**CHAPTER-1**

**INTRODUCTION**

* 1. **BIOPHARMACEUTICAL CLASSIFICATION SYSTEM & BIOAVAILABILITY**

Solubility of a drug plays a very important role in determining the dose of the drug to be taken since it has a major impact on the bioavailability/ therapeutic efficiency. Presently there is a considerable interest in improving the solubility of poorly water-soluble drugs. Due to the poor bioavailability of the new drug entities, high inter/ intra subject variability is being observed in patients consuming these drugs. When the drugs suffer from highly variable bioavailability, it becomes difficult for the clinician to fix a dosage regimen. The drug must get solubilised in the gastro intestinal fluids or in aqueous medium and also should possess permeability properties for good membrane diffusion in order for it to reach the blood stream and show good bioavailability. For this purpose drug substances are categorized into four classes based on their solubility and permeability parameters namely, Biopharmaceutical Classification System (BCS). BCS considers into account the following three *in vitro* parameters i.e. solubility, permeability and dissolution1.

**Objectives of BCS**

1. To improve the efficiency of the drug development and review process by recommending a strategy for identifying expendable clinical bioequivalence test.

2. To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on *in vitro* dissolution tests.

3. To recommend methods for classification according to dosage form dissolution along with the solubility–permeability characteristics of the drug product2.

**Classes of BCS**

Class I: High Solubility - High Permeability

Class II: Low Solubility - High Permeability

Class III: High Solubility - Low Permeability

Class IV: Low Solubility - Low Permeability

**Class I** drugs exhibits high absorption and as well as high dissolution rate. Drug dissolution is the rate limiting step and if the dissolution is very fast then the gastric emptying rate becomes the rate determining step. Rate of absorption is higher than rate of excretion. E.g. metoprolol, diltiazem, verapamil and propranolol.

**Class II** drugs have high absorption rate but their dissolution rate is low. *In vivo* drug dissolution is the rate limiting step for absorption except at a higher dose value. The absorption for Class II drugs is slower than that of Class I drugs and occurs over longer periods of time. *In vitro-in vivo correlation (IVIVC)* is usually accepted for Class I and Class II drugs. E.g. phenytoin, danazol, ketoconazole, mefenamic acid and nifedipine.

Permeability is a rate limiting step in the case of **Class III** drugs. Drug absorption exhibits there is high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. E.g. cimetidine, acyclovir, neomycin B and captopril.

**Class IV** drugs present a number of problems when given Class IV drugs are considered to be suffering from variable bioavailability. Some examples of class IV drugs are taxol and griseofulvin3.

**Parameters of BCS**

In BCS the drugs are classified on the basis of their solubility and permeability and dissolution parameters. The class boundaries for the parameters are:

1. **Solubility class boundaries**- A drug substance is considered to be highly soluble when the highest dose strength is soluble in 250 mL of water over a pH range 1 to 7.5.

2. **Permeability class boundaries**- A drug is considered to be highly permeable when the extent of absorption in humans is found to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.

3. **Dissolution class boundaries**- A drug product is considered to be dissolving rapidly when 85% of the labelled amount of the drug substance dissolves within 30 minutes, upon usage of USP apparatus I or II in a volume of 900 mL buffer solution3.

**SOLUBILITY DETERMINATION**

Solubility can be defined as the amount of substance that has passed into solution when equilibrium is attained between the solution and excess (undissolved substance) at a given temperature and pressure. A drug substance or an active pharmaceutical ingredient (API) is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous medium over a specific pH range. The pH solubility profile of the drug substance is determined at 37±1ºC in aqueous medium with pH in the range of 1-7.5, 1.2-6.8 and 1-8 as per United States Food and Drug Administration (USFDA), World Health Organization (WHO) and European Medicines Academy (EMEA) guidelines. A number of pH conditions for the accurate pH-solubility profile should be evaluated and it depends upon the ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility in each pH condition should be carried out for accurate results. Standard buffer solutions described in pharmacopoeiae are considered appropriate in solubility studies. Methods other than shake-flask method can also be used to predict the equilibrium solubility of test drug substance. If degradation of drug has occurred because of buffer composition and/or pH, it should be taken into consideration. The concentration of drug substance in selected buffers or pH conditions should be determined using a validated solubility indicating assay method that can distinguish the drug substances from its degradation products4.

