 10-25% as a filler binder disintegrant. MCC can be used as a disintegrant at a level of 5-15%. Avicel has a fast wicking rate for water, hence this and starch makes an excellent combination for effective and rapid disintegration in tablet formulation. (Sunita, 2010).

7. Alginates:

Alginates are hydrophilic colloidal substances which has high sorption capacity. Chemically, they are alginic acid and salts of alginic acid. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, it should be used in only acidic or neutral granulation. (Vora and Rana, 2008)

8. Ion-exchange resin:

Ion exchange resin (Ambrelite IPR-88) has highest water uptake capacity than other disintegrating agents like starch and Sodium CMC. It has a tendency to adsorb certain drugs.

9. Gums:

Gums have been used as disintegrants because of their tendency to swell in water. They can display good binding characteristics (1 to 10 percent of tablet weight). This property can oppose the desired property of assisting disintegration and the amount of gum must be
carefully titrated to determine the optimum level for the tablet. Common gums used as
disintegrant include agar, locust bean, karaya, pectin and tragacanth.

10. Gum Karaya:

Karaya has the natural gum exudates from the traces of Sterculia urens belonging to
family sterculiacea. Chemically the gum has an anionic polysaccharide, containing 43%. D-
galacturonic acid, 13% D-galactose and 15 percent L-rhamnose. The high viscosity nature of
gum limits its uses as binder and disintegrant in the development of conventional dosage
form. Gum karaya prepared from gum karaya by heat treatment can be used as disintegrant
(because of low viscosity). (Murali Mohan Babu, 2002).

Mechanism of Dissolution Rate of Solid Dispersions

The mechanism of dissolution rate enhancement of a lipophilic drug incorporated in a
solid dispersion is still to a large extent unclear. Publications on the fast release of drugs from
solid dispersions are ubiquitous, but some scientists correctly stated that only few of them
focus on the mechanism of release and the parameters that dominate the dissolution process.
(Duncan Craig, 2001) The influence of matrix-type is not fully understood. Moreover, the
effect of drug load on the release rate of drugs from solid dispersions is ambiguous. In some
studies a faster release of drug was observed upon lowering the drug load, while in other
studies a faster release of drug was seen at higher drug-loads.

1.1.4 Dissolution Kinetics:

Dissolution of a Pure Solid:

A description commonly used to explain the dissolution of a solid, was originally
developed by Noyes and Whitney. (Dokoumetzidis, 2008). They claimed that the dissolution
rate was proportional to the difference between bulk concentration and concentration at the
dissolving interface. Nernst and Brunner were the first to propose the diffusion layer model. (Snopal, 2011). They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk was completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface.

The dissolution rate of a solid is given by Eq. 1:

\[
\frac{dm}{dt} = A \frac{D}{\delta} (C_s - C_{\text{bulk}}) \quad \text{(Eq. 1)}
\]

in which \( \frac{dm}{dt} \) is the dissolution rate. In fact, all five parameters at the right hand side of the equation can be affected in order to accelerate the dissolution rate:

1.) 'A' represents the surface area available for dissolution. Micronization of drug particles increases the surface area and has been shown to accelerate dissolution. (Markus, 2008). Therefore, the drug in solid dispersions should be dispersed in particles as small as possible, preferably mono-molecularly.

2.) A high diffusivity of the dissolving compound, D, establishes fast transport through the stagnant layer. The diffusivity in solutions can be calculated by the Einstein-Stokes relation:

\[
D = \frac{kT}{3\pi\eta d} \quad \text{(Eq. 2)}
\]

in which '\( \eta \)' is the dynamic viscosity of the medium, i.e. the viscosity of the solvent in the boundary layer, and 'd' is the diameter of the diffusing molecule, 'k' is the Boltzmann constant and 'T' is the temperature. Therefore, for a certain drug and temperature, only viscosity of the medium can be used to change the diffusivity.

