## Chapter - 1

### Chapter - 1. INTRODUCTION

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1. INTRODUCTION

1.1 GENERAL 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\(^1\,^2\). 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\(^3\,^4\). Drug absorption from the gastrointestinal 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 gastrointestinal tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption\(^5\). 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 provides some hints as how the dissolution rate of poorly soluble drugs might
be improved to minimize the limitations to oral bioavailability\textsuperscript{6, 7}. 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\textsuperscript{8} 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 relevant 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\textsuperscript{9, 10, 11} and spray drying,\textsuperscript{12} administration of liquid solutions from which upon dissolution with gastric fluids, the dissolved drug may precipitate in very fine particles\textsuperscript{13} 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 \textit{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\textsuperscript{14}. Numerous solid dispersion
systems have been demonstrated in the pharmaceutical literature to
improve the dissolution properties of poorly soluble drugs\textsuperscript{15,16}. 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\textsuperscript{17}. 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\textsuperscript{18}. 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.

**1.1.1 Solid Dispersions:**

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. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles\textsuperscript{19}.

**1.1.2 Advantages:**

i. 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\textsuperscript{20,21}.

ii. 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\textsuperscript{22}.

iii. Solid dispersions produce larger and more porous micro particles and therefore results in a higher dissolution rate\textsuperscript{23}.
iv. In solid dispersions poorly water soluble crystalline drugs are presented as amorphous state having higher solubility\textsuperscript{24}.

v. Solid dispersion systems can also be used for sustained release of drugs\textsuperscript{25}.

vi. Solid dispersion systems can also be used for enhanced release of drug from ointment and suppository bases.

vii. Solid dispersion systems can be used for increasing the solubility and stability of drugs.

viii. The equipments used for preparation are available at small and large scale and methods of preparation are easy.

\textbf{1.1.3 Disadvantages:}

i. Some carriers used in solid dispersions are hygroscopic in nature and may absorb moisture that may result in crystal growth\textsuperscript{26, 27}.

ii. Difficulty in understanding the physical structure of solid dispersions.

iii. Problems of residual solvents employed during its preparation\textsuperscript{28}.

\textbf{1.1.4 Classification of Solid Dispersions:}

Solid dispersions can be classified into six types based on the molecular arrangement.

1. Simple eutectic mixtures
2. Amorphous precipitation in crystalline matrix

3. Solid solutions
   i. Continuous solid solutions
   ii. Discontinuous solid solutions
   iii. Substitutional solid solutions
   iv. Interstitial solid solutions

4. Glass suspension

5. Glass solution

6. Complex formation between the drug and carrier

**Simple Eutectic Mixtures:**

An 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. The increase in specific surface area is responsible for increased rate of dissolution\(^{29,30}\).

![Fig: 1.1 Phase Diagram for a Eutectic System](image)
**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\(^{31,32}\).

![Diagram of Amorphous Precipitation](image)

**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\(^{33,34}\).

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](image)

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\(^{35-37}\).
**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 this 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$^{38}$. 

**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\(^{39}\).

**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\(^{40}\).

**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\(^{41}\).

**1.1.5 Methods of Preparation of Solid Dispersions:**

**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\textsuperscript{42}.

**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\textdegree 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\textsuperscript{43,44}.

**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\textsuperscript{45}.

**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\textsuperscript{46,47}.

**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 is 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\textsuperscript{48,49}.

**Lyophilisation Technique / Freeze Drying:**

It is the promising and suitable technique to incorporate drug substances in stabilizing matrices\textsuperscript{50}. It is an alternative technique to solvent evaporation technique. Lyophilisation technique is a molecular mixing technique where the drug and carrier are co dissolved in
common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. The freeze drying process involves four steps i.e., pre-treatment, freezing, primary drying and secondary drying.

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:**

Sufficiently dry, sufficiently porous, sterile, free of pyrogens, free of particulates, chemically stable.

**Advantages:**

i. Lyophilisation has many advantages compared to other drying and preserving techniques.

ii. Lyophilisation maintains quality of the product because they remain at a temperature that is below the freezing-point during the process of sublimation.

iii. Lyophilized products can usually be stored without refrigeration, which results in a significant reduction of storage and transportation costs.

iv. Lyophilisation greatly reduces weight, and this makes the products easier to transport.
v. They are porous, most freeze-dried products can be easily rehydrated. Lyophilisation 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\(^5^2\).

**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\(^5^3\). 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)\textsuperscript{54}.

**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\textsuperscript{55}.  
**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\textsuperscript{56}.