**PERMEABILITY DETERMINATION**

Permeability and solubility form the backbone of BCS that helps in assessing oral absorption of drug molecules. Different methods used for the determination of permeability are as follows:

1. Pharmacokinetic studies in human subjects including mass balance studies and absolute bioavailability (BA) studies or intestinal permeability methods.
2. *In vivo* or *in situ* intestinal perfusion in a suitable animal model.
3. *In vitro* permeability methods using excised intestinal tissues.
4. Monolayers of suitable epithelial cells e.g. Caco-2 cells or TC-7 cells.

**In mass balance studies,** to determine the extent of drug absorption, unlabeled, stable isotopes or radiolabeled drug substances are used. **In absolute BA studies,** oral BA is determined and as reference it is compared against the intravenous BA. **Intestinal perfusion models** and ***in vitro* methods** are recommended for passively transported drugs. An interesting alternative to intestinal tissue models is the use of *in vitro* systems based on the human adenocarcinoma cell line Caco-2. These cells serve as a model of small intestinal tissue due to their ability to transport ions, sugars and peptides. The differentiated cells exhibit the micro-villi typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzymes. They also form the fluid-filled domes typical of a permeable epithelium4.

**DISSOLUTION DETERMINATION**

*In vitro* drug dissolution is mainly influenced by formulation composition and the manufacturing process. According to BCS a drug product is classified as rapidly dissolving when not less than 85 % of the labelled amount of the drug substance dissolves in 30 min using the following:

• USP Apparatus 1 (basket) at 100 RPM or USP Apparatus 2 (paddle) at 50 RPM.

• Dissolution medium volume of 900 mL or less in each of the following:

1. 0.1 N HCI or simulated gastric fluid (SGF) USP without enzymes

2. pH 4.5 buffer

3. pH 6.8 buffer or simulated intestinal fluid (SIF) USP without enzymes.

Different physicochemical and physiological parameters necessary for drug dissolution in gastro intestinal tract are shown in **Table.1.1.1**.

**Table.1.1.1: Physicochemical and physiological parameters important to drug dissolution in gastro intestinal tract**

|  |  |  |
| --- | --- | --- |
| **Factor** | **Physicochemical properties** | **Physiological properties** |
| Surface area of drug | Particle size, wettability | Surfactants in gastric juice and bile |
| Diffusitivity of drug | Molecular size | Viscosity of luminal contents |
| Boundary layer thickness | Concentration of the drug | Motility patterns and flow rate |
| Solubility | Hydrophilicity, crystal structure, solubilisation | pH, buffer capacity, bile and food composition |
| Amount of drug already dissolved | Hydrophilic, lipophilic nature of the drug | Permeability |
| Volume of solvent available | Depends upon type of body fluid | Secretion, co-administered fluids |

**Methods for enhancing the dissolution and absorption of BCS class II drugs**

**Methods for enhancing the solubility of drugs**

* Buffering the pH of microenvironment.
* Use of salts of weak acids and weak bases.
* Use of solvates and hydrates.
* Use of selected polymorphic forms.
* Complexation.
* Prodrug approach.
* Use of surfactants3.

**Methods enhancing the surface area of the drug**

* Micronization.
* Use of surfactants (Enhancing effective surface area by facilitating proper wetting).
* Solvent deposition (Depositing poorly soluble drugs on inert materials).
* Solid dispersions (dispersions of drugs in solid matrices of water-soluble carriers) 3.

**1.2. SOLID DISPERSIONS**

Among the various techniques, solid dispersion is one of the most employed techniques for solubility enhancement. 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; basically an amorphous form is having a better solubility than a crystalline substance because no energy is required to break up the crystal lattice of a drug during the dissolution process. Drug solubility and wettability may be increased by the presence of the surrounding hydrophilic carriers5, 6.

**TYPES OF SOLID DISPERSIONS**

* **Simple eutectic mixtures**

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but miscible 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 7,8,9.

* **Amorphous precipitation in crystalline matrix**

This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form7.