3.) The thickness of the stagnant layer for diffusion \( \delta \) should be minimized. This layer becomes thinner as the bulk surrounding the tablet is stirred more vigorously, e.g. in vitro when the rotation speed of the impeller (\( \omega \)) is increased or in-vivo when the intestinal
mobility is higher. However, according to Nelson a low dynamic viscosity ($\eta$) and a high density ($\rho$) of the dissolution medium minimizes the diffusion-layer thickness. (Kristyn and Theodore, 2011)

$$\delta = \sqrt{\frac{\eta}{\rho \omega}} \quad \text{(Eq. 3)}$$

4.) An increase in drug solubility ($C_s$) accelerates the dissolution. Solubilizers like cyclodextrins or surfactants are added to solid dispersions for this purpose. $C_s$ is also increased by reducing the size of the particles according to Kelvin’s Law. (Ashok, 2007)

$$C_{s,\text{curved}} = C_{s,\text{flat}} \cdot \exp \left[ \frac{2\gamma_{d,s} \cdot M_d \cdot RT \cdot \rho_d \cdot r}{\rho} \right] \quad \text{(Eq. 4)}$$

in which $\gamma_{d,s}$ is the interfacial tension of the drug-solution interface, $M_d$ is the molar mass of the drug, $\rho_d$ the density of the drug and $r$ the radius of curvature of the dissolving interface. Thus, equation 4 provides the second reason for reducing the drug particle size. Furthermore it is known that amorphous material has higher solubility than crystalline material. The higher solubility of amorphous drugs can be expected based on thermodynamic considerations and was confirmed with experiments. (Bruno, 2000) For example, amorphous novobiocin showed 10 times higher equilibrium solubility compared to the crystalline form.

5.) $C_{\text{bulk}}$ is the concentration in the bulk and can be lowered in-vitro by increasing the dissolution volume and in vivo by increasing the permeation rate over the intestinal membrane and inhibiting P-glycoprotein-like transporters.

**Dissolution of a Binary Solid:**

The Nernst-Brunner equation (Eq.1) is applicable for pure solids but dissolution of a binary solid is more complex. The dissolution rate of two components, intimately mixed in solid dispersions, mutually affect each other. Higuchi investigated a uniform, intimate, nondisintegrating mixture of two dissolving compounds both in crystalline state. One of the
compounds (e.g. the polymer C) dissolves faster, resulting in a porous layer consisting of the other compound (e.g. the lipophilic drug D).

Fig 1.6: Schematic Representation of Dissolution of Solid Dispersion like Binary Mixture.

Higuchi investigated the effect of this layer and the composition of mixture on the dissolution rate of fast dissolving component 'C'. In fact, the deceleration of the dissolution of C was discussed while dissolution of D was considered to remain unchanged. He considered only the steady state portion of the problem and assumed that in the porous layer the concentration of D is equal to its solubility (\( C_s, \text{Drug} = C_s, \text{Drug} \)). This implies that no super saturation of D occurs in the liquid compartment of the porous layer. It also implies a constant flux of D to the bulk, since the thickness of the stagnant boundary layer \( \delta \) will be constant.

It is unlikely that amorphous solid dispersions can be described in this way:

- Firstly because D will be supersaturated during dissolution of a solid dispersion. Without super saturation it is impossible to obtain accelerated dissolution from a non-disintegrating solid dispersion tablet.
• A second complication is that the degree of super saturation can increase in time especially when C dissolves rapidly.

• And due to this super saturation, crystallization of the lipophillic drug at the tablet surface can occur. It has been observed that crystallization can influence dissolution behaviour of solid dispersions. Both super saturation and crystallization kinetics will affect the time needed to reach steady state dissolution. (Dirk-Jan, 2005) (Patidar, 2010) (Van Drooge, 2004).

**Weibull Plot:**

A general function that is applicable to a number of common types of dissolution curve is, the Weibull equation.

\[ M = 1 - \exp\left[-\left(t - T_i\right)^b \left(1/a\right)\right] \]  \hspace{1cm} (Eq. 5)

'M' - accumulated fraction of the material in solution at time; 'a' - scale parameter that defines the time scale of the process; 'T_i' - location parameter that represents the time lag before the onset of dissolution; 'b' - Shape parameters that characterize the curves as being curved upwards (b>1).

