Introduction:

The most important property of a drug delivery system is its ability to deliver the active pharmaceutical ingredient (API) to the site of action in the body in an amount sufficient to produce the desired therapeutic response. This property of the drug delivery system is referred to as bioavailability. Bioavailability is more precisely defined as the rate and extent of absorption (availability) of drug to the systemic circulation. About 95% of all new potential therapeutics (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under BCS and pose challenging problems in their pharmaceutical product development process. The drug in solid dosage form (tablet) must undergo dissolution before it is available for absorption from gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Several modern organic drugs belong to class II category under BCS and exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, microemulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs.

Among the various approaches, cyclodextrin complexation and solid dispersions in water dispersible excipients are simple, industrially useful approaches, for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

The following two techniques will be tried for enhancing the solubility, dissolution rate, dissolution efficiency and oral bioavailability of selected anti hypertensive drugs of BCS class II category.

- Cyclodextrin complexation using β- cyclodextrin and hydroxyl propyl β- cyclodextrin with and without surfactants (SLS/Tween 80/Poloxamer)
- Solid dispersions in water dispersible excipients such as superdisintegrants and modified starches.
LITERATURE ON CYCLODEXTRIN COMPLEXATION:

Complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies.

Cyclodextrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug.

The α-, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist. Chemical and physical properties of the four most common cyclodextrins are given in Table 1. The melting points of α-, β- and γ-cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure.
Table 1

Some Characteristics of α-, β-, δ- and £-Cyclodextrins

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>δ</th>
<th>£</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of glucopyranose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>1459</td>
</tr>
<tr>
<td>Central cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>5.2-8.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Water solubility at 25°C (g/100 ml)</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
<td>8.19</td>
</tr>
</tbody>
</table>

They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyltransferase produced by B. macerans acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated\textsuperscript{11}. The structure of the most important CD, -cyclodextrin is shown in Fig. 1.

Fig.1: The Structure of -cyclodextrin
The 'torus' shaped macro-ring is built of \(-1,4\)-D-glucose units. As a consequence of conformation of glucopyranose units, all secondary OH- groups are located on one edge (wider edge) of the ‘torus’ like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.

**Pharmacokinetics of Cyclodextrins**\(^{12}\):

- The parent CDs are poorly absorbed from the g.i. tract
- Oral absorption studies have shown \(\leq 2\%\), 0.1-0.3\% and \(\leq 0.1\%\) absorption respectively with \(\alpha\)-, \(\beta\)-, and \(\gamma\) - CDs.
- Intravenously administered CDs disappear rapidly from systemic circulation; excreted mainly through kidney. The \(t_{1/2}\) of \(\beta\)-CD 23.9 – 50.2 min in rat.
- The \(t_{1/2}\) of HP-\(\beta\)-CD is 24 min in rat, 48 min in dog and 72-108 min in human.
- \(\alpha\)- and \(\beta\)-CDs are excreted almost completely in their intact form
- Little or no distribution of most CDs into other tissues or storage compartments is observed.

**Safety of Cyclodextrins:**

- Parent CDs are reported to be non-toxic and safe even at high oral doses.
- The \(LD_{50}\) in rats is reported to be greater than 12.5, 18.8 and 8.0 g /kg body weight for \(\alpha\)-, \(\beta\)-, and \(\gamma\)-CD respectively.
- \(\alpha\)-and\(\beta\)-CDs produced no toxic effects when fed to rats for 30-90 days at 1\%, of the diet or at 1 and 2 g /kg daily doses.

**Regulatory Status of Cyclodextrins:**

- Accepted as new pharmaceutical excipients by USFDA
- A monograph on \(\beta\) CD in USP 23/NF 18, 1995 and European Pharmacopoeia 3\(^{rd}\) Ed., 1997

**Formation of Complexes:**
One of the most important characteristics of CDs are their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide variety of drug molecules resulting in the formation of monomolecular inclusion complexes. Usually 1 : 1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2 : 1 (CD : drug) or sometimes 3 : 1 or 4 : 1 complexes. It may also be possible to form 1 : 2 and 1 : 3 (CD : drug) complexes. The central cavity of the cyclodextrin molecule is linked with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic, the polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity Measurements of stability or equilibrium constants ($K_c$) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

**LITERATURE ON SOLID DISPERSIONS:**

Chiou and Riegelman defined solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. Therefore, based on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished.

**TYPES OF SOLID DISPERSIONS**:

**Eutectic Mixtures:** A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid
solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution.

**Solid Solutions:**

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier. According to their miscibility two types of solid solution are known.

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

**Discontinuous Solid Solutions:** In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.

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

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

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

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

Glass Solutions and Glass Suspensions:

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature.

Carriers for Solid Dispersions\textsuperscript{17}:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of poorly soluble drugs.

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

First generation carriers\textsuperscript{18}: Example: Crystalline carriers: Urea, Sugars, Organic acids.

Second generation carriers\textsuperscript{19}: Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly
composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrine.

**Third generation carriers**: Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14

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

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

**BCS CLASS – II DRUGS SELECTED**: Three relatively new anti hypertensive drugs namely valsartan, irbisartan and telmisartan are selected for enhancing their solubility, dissolution rate, bioavailability and formulation development. The profiles of the selected drugs are as follows.

**VALSARTAN PROFILE**

**Pharmacological Properties**: Valsartan, a specific angiotensin II type 1 antagonist, is used alone or with other antihypertensive agents to treat hypertension. Unlike the angiotensin receptor antagonist Valsartan does not have an active metabolite or possess uricosuric effects. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity
and circulating angiotensin II levels do not overcome the effect of Valsartan on blood pressure. The antihypertensive actions of Valsartan are potentiated when used in combination with either thiazide diuretics or CCBs.

**Mechanism of action**

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT$_1$ receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. Valsartan has more than a 12,500-fold greater affinity for the AT$_1$ receptor than for the AT$_2$ receptor.

**Dosing:** Valsartan is supplied as 10, 20, 40, 80, 160 and 320 g tablets. In general clinical practice, therapy is initiated with 80 mg once daily appropriate dosage in hypertensive patients as a functional blockade of AT receptor has been shown to occur in humans after single doses of 80 mg valsartan in 2 to 24 h.

**IRBESARTAN$^{25-28}$**

**Therapeutic Category:** Antihypertensive

- **Mechanism of Action:**

  Angiotensin II is a potent vasoconstriction formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kinase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal, cardiac contraction, renal reabsorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Ibesartan blocks the vasoconstriction and aldosterone-secreting effects of angiotensin II by selectively blocking in a non competitive manner the binding of angiotensin II to the AT$_1$ receptor found in many tissues. Ibesartan has no agonist activity at the AT$_1$ receptor. AT$_2$ receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. Ibesartan has essentially no affinity for the AT$_2$ receptors. Ibesartan do not inhibit
angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect rennin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis.

**TELMISARTAN PROFILE**

**Pharmacological Properties:**

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT\(_1\) receptor subtype. It has the highest affinity for the AT\(_1\) receptor among commercially available ARBS and has minimal affinity for the AT\(_2\) receptor. New studies suggest that telmisartan may also have PPAR\(\gamma\) agonistic properties that could potentially confer beneficial metabolic effects, as PPAR\(\gamma\) is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

**Mechanism of action**

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT\(_1\) receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.