* **Solid solution**

In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug is reduced to its molecular size. Thus, a solid solution can achieve dissolution rate more rapidly than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In the second method, they may be classified based on the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous). In **continuous solid solutions**, the two components are miscible in the solid state in all proportions. This means that the bonding strength between the two components is stronger than the strength between the molecules of each of the individual components. In **discontinuous solid solutions**, the solubility of each of components in the other component is limited. In **substitutional crystalline solid dispersions**, solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. In **interstitial crystalline solid dispersions**, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice whereas in **amorphous crystalline solid dispersions**, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent 7,8,9.

* **Glass solution and glass suspension**

A glass solution is a homogeneous glassy system in which a solute dissolves in a glassy solvent. Glass suspensions are mixtures in which precipitated particles are suspended in glass solvent. The lattice energy is much lower in glass solution and suspension7,8,9.

All the above mentioned different types of solid dispersion are further summarized in **Table 1.2.1**.

**Table 1.2.1: TYPES OF SOLID DISPERSION**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S. no** | **Type of Solid dispersion** | **Matrix\*** | **Drug\*\*** | **Remarks** | **Phases** | **Ref no.** |
| 1. | Eutectics | C | C | First type of solid dispersion prepared | 2 | 13 |
| 2. | Amorphous precipitation in crystalline matrix | C | A | Rarely encountered | 2 | 15,16 |
| 3. | Solid solution | - | - | - | - | - |
| (i) | Continuous solid solution | C | M | Miscible at all composition, never prepared | 1 | 17 |
| (ii) | Discontinuous solid solution | C | M | Partially miscible, 2 phases even though drug is molecularly dispersed | 2 | 18 |
| (iii) | Substituted solid solution | C | M | Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) | 1 or 2 | 19,20 |
|  |  |  |  | diameter. In that case the drug and matrix are substitutional. Can be continuous or dis-continuous. When discontinuous: 2 phases even though drug is molecularly dispersed. |  |  |
| 4. | Interstitial solid solution | C | M | Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG. | 2 | 13,14 |
| 5. | Glass suspension | A | C | Particle size of dispersed phase dependent on cooling/ evaporation rate. Obtained after crystallization of drug in amorphous matrix | 2 | 14,21 |
| 6. | Glass suspension | A | A | Particle size of dispersed phase dependent on cooling/ evaporation rate. Many solid dispersions are of this type | 2 | 14,21 |
| 7. | Glass solution | A | M | Requires miscibility or solid solubility, complex formation upon fast cooling or evaporation during preparation, many (recent) examples especially with PVP | 1 | 22 |

\* A: matrix in the amorphous state, C: matrix in the crystalline state

\*\* A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

**ADVANTAGES OF SOLID DISPERSION**

* Reduces the particle size of drug
* Improves the wettability
* Improves the porosity of drug
* Converts the crystalline structure of drug into amorphous form
* Masks the bitter taste of the drug substance
* Useful in preparation of rapid disintegrating oral tablets.
* Solid dispersion carriers (mainly surface active agents) can maintain super saturation in GI tract, 10.

**DISADVANTAGES OF SOLID DISPERSION**

* Difficulty in understanding the physical structure of solid dispersions and relationship between physical structure and drug release7.
* Solid dispersions may be degraded or the physicochemical properties of the drugs themselves and carriers may change during the manufacturing processes.
* Melting temperatures are very high in the melting methods which could degrade drugs and carriers14. Also, cooling and solidifying molten mixtures are difficult steps in manufacturing solid dispersions13, 14, 18. In solvent evaporation methods, to dissolve the hydrophobic drugs, the volume of organic solvents are large and the amount of drugs relatively minimal.
* The major disadvantage of solid dispersions is their instability. Several systems were known to have shown changes in crystallinity and a decrease in dissolution rate with aging9,10.

**METHODS OF SOLID DIEPERSION**

* **Melting method/ fusion method**

In this method the drug or drug mixture and carrier are melted together by heating. The melted mixture is cooled and then solidified rapidly in an ice-bath under vigorous stirring and finally the solid mass is crushed, pulverized and sieved. The main advantage of this method is its ease and lower cost. The disadvantage is that drug degradation and decomposition happens on melting. This method is not suitable for volatile drugs and drugs that decompose on melting7,8,9,11.