The Weibull distribution functions can be arranged in the form of a more useful equation as follows: (Langenbucher, 1972)

\[ (1-m)\exp = \left[-\left(t - T_i\right)^b \left(1/a\right)\right] \]  \hspace{1cm} (Eq. 6)

\[ -\ln(1-m) = \left(t - T_i\right)^b \left(1/a\right) \]  \hspace{1cm} (Eq. 7)

\[ \log [-\ln(1-m)] = b \log (t-T_i) - \log a \]  \hspace{1cm} (Eq. 8)

Using the linear relationship given by above equation, the shape parameter ‘b’ and the scale parameter ‘a’ can be obtained.
The scale parameter ‘a’ is normally replaced by means of a more informative team, the dissolution time $T_d$, which is defined by:

$$T_d = a^{1/b} \quad (\text{Eq. 9})$$

Then the above Equation gives the time required to dissolve 63.2% of the drug. It can also be read from the graph directly as the time value corresponding to the ordinate value of zero.

The condition is satisfied when $m = 0.63212$, i.e.

$$\log [-\ln (1-0.63212)] = 0 \quad (\text{Eq. 10})$$

**First order kinetic model:**

The first order rate equation to explain dissolution profiles is mathematically given by:

$$\log (W_\infty - W) = \log M - K/2.303(t-t_0) \quad (\text{Eq. 11})$$

$W_\infty$ - amount of drug in the solution at infinite time; $W$ – amount of drug in the solution at time $t$; $M$- interaction constant; $T_0$ - the time before the onset of dissolution; $K$-apparent first order dissolution rate constant.

The equation is modified by using percent drug dissolved at time $t$ as $W$, and using a value of 100 for $W_\infty$. The time lag, too, for a powder formulation can be taken to be zero for all practical purposes. Thus the equation becomes,

$$\log (100\%-\text{dissolved}) = \log M - Kt/2.303 \quad (\text{Eq. 12})$$

If the dissolution profile follows first order kinetics, a straight line should result when log (100% dissolved) plotted against $t$. The rate constant $K$ is then obtained from the slope of the line.
Second order kinetics model: This is given by,

\[ \frac{W}{(W_e (W_e - W))} = K_2 t \]  \hspace{1cm} (Eq. 14)

'W'-Weight of the drug in the solution at time \( t \); 'W_e' – maximum amount of drug available for dissolution follows second order kinetics. The apparent second order dissolution rate constant 'K_2' is given by slope of the line.
1.2 AIM AND OBJECTIVES OF WORK

The aim of the work is to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble drugs lovastatin and simvastatin by formulating it as solid dispersions using various techniques with PEG-6000 as a carrier and subsequent preparation of fast dissolving tablets with the prepared solid dispersions using different concentrations of super disintegrants and comparing them with that of the marketed product.

Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach was fast dissolving tablets which have gained acceptance and popularity in the recent time. Several pharmaceutical industries prepared fast dissolving tablets by direct compression technique by selecting suitable super disintegrants. Direct compression technique offers important advantages such as increased output, reduced cost, less machinery and improved drug stability when compared to wet granulation method.

The drugs such as lovastatin, simvastatin were selected taking into consideration their physicochemical and biopharmaceutical properties.

Lovastatin is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidaemias and prevention of ischaemic heart disease. It is practically insoluble in water, sparingly soluble in alcohol and soluble in acetone. Lovastatin is absorbed from the gastrointestinal tract and is hydrolysed in the liver to its active beta hydroxy form. Peak plasma concentration occurs with in 2-4 hours. The half life of active metabolite is 1 to 2 hours. (Modi, 2007)

Simvastatin is a lipid regulating drug; it is a competitive inhibitor of HMG-CoA used to reduce LDL-cholesterol, apolipoprotein B and to increase HDL-cholesterol in the treatment of hyperlipidaemias, including hypercholesterolaemias, combined hyperlipidaemia, hypertriglyceridaemia and dysbetalipoproteinaemia. It is practically insoluble in water, freely
soluble in alcohol and soluble in dichloromethane. Simvastatin is absorbed from the gastrointestinal tract and is hydrolysed to its beta hydroxy form. The half-life of the active beta hydroxyacid metabolite is 1.9 hours. (Pinnamaneni, 2002)

Based on their physicochemical and biopharmaceutical properties, lovastatin and simvastatin were selected as drug candidates for developing solid dispersions formulations for improving its solubility and bioavailability by improving the dissolution rate.