**1.1.6 Mechanism of Dissolution:**

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

i. 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.

ii. 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.

iii. 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.
iv. In glass solution glassy or vitreous form of the carrier solubilises drug molecules in the matrix.

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

vi. Co-precipitate interacts with water in its vicinity.

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

1.1.7 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 whereas 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\textsuperscript{57,58}.

Effect of Polyethylene Glycol Molecular Weight:

The dissolution rate of pure Polyethylene glycol decreases with increasing molecular weight\textsuperscript{59}. 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 Poly ethylene glycol. This phenomenon is observed for tolbutamide and indomethacin\textsuperscript{60}. 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\textsuperscript{61}. 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\textsuperscript{62}. It is due to high molecular weight of poly ethylene 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\textdegree 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 poly vinyl pyrrolidone will decrease the dissolution rate of most drugs. Lower molecular weight
poly vinyl pyrrolidone undergoes short swelling time prior to dissolution resulting in an increase in dissolution rate of polymer and drug. Poly vinyl 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\textsuperscript{63}.

**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\textsuperscript{64}. 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\textsuperscript{65}. 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\textsuperscript{66}.

**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.

**Polyvinyl alcohol (PVA), Crospovidone (PVP-CL), Polvinyl pyrrolidone-polyvinyl acetate 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. 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.

**Hydroxypropyl methyl cellulose (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 15,00,000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane\textsuperscript{69}.

**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. The use of Hydroxypropylcellulose as carrier in solid dispersions has been shown to lead to enormous increase in the drug release rate\textsuperscript{70}.

**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\textsuperscript{71}. Solid dispersions of nifedipine and spironolactone show enormous increase in the dissolution rate of the drug with CMEC as carrier \textsuperscript{72}.

**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\textsuperscript{73}.

**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\textsuperscript{74}.

**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\textsuperscript{75,76}.

**1.1.8 Methods of Preparation of Fast Dissolving tablets (FDT's)**

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

**Freeze-Drying or Lyophilisation:**

It is the promising and suitable technique to incorporate drug substances in stabilizing matrices. It is an alternative technique to solvent evaporation technique. Lyophilisation 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.

**SuperDisintegrants:**

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\textsuperscript{77}.

**Mechanism of Addition of SuperDisintegrants:**

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 SuperDisintegrants:**

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\(^78\).
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\(^7\).

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\(^8\).

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 process81.

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.

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.

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)\textsuperscript{84}.

1.1.9 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\textsuperscript{85}. 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.

1.1.10 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\textsuperscript{86}. 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\textsuperscript{87}. 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:

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

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\textsuperscript{88}. 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:

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

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\(^\text{89}\). (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\(^\text{90}\).
\[ C_{s, \text{curved}} = C_{s, \text{flat}} \cdot \exp \left[ 2 \gamma_{d,s} \cdot \frac{M_d}{RT \rho_d r} \right] \]  

(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\(^91\). 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 a 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, Drug = Cs, 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 δ will be constant.

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

i. 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.

ii. A second complication is that the degree of super saturation can increase in time especially when C dissolves rapidly.

iii. 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\textsuperscript{92-94}.

**Weibull Plot:**

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

\[
M = 1 - \exp \left[- \left(\frac{t-T_i}{a}\right)^b \right] \quad (\text{Eq. 5})
\]

'\(M\)' - 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\textsuperscript{95}:

\[
(1-m)\exp = \left[- \left(\frac{t-T_i}{a}\right)^b \right] \quad (\text{Eq. 6})
\]
\[-\ln(1-m) = (t-T_i)^b \left(1/a\right)\]  \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:

$$T_d = a^{1/b}$$  \hspace{1cm} (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.

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

**First order kinetic model:**

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

$$\log (W_\infty - W) = \log M - K/2.303(t-t_0)$$  \hspace{1cm} (Eq. 11)

$W_\infty$ is the amount of drug in the solution at infinite time; $W$ is the amount of drug in the solution at time $t$; $M$ is the interaction constant; $T_0$ is lag time before the onset of dissolution; $K$ is 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,

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

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,

\[
\frac{W}{[(W_e (W_e-W))] = K_2t} \quad (\text{Eq. 13})
\]

'\( W \)' is the Weight of the drug in the solution at time \( t \); '\( W_e \)' is the 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 Atorvastatin Calcium and Rosuvastatin Calcium by formulating them 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 Atorvastatin Calcium, Rosuvastatin Calcium were selected taking into consideration their physicochemical and biopharmaceutical properties.