* **Solvent method**

This method is prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The main advantage of this method is thermal decomposition of drugs or carriers can be prevented because low temperatures are required for the evaporation of organic solvents. High cost preparation and difficulty in complete removal of the solvent are some of the disadvantages7,8,9.

* **Melt evaporation method ( Melting solvent method)**

The drug is dissolved in a suitable liquid solvent and then the drug solution is directly incorporated into the melt of poly ethylene glycol (PEG), which is then evaporated until a clear, solvent free film is left. The film was further dried to constant weight. The 5 – 10% (w/w) of liquid compounds can be incorporated into PEG 6000 without significant loss of its solid property. The selected solvent or dissolved drug may not be miscible with the melt of the PEG and the polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent. This method possesses the advantages of both the melting and solvent methods7,8,9,11.

* **Melt extrusion method**

Solid dispersion by this method is composed of active ingredient and carrier, and is prepared by hot-stage extrusion using a co-rotating twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded to get into shape of tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables the drugs that are somewhat thermo labile to be processed. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100,130,170,180,1850C from freedom to die. The extrudates are collected after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieved to exclude particles >355µm9,11.

* **Melt agglomeration process**

In this technique, binder acts as a carrier. Solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure). Instruments like rotary processor are preferable for high melt agglomeration as it is easier to control the temperature and higher binder content can be incorporated in the agglomerates. Melt-in method gives a higher dissolution rates than the spray-on method with PEG 3000, poloxamer 188 and gelucire 50/13. Enhanced homogeneous distribution of drug in agglomerate can be achieved by the melt-in method. Larger particles results in densification of agglomerates where as fine particles cause complete adhesion to the mass after melting attributed to distribution and coalescence of the fine particles7,8,9,11.

* **Lyophilisation technique**

This technique was proposed as an alternative technique to solvent evaporation. It is molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An advantage of this method is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is converted into glass or a glassy substance7,8,9,11.

* **Electro spinning**

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. It involves application of a strong electrostatic field over a conductive capillary attached to a reservoir containing polymer solution or melt and a conductive collection screen. Increasing the electrostatic field strength, not exceeding a critical value, results in accumulation of charged species on the surface of a pendant drop that destabilize the hemispherical shape into a conical shape. Beyond the critical value, ejection of a charged polymer jet from the apex of the cone occurs. The ejected charged jet is then carried to the collection screen via the electrostatic force. Thinning down of the charged jet is limited. Increase in viscosity results in drying of the charged jet. This technique has tremendous potential for the preparation of nano fibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future 8,9.

* **Super critical fluid (SCF) technology**

This technique can be employed for the preparation of solvent free dosage forms. Super critical fluid is the one which exists as a single fluid phase above their critical temperature and pressure. Carbon dioxide is the most commonly used super critical fluid as it is chemically inert, non-toxic and non-flammable. After the drug particles are solubilized within super critical fluid, they can be recrystallized with reduced particle sizes as per the requirement 8,9.

* **Use of surfactant**

Adsorption of surfactant on solid surface modifies their hydrophobicity, surface charge, and also controls other interfacial properties such as flocculation/dispersion, floating, wetting, solubilization, corrosion inhibition and enhanced oil recovery. Use of surfactants results in solvation/ plasticization, reduction of melting active pharmaceutical ingredient, glass transition temperature and combined glass transition temperature of solid dispersion8,9,11.

**IDEAL PROPERTIES OF CARRIER USED IN SOLID DISPERSION**

Carriers play an important role in pharmaceutical formulations especially in solid dispersion. Without carriers drug cannot be administered or the desired pharmacological effect of drug cannot be obtain. Different generation carriers used in solid dispersions are shown in **Table 1.2.2** with examples7,12.

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug:

* Freely water-soluble with intrinsic rapid dissolution properties
* Non-toxic and pharmacologically inert
* Heat stable with a low melting point for the melt method
* Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method
* Able to preferably increase the aqueous solubility of the drug
* Chemically compatible with the drug and not other ingredients9,12.