The present research work has been carried out with an aim to increase the solubility and dissolution rate of lovastatin and simvastatin by solid dispersion techniques and further optimized solid dispersions were formulated as fast dissolving tablets with super disintegrants to improve the wettability and dispersion time as well as to reduce disintegration time and finally to improve the drug release characteristics for enhancing the bioavailability.

The major objectives of investigation are as follows:

- To perform saturated solubility studies of lovastatin and simvastatin to optimize the dissolution medium.
- To prepare solid dispersions of poorly soluble drugs, lovastatin and simvastatin using PEG-6000 as a carrier by physical mixing, fusion, solvent evaporation and lyophilization methods.
- To evaluate the flow properties of prepared solid dispersions by angle of repose, carr’s index, and to determine the particle size.
- To evaluate the drug release from the solid dispersions by in vitro dissolution studies.
- To evaluate the kinetics and mechanisms of drug release from the solid dispersions tablets by in vitro dissolution studies.
• To prepare the fast dissolving tablets from the optimized solid dispersions by using super disintegrants like sodium starch glycolate, croscarmellose sodium, pregelatinised starch and crospovidone by employing direct compression technique.

• To evaluate the physical parameters of the tablet such as weight uniformity, hardness, friability, wetting time, dispersion time and drug content.

• To evaluate the kinetics and mechanisms of drug release from the fast dissolving tablets by *in vitro* dissolution studies.

• To evaluate the surface characteristics of some selected solid dispersions by scanning electron microscopy analysis.

• To check the drug-polymer interaction and crystal morphology of optimized solid dispersions by differential scanning calorimetry and X-ray diffraction studies.

• To evaluate pharmacokinetics of lovastatin and simvastatin from selected fast dissolving tablets.

• To conduct the accelerated stability studies for the selected fast dissolving tablets.
1.3 DRUGS USED IN PRESENT STUDY

LOVASTATIN

Drug Name: Lovastatin

Chemical Formula: C_{24}H_{36}O_{5}

Molecular Weight: 404.55

Chemical Structure:

![Chemical Structure Image]

Chemical Name:

Lovastatin is \([1S-\{1\alpha(R^*)\},3\alpha,7\beta,8\beta(2S^*,4S^*), 8a\beta}\]-1,2,3,7, 8,8a-hexahydro-3,7-dimethyl-8-[2(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.

(Maryadele, 2006)

Description:

It is white to off-white crystalline powder. Insoluble in water, sparingly soluble in alcohol, practically insoluble in petroleum spirit, freely soluble in chloroform, soluble in acetone, in
acetonitrile, and in methyl alcohol. Store under nitrogen in air tight containers at a temperature not exceeding 8°C.

**BCS Classification:** Class II

**Pharmacokinetics:**

**Absorption & Distribution:**

It is absorbed from the gastrointestinal tract and is hydrolysed in the liver to its active beta-hydroxyacid form. (Desager, 1996)

**Metabolism:**

It undergoes extensive first pass metabolism in the liver, its primary site of action, and less than 5% of the oral dose has been reported to reach the circulation. Lovastatin is metabolised by cytochrome P450 isoenzyme CYP3A4. The major active metabolites present in human plasma are the beta-hydroxyacid of Lovastatin, its 6-hydroxy derivative and two additional metabolites. Peak plasma concentration occurs within 2-4hrs and steady state concentrations are achieved after 2 to 3 days with daily administration. Both Lovastatin and its beta-hydroxyacid metabolite are more than 95% bound to plasma proteins. (Lennernas, 1997)

**Excretion:**

It is mainly excreted in the bile: about 85% of a dose has been recovered from the faeces and about 10% from the urine. The half-life of the active metabolite is 1 to 2 hours. (Wiggam, 1997)
**Action:**