Atorvastatin Calcium is a HMG-CoA reductase inhibitor used in the treatment of dyslipidemia and prevention of cardiovascular disease. It is very slightly soluble in water, slightly soluble in ethanol and freely soluble in methanol. Atorvastatin Calcium is rapidly absorbed after oral administration with absolute bioavailability of parent drug is approximately 12% and is hydrolysed in the liver to ortho and para hydroxylated derivatives. Peak plasma concentrations achieved with in 1-2hours. The half life is 14 hours.

Rosuvastatin is a lipid regulating drug, it is a competitive inhibitor of HMG-CoA used to reduce cholesterol, used in the
treatment of osteoporosis, benign prostatic hyperplasia, dysbetalipoproteinemia and alzheimer's disease. It is sparingly soluble in water, ethanol and soluble in methanol. Rosuvastatin Calcium is absorbed from the gastrointestinal tract and is metabolised in the liver. Peak plasma concentration achieved with in 3-5 hours. The half life is 19 hours.

Based on their physicochemical and biopharmaceutical properties, Atorvastatin Calcium and Rosuvastatin Calcium were selected as a drug candidates for developing solid dispersions formulations for improving its solubility and bioavailability by improving the dissolution rate\(^{96,97}\).

The present research work has been carried out with an aim to increase the solubility and dissolution rate of Atorvastatin Calcium and Rosuvastatin Calcium, 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.

1.2.1 The major objectives of investigation are as follows:

i. To perform saturated solubility studies of Atorvastatin Calcium and Rosuvastatin Calcium to optimize the dissolution medium.

ii. To prepare solid dispersions of poorly soluble drugs, Atorvastatin Calcium and Rosuvastatin Calcium using PEG-
6000 as a carrier by physical mixing, fusion, solvent evaporation and Lyophilisation methods.

iii. To evaluate the flow properties of prepared solid dispersions by angle of repose, carr’s index, and to determine the particle size.

iv. To evaluate the drug release from the solid dispersions by in vitro dissolution studies.

v. To evaluate the kinetics and mechanisms of drug release from the solid dispersions tablets by in vitro dissolution studies.

vi. 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.

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

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

ix. To check the drug-polymer interaction and crystal morphology of optimized solid dispersions by differential scanning calorimetry, infra red spectroscopy and X-ray diffraction studies.

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

xi. To evaluate pharmacokinetics of Atorvastatin Calcium and Rosuvastatin Calcium from selected fast dissolving tablets.
xii. To conduct the accelerated stability studies for the selected fast dissolving tablets.

1.3 DRUGS USED IN PRESENT STUDY

1.3.1 Atorvastatin Calcium

**Drug Name:** Atorvastatin Calcium

**Chemical Formula:** $\text{C}_33\text{H}_{34}\text{FN}_2\text{O}_5\text{Ca}.3\text{H}_2\text{O}$

**Molecular Weight:** 1209.42

**Chemical Structure:**

![Chemical Structure Image]

**Chemical Name:**

Atorvastatin Calcium is $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})-\beta,\delta$-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole -1-heptanoic acid, calcium salt (2:1) trihydrate.

**Description:**

It is white to off-white crystalline that is insoluble in aqueous solutions of pH 4.0 and below. Atorvastatin Calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol and freely soluble in methanol.
**Mechanism of Action:**

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3- hydroxy 3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic low density lipoprotein receptors on the cell surface to enhance uptake and catabolism of low density lipoproteins 98.

**Pharmacokinetics:**

**Absorption:**

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentration occurs within 1 to 2 hours. The absolute bioavailability of Atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and first-pass metabolism 99.

**Distribution:**

Mean volume of distribution of Atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. a blood/
plasma ratio of approximately 0.25 indicates poor penetration into red blood cells. Atorvastatin is likely to be secreted in human milk.

**Metabolism:**

Atorvastatin is extensively metabolized to ortho and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho and parahydroxylated metabolites is equivalent to that of Atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

**Excretion:**

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic or extrahepatic metabolism. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

**Uses:**

It is used for prevention of cardiovascular disease and reduce the risk of myocardial infarction.

It used to reduce the risk for revascularization procedures, stroke and angina.
As an adjunct to diet to reduce elevated total cholesterol and low density lipoprotein cholesterol triglyceride levels and to increase high density lipoprotein cholesterol levels in patients with primary hypercholestrolemia and mixed dyslipidemia.

It used for the treatment of patients with primary dysbetalipoproteinemia who do not adequately respond adequately to diet\textsuperscript{102}.