**Table 1.2.2: Different generation carriers used in solid dispersions**

|  |  |  |
| --- | --- | --- |
| **FIRST GENERATION CARRIERS** | **SECOND GENERATION CARRIERS** | **THIRD GENERATION CARRIERS** |
| **Crystalline carriers:**   * Urea * Sugars * Organic acids | **Synthetic polymers :**   * Povidone (PVP) * Polyethylene glycols (PEG) * Polymethacrylates   **Natural polymers:**   * Hydroxy propyl methyl cellulose (HPMC) * Ethyl cellulose * Hydroxy propyl cellulose * Starch derivates like Cyclodextrins. | **Surface active self-emulsifying carriers:**   * Poloxamer 408 * Tween 80 * Gelucire 44/14 * Inulin * Inutec SP 1. |

**LIST OF SOLVENTS USED IN SOLID DISPERSION**

Solvents used in solid dispersion are listed out in **Table 1.2.3**.Solvents should be selected on the following criteria:

* Dissolve both drug and carrier
* Toxic solvents should be avoided due to the risk residual level after preparation
* Water based systems is preferable
* Surfactant may be added to aid in dissolution but care should be taken because they can reduce glass transition temperature.
* Ethanol can be used as alternative as it is less toxic9.

**Table 1.2.3: List of solvents used in solid dispersions**

|  |  |  |  |
| --- | --- | --- | --- |
| **S. no** | **Solvent** | **Melting**  **Point (0C)** | **Boiling**  **Point (0C)** |
| 1. | Water | 0 | 100 |
| 2. | Methanol | -93.9 | 65 |
| 3. | Ethanol | -117 | 78.5 |
| 4. | Acetic acid | 17 | 118 |
| 5. | 1-propanol | -85 | 97.4 |
| 6. | 2-propanol | -127 | 82.4 |
| 7. | Chloroform | -63 | 622 |
| 8. | DMSO\* | 19 | 189 |

\*DMSO= Dimethyl sulfoxide

**CHARACTERIZATION OF SOLID DISPERSION**

**Detection of crystallinity in solid dispersions**

Solid dispersions encounter a number of molecular structures of the drug in the matrix. To investigate its molecular arrangement, much effort has been put into differentiate between amorphous and crystalline material. For that, many techniques that detect the crystalline material in the dispersion are available. The amount of amorphous material is never measured directly but mostly it is derived from the amount of crystalline material in the sample9,11.

The following techniques are available to detect the degree of crystallinity:

* Powder X-ray diffraction
* Infrared spectroscopy
* Fourier transform infrared spectroscopy
* Water vapour sorption
* Isothermal microcalorimetry
* Dissolution calorimetry
* Differential scanning calorimetry

**Detection of molecular structure in amorphous solid dispersions**

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behaviours are different for solid dispersions that do not contain any crystalline drug particles, i.e. solid dispersions of type V and VI or for type II and III. Apart from their physical state (crystalline or amorphous); the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is one of the important properties of the solid dispersion. Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures.

1. **Using IR or FTIR,** the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than the drug is present in amorphous clusters or other multi-molecule arrangements.

2. Temperature modulated differential scanning calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional differential scanning calorimetry (DSC). Therefore this technique can be used to assess the amount of molecularly dispersed drug, and from that the fraction of drug that is dispersed as separate molecules is calculated9,11.

**APPLICATIONS**

* To enhance the absorption of drug.
* To obtain a homogeneous distribution of a small amount of drug in solid state.
* To stabilize unstable drugs and protect against decomposition by process such as oxidation, hydrolysis, racemisation, photo oxidation, etc.
* To dispense liquid or gaseous compounds.
* To formulate a fast releasing priming dose in a sustained release dosage form.
* To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
* To reduce side effects:

(a). The binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex.

(b). The damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound.

* To mask unpleasant taste and smell.
* To convert liquid compounds into formulations.
* Liquid drugs can be manufactured as solid drug formulations via solid dispersions.
* To reduce pre systemic inactivation of drugs like morphine and progesterone8,9.