The primary action is to increase the expression of low density lipoprotein receptors in the liver, which occurs in response to inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol synthesis. This leads to increased clearance of low density lipoproteins-cholesterol from the plasma, with a subsequent reduction in both low density lipoproteins and cholesterol. (Maron, 2000)

**Uses:**

Lovastatin, a HMG-CoA reductase inhibitor is used to reduce cholesterol in the treatment of hyperlipidaemias, particularly in type IIa and IIb hyperlipoproteinaemias. It is also given prophylactically for both primary and secondary prevention of ischaemic heart disease. (Curran, 2003)

**Administration:**

Lovastatin is given in an initial dose of 10 to 20 mg daily in the evening with food, increased if necessary, at intervals of 4 weeks or more to 80 mg daily in single or divided doses. (Pai, 2000)
SIMVASTATIN

Drug Name: Simvastatin

Chemical Formula: $C_{25}H_{38}O_5$

Molecular Weight: 418.57

Chemical Structure:

![Chemical Structure Image]

Chemical Name:

$[1s-[1\alpha, 3\alpha, 7\beta, 8\beta (2s*, 4s*), 8\alpha\beta]]-1, 2, 3, 7, 8, 8a$-Hexahydro-3, 7-dimethyl-8-[2-(Tetrahydro-4-hydroxy-6-oxo2H-pyran-2-yl)-i-naphthalenyl2,2-dimethylbutanoate.

Description:

It is white or almost white crystalline powder. Practically insoluble in water, freely soluble in alcohol, chloroform and methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store under nitrogen. (Sean, 2005)
**Pharmacokinetics:**

It is pharmacologically inactive prodrug for several active metabolites which are HMG-CoA reductase inhibitors. The metabolites, of which the most potent with respect to HMG-CoA reductase inhibition is simvastatin $\beta$-hydroxyacid, are formed by hydrolysis of lactone ring. (Mauro, 1993)

**Absorption & Distribution:**

It is rapidly absorbed by the liver after oral administration and undergo metabolism. The bio-availability of the $\beta$-hydroxy acid after administration of simvastatin is therefore low. (Wiliams, 2002)

**Metabolism & Excretion:**

It undergoes extensive first pass metabolism in the liver. Studies with radio labelled drug have shown that levels of circulating total inhibitors accounted for 42% of the AUC, indicating that most of the metabolites were inactive or weak inhibitors. Less than 0.5% of the administered drug was present as the active inhibitors in the urine. In humans, the main metabolite is the beta-hydroxyacid. Other active metabolites are the 3-hydroxy-3-methyl, and 3-exomethylene derivatives. Biliary metabolites include (as hydroxyl acids & lactones) the 6-hydroxymethyl-and 6-carboxylic acid analogues, in both of which the chiral centre at position 6 has been inverted. (Lennernas, 1997).

**Action:**

The primary action is to increase the expression of low density lipoprotein receptors in the liver, which occurs in response to inhibition of HMG-CoA reductase, the rate limiting
enzyme in cholesterol synthesis. This leads to increased clearance of low density lipoproteins-cholesterol from the plasma, with a subsequent reduction in both low density lipoproteins and cholesterol. (Chong, 2001).

Uses:

It is used to reduce LDL-cholesterol, apolipoprotein B, triglycerides and to increase HDL-cholesterol in the treatment of hyperlipidaemias, including hypercholesterolemias, combined hyperlipidaemia, hypertriglyceridaemia and primary dystalipoproteinaemia. Statins can be effective as adjunct therapy in patients with homozygous familial hypercholestrolaemia who have some LDL-receptor function. Simvastatin is also given prophylactically to patients with ischemic heart disease. (Schetman, 1996).

Administration:

Simvastatin is given by mouth in a usual initial dose of 10 to 20 mg in the evening; an initial dose of 40 mg may be used in patients who are at high cardiovascular risk. The dose may be adjusted at intervals of not less than 4 weeks up to a maximum of 80 mg once daily in the evening. (White, 1999).
In the present study Polyethylene glycol 6000 was used as a carrier. The properties of the carrier were as follows.