**Administration:**

The starting dose of Atorvastatin is 10 or 20 mg once in a day. Patients who require a large reduction in low density lipoprotein cholesterol may be started at 40 mg once in a day\textsuperscript{103}.

**1.3.2 Rosuvastatin Calcium**

**Drug Name:** Rosuvastatin Calcium

**Chemical Formula:** (C\textsubscript{22}H\textsubscript{27}N\textsubscript{3}O\textsubscript{6}S\textsubscript{2})

**Molecular Weight:** 1001.14

**Chemical Structure:**

![Chemical Structure of Rosuvastatin Calcium]
**Chemical Name:**

bis[(E)-7-[(4-(4-fluorophenyl)-6-isopropyl-2-methyl (methylsulfonyl) amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6enoic acid] calcium salt.

**Description:**

It is white amorphous powder that is sparingly soluble in water and methanol and slightly soluble in ethanol.

**Mechanism of Action:**

Rosuvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy 3-methylglutaryl-coenzyme A to mevlonate, a precursor of sterols, including cholesterol. Rosuvastatin reduces triglycerides and produces increases high density lipoprotein cholesterol in patients with hypertriglyceridemia.

**Pharmacokinetics:**

**Absorption:**

It is incompletely absorbed from the gastrointestinal tract, with a bioavailability of 20%. Peak plasma concentrations can be achieved with in 3 to 5 hours after oral adminstration. Both peak concentration and area under the plasma concentration-time curve increases with in proportion to dose of the drug. Administration of Rosuvastatin with food decreased the rate of drug absorption by 20%.104.
Distribution:

Mean volume of distribution at steady state of Rosuvastatin is approximately 134 litres. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentration.

Metabolism:

It is taken up by the liver, its primary site of action, and undergoes limited metabolism, mainly by cytochrome P450 2C9. The major metabolite is N-desmethyl Rosuvastatin, and in vitro studies demonstrated that N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. Overall greater than 90% of active plasma HMG-CoA reductase activity is accounted for by Rosuvastatin\textsuperscript{105}.

Excretion:

Approximately 90% of an oral dose of Rosuvastatin is excreted in the faeces, including absorbed and non-absorbed drug, and the remaining is excreted in the urine; about 5% of a dose is excreted in urine\textsuperscript{106}.

Uses:

It is used to reduce LDL-cholesterol, apolipoprotein B and to increase HDL-cholesterol in the management of hyperlipidaemias
including primary hypercholesterolaemia, mixed dyslipidaemia and hyperglyceridaemia.\textsuperscript{107}

**Administration:**

Rosuvastatin is given by mouth in a usual initial dose of 10 mg once in a day, increased after 4 weeks, if necessary, to 20 mg once in a day. A maximum dose of 40 mg once in a day may be given to patients at high risk of myopathy, including those receiving fibrates; usage with cyclosporin is contraindicated.\textsuperscript{108}

**1.4 CARRIER USED IN THE PRESENT INVESTIGATION**

In the present study Polyethylene glycol 6000 was used as a carrier. The properties of the carrier were as follows.

**1.4.1 Polyethylene Glycol**

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

Polyethylene glycol (USPAC).

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

**Description:**

The USPAC\textsuperscript{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\textsuperscript{109}.

**Solubility:**

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols.

**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.

**Incompatibilities:**

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

**Safety:**

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally they are regarded as non-toxic and non-irritant materials\textsuperscript{110}.
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\(^{111}\).

5. In film coatings, solid grades of PEG can be used alone for film coating of tablets.

1.5 SUPERDISINTEGRANTS USED IN THE PRESENT INVESTIGATION

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

1.5.1 Crospovidone:

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

Crospovidone (USP)

**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.

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 in tablets prepared by direct compression or wet and dry granulation methods\textsuperscript{112,113}. 
2. Crospovidone can also be used as solubility enhancer\textsuperscript{114}.

1.5.2 Croscarmellose Sodium

**Non proprietary names:**  Croscarmellose Sodium (BP)
                         Croscarmellose Sodium (USP)

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

**Description:**

Croscarmellose Sodium occurs as odourless, white or greyish white powder\textsuperscript{115}.

**Solubility:**

Insoluble in water, practically insoluble in ethanol and toluene.

**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\textsuperscript{116}. 
1.5.3 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\(^{117}\).

**Solubility:**

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

**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\(^{118}\).

1.5.4 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.

**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.

**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\textsuperscript{119}.

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\textsuperscript{120}.

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