**MARKETED PRODUCTS OF SOLID DISPERSION**

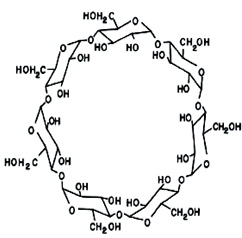
A number of marketed products of solid dispersion are available, in **Table 1.2.4** a few of those products are tabulated11.

**Table 1.2.4: MARKETED PRODUCTS OF SOLID DISPERSION**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.no** | **Product/substance** | **Dispersion polymers or carriers** | **Technology used** | **Company** |
| 1. | Gris-PEG® (Griseofulvin) | PEG | Melt process | Novartis |
| 2. | Cesamet®  (Nabilone) | Povidone | Process unknown | Lilly |
| 3. | Spromax capsules (Itraconazole) | HPMC | Spray layering | Janseen pharmaceuticals |
| 4. | Kaletra (lopinavir and ritonavir) | PVP/polyvinyl acetate | Melt-extrusion | Abbott laboratories |
| 5. | Torcetrapib | HPMC acetate/succinate | Spray drying | Pfizer |
| 6. | Ibuprofen | Various | Melt-extrusion | Soliqs |
| 7. | Isoptin SRE-240 (Verapamil) | Various | Melt-extrusion | Soliqs |
| 8. | Rezulin  (Troflitazone) | PVP | Melt-extrusion | Soliqs |
| 9. | LCP-Tacro (Tacrolimus) | HPMC | Melt-granulation | Lifecycle pharma |
| 10. | Intelene  (Etavirine) | HPMC | Spray drying | Tibotec |
| 11. | Certican  (Everolimus) | HPMC | Melt or Spray drying | Novartis |
| 12. | Afeditab  (Nifedipine) | Poloxamer or PVP | Melt/absorb on carrier | Elan corp |

**1.3. CYCLODEXTRIN COMPLEXATION**

Cyclodextrins (CDs), also known as cycloamyloses, cyclomaltoses and Schardinger dextrins are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity which can accommodate a variety of lipophilic drugs. Cyclodextrins are obtained biotechnologically in large scale by the enzymatic degradation of starch, using glycosyl transferase from *bacillus macerans*. As a consequence of inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably enhanced23.

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**Figure 1.3.1: Chemical structure of cyclodextrin**

**Properties of cyclodextrins**

Cyclodextrins are of three types: α-CD, β-CD and γ-CD, referred to as first generation or parent cyclodextrins. α-, β- and γ-cyclodextrins are composed of six, seven and eight α-(1, 4)-linked glycosyl units, respectively. Among the all β-CD is the most accessible because:

* Its cavity diameter is the best one for guest molecules
* Its production procedure does not require sophisticated technologies and
* It is cheaper.

On the reaction of β-CD in alkaline solution with propylene oxide, a 2-hydroxypropyl group will be connected to one or more hydroxy groups of the β-CD, or to the hydroxy groups of the 2-hydroxypropyl groups already linked to the β-CD molecule. HP-β-CD is very soluble in water. Substitution of the hydroxy groups of β-CD disrupts the network of hydrogen bonding around the rim of β-CD. As a result of this disruption, the hydroxy groups interact much more strongly with water, resulting in an increased solubility as compared with β-CD23,24.

As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping the guest molecules in their internal cavity. No covalent bonds are formed or broken during drug-CD complex formation, and in aqueous solution the complexes readily dissociate and free drug molecules remain in equilibrium with the molecules bound within the CD cavity. **Table 1.3.1** lists the characteristics of α-CD, β-CD, γ-CD and hydroxypropyl-β-CD (HP-β-CD) 25. The main reason for the solubility enhancement in these derivatives is that chemical manipulation frequently transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives23,24.