1. POLYETHYLENE GLYCOL

**Non-proprietary names:** Macrogol (BP).

Polyethylene glycol (USPAC).

**Synonyms:** Carbowax, carbowaxsentry, polyoxyethylene.

**Description:**

The USP 23 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. Liquid grades (PEG 200-600) occur as clear, colourless or slightly yellow colour, viscous liquids. They have slight but characteristics odour and a bitter, slightly burning taste. PEG-6000 can occur as a solid at ambient temperatures. Solid grades (PEG > 1000) are white or off-white in colour and range in consistency from pastes to waxy flakes; they have a faint, sweet odour. Grades of PEG 6000 and above are available as free-flowing milled powders. (Mohl, 2004).

**Solubility:**

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols.
Pharmacopoeial Specifications for Polyethylene glycol:

<table>
<thead>
<tr>
<th>Test</th>
<th>USP AC 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (5%w/v dispersion)</td>
<td>≤ 4.5-7.5</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 5μg/g</td>
</tr>
<tr>
<td>Limit of ethylene glycol and diethylene glycol</td>
<td>≤ 0.5%</td>
</tr>
<tr>
<td>Sulphated ash</td>
<td>----</td>
</tr>
<tr>
<td>Residue on Ignition</td>
<td>≤ 0.1%</td>
</tr>
</tbody>
</table>

**Stability and Storage Conditions:**

Polyethyleneglycols 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.

**Incompatibilities:**

Liquid and solid polyethyleneglycol grades may be incompatible with some coloring agents.

**Safety:**

Polyethyleneglycols are widely used in a variety of pharmaceutical formulations. Generally they are regarded as non-toxic and non-irritant materials. (Okhamafe, 1982).
Applications in Pharmaceutical Formulations:

1. PEG’s are widely used in a variety of pharmaceutical formulations including parenterals, topical, ophthalmic, oral and rectal preparations.
2. It has been used experimentally in biodegradable polymeric materials used in controlled-release systems.
3. Aqueous PEG solutions can be used either as suspending agent or to adjust viscosity and consistency of other suspending vehicles.
4. PEG’s can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions. (Marishita, 1982).
5. In film coatings, solid grades of PEG can be used alone for film coating of tablets.

1.5 SUPER DISINTEGRANTS USED IN THE PRESENT INVESTIGATION

In the present study Crospovidone, Pregelatinized starch, Croscarmellose sodium, Sodium starch glycolate were used. The properties of the super disintegrants were as follows

1. CROSPOVIDONE:

**Non-proprietary names:** Crospovidone (BP)

Crosovidone (USPAC)

**Synonyms:** Kollidon cl, Polyplasdone xl-10.
Description:

Crospovidone is a white creamy, finely divided, free flowing, and practically tasteless, odorless, hygroscopic powder.

Solubility: Practically insoluble in water and most common organic solvents.

Pharmacopoeial Specifications for Crospovidone

<table>
<thead>
<tr>
<th>Test</th>
<th>USP AC 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (1% suspension)</td>
<td>≤ 5.0 -8.0</td>
</tr>
<tr>
<td>Water</td>
<td>≤ 5.0 %</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>≤ 0.4 %</td>
</tr>
<tr>
<td>Water soluble substances</td>
<td>≤ 1.5 %</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 0.001 %</td>
</tr>
<tr>
<td>Vinyl Pyrrolidone</td>
<td>≤ 0.1 %</td>
</tr>
</tbody>
</table>

Stability and Storage:

Crospovidone is hygroscopic. It should be stored in a tight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with organic and inorganic pharmaceutical ingredients. When exposed to high water level. Crospovidone may form molecular adducts with some materials.
Safety:

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as non-toxic and non-irritant material.

Applications in Pharmaceutical Formulations:

1. Crospovidone is water insoluble tablet disintegrant and dissolution agent used at 2-5 % concentration (Schiemeir, 2002) in tablets prepared by direct compression or wet and dry granulation methods. (Hipasawa, 2004).

2. Crospovidone can also be used as solubility enhancer. (Jagawa, 2003).

2. CROSCARMELLOSE SODIUM

Non proprietary names: Croscarmellose Sodium (BP)

Croscarmellose Sodium (USPAC)

Synonyms: Ac-Di-sol; cross linked carboxy methylcellulose sodium.

Description:

Croscarmellose Sodium occurs as odourless, white or greyish white powder. (Gissinger, 1980).

Solubility: Insoluble in water, practically insoluble in ethanol and toluene.
Pharmacopoeial Specifications for Croscarmellose Sodium

<table>
<thead>
<tr>
<th>Test</th>
<th>USPAC 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (1%w/v dispersion)</td>
<td>(\leq 5-7)</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>(\leq 10%)</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>(\leq 0.001%)</td>
</tr>
<tr>
<td>Sodium chloride and Sodium glycolate</td>
<td>(\leq 0.5%)</td>
</tr>
<tr>
<td>Degree of substitution</td>
<td>0.60- 0.85</td>
</tr>
<tr>
<td>Content of water soluble material</td>
<td>1-0-10%</td>
</tr>
<tr>
<td>Setting volume</td>
<td>10.3-30ml</td>
</tr>
</tbody>
</table>

**Stability and Storage:**

Croscarmellose Sodium is not compatible with strong acids or with soluble salts of iodine and some other metals such as aluminum, mercury, zinc.

**Safety:**

It is generally regarded as nontoxic, nonirritant.
Applications in Pharmaceutical Formulations:

Croscarmellose sodium is used in oral, pharmaceutical formulations as a disintegrant for tablets, capsules and granules. Croscarmellose sodium at concentration up to 5% w/v may be used as tablet disintegrant. (Botozolakis, 1988).

3. PREGELATINISED STARCH:

Non-Proprietary names: Pregelatinizedstarch (BP)

Pregelatinizedstarch (USPAC)

Synonyms: Compressible starch

Description:

Pregelatinized starch occurs as coarse to fine white to off-white colored powder. It is odourless and has a slight characteristic taste. (Mandhere, 1969).

Solubility:

Practically insoluble inorganic solvents, slightly soluble in cold water depending upon degree of pregelatinization.

Pharmacopoeial Specifications for Pregelatinised Starch

<table>
<thead>
<tr>
<th>Test</th>
<th>USPAC 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (10% W/V slurry)</td>
<td>4.5-7.0</td>
</tr>
<tr>
<td>Iron</td>
<td>≤0.002 %</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Sulfurdioxide</strong></td>
<td>≤ 0.008%</td>
</tr>
<tr>
<td><strong>Loss on drying</strong></td>
<td>≤ 14%</td>
</tr>
<tr>
<td><strong>Residue on ignition</strong></td>
<td>≤ 14%</td>
</tr>
</tbody>
</table>

**Stability and Storage Conditions:**

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well closed container in a cool, dry place.

**Safety:**

Pregelatinized starch is generally regarded as a nontoxic, non-irritant excipient.

**Applications in Pharmaceutical Formulations:**

Pregelatinized starch is modified starch used in oral capsule and tablet formulations as a binder, diluent, disintegrant. (Rudni, 1982).

**4. SODIUM STARCH GLYCOLATE:**

**Non-proprietary Names:** Sodium Starch Glycolate (BP)

Sodium Starch Glycolate (Ph Eur)

Sodium Starch Glycolate (USP-NF)

**Synonyms:** Carboxymethyl starch, sodium salt, Primojel; Tablo; Vivastar P.
Description:

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder.

Solubility:

Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Pharmacopoeial Specifications for Sodium Starch Glycolate

<table>
<thead>
<tr>
<th>Test</th>
<th>USP32</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (1%w/v dispersion)</td>
<td>≤ 5.5-7.5</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 10%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 0.002%</td>
</tr>
<tr>
<td>Sodium chloride and Sodium glycolate</td>
<td>≤ 0.7% and ≤ 0.2%</td>
</tr>
</tbody>
</table>

Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.
Applications in Pharmaceutical Formulation:

1. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.

2. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. (Gebremarian, 1996).

3. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. (Hannula, 1989).

4. Sodium starch glycolate has also been investigated for use as a suspending vehicle.