**Table 1.3.1: Characteristics of α-CD, β-CD, γ-CD and HP-β-CD**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PROPERTY** | **α CD** | **β CD** | **γ CD** | **HP β CD** |
| Number of glucopyranose units | 6 | 7 | 8 | 7 |
| Molecular weight (g/mol) | 972 | 1135 | 1297 | 1193 |
| Solubility in water at 25 ◦C (%, w/v) | 14.5 | 18.5 | 23.2 | >50 |
| Outer diameter (Å) | 14.6 | 15.4 | 17.5 |  |
| Cavity diameter (Å) | 4.7-5.3 | 6.0-6.5 | 7.5-8.3 | 0.78 |
| Height of torus (Å) | 7.9 | 7.9 | 7.9 | - |
| Cavity volume (Å3) | 174 | 262 | 427 |  |
| Crystal water constant (%) | 10.2 | 13.2-14.5 | 8.13-17.7 | 1-2 |
| Diffusion constant (40 0C) | 3.44 | 3.22 | 3.00 | - |
| pK (20 0C) | 12.33 | 12.20 | 12.08 | - |

**INCLUSION COMPLEXATION**

Cyclodextrins are typical host molecules and may trap a great variety of molecules having a size of one or two benzene ring or even large ones carrying a side chain of comparable size, to form crystalline inclusion complexes.

The ability of a cyclodextrin to form an inclusion complex with a guest molecule is a function of two important factors. The first one is stearic which depends on the relative size of the cyclodextrin to the size of the guest molecule or certain key functional groups within the guest. If the guest is of wrong size, it will not fit properly into the cyclodextrin cavity. The second critical factor is the thermodynamic interactions between the different components of the system like cyclodextrin, guest and the solvent. For a complex to form there must be a favourable net energetic driving force that pulls the guest into the cyclodextrin23.

In general, there are four favourable interactions for the inclusion complex formation:

* The displacement of polar water molecules from the apolar cyclodextrin cavity.
* The increased number of hydrogen bonds formed as the displaced water returns to the large pool.
* A reduction of the repulsive interaction between the hydrophobic guest and the aqueous environment.
* An increase in the hydrophobic interactions as the guest inserts itself into the apolar cyclodextrin cavity24.

**FACTORS AFFECTING COMPLEXATION**

• **Steric effects**

Cyclodextrins are capable of forming inclusion complexes with compounds having a size compatible with the dimensions of the cavity. Complex formation with molecules significantly larger than the cavity may be possible only for certain groups that can penetrate into the carbohydrate channel. The three natural CDs namely α, β, and γ have different internal diameters and are able to accommodate molecules of different size. The existence of bulky groups can sterically block entrance of CD cavity. Some groups, depending on their number, flexibility, and position of attachment, may actually act to extend the cavity and to provide a better complexation.

• **Electronic effects**: Electronic effects seem to be more of a factor than stearic effects. The ionic substituents which are too close to the CD cavity adversely disrupt the thermodynamics driving the inclusion complexation.

**• Miscellaneous:** The effect of proximity of charge to CD cavity: Moving the charge away from the cavity re-establishes the complexation characteristics but this is dependent on the charge density in the structure. The effect of charge density and charge state of the CD and drug are important considerations.

**Temperature, additives, and co-solvent effects:** In most cases, as the temperature

increases, the binding constant will decrease24,25.

**RELEASE FROM THE COMPLEX**

Complexation improves the drug’s delivery characteristics and does not interfere with their activity because it is a rapidly reversible process. In aqueous solution, drug: CD complexes are continually forming and dissociating. Although slower kinetics of dissociation is seen with stronger binding, the rates are still fast and essentially instantaneous. After administration, the drug is released from the complex upon dilution, and in some cases with contributions from competitive displacement with endogenous lipophiles, as well as binding to plasma and tissue components. Drug uptake into tissues is not available to the complex, and rapid elimination of the CD occurs.

**Mechanism of drug release from CD complexes**

Different mechanisms play an important role in drug release from the drug-CD complex. Complexation of the drug (D) to CD occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the drug molecule continuously associates and dissociates from the host CD. Assuming a 1:1 complexation, the interaction will be as follows:

D free + CD free DCD complex

Two parameters, the complexation constant (K) and the lifetime of the complex, are very important for the drug release mechanism.

**1. Dilution:** Dissociation due to dilution appears to be a major release mechanism. An example for this was recently reported by Piel *et al*. for miconazole26, a more strongly bounded drug compared to prednisolone, supports the probable role of dilution. Dilution is minimal when a drug-CD complex is administered ophthalmically. Efficient corneal absorption is further exacerbated by contact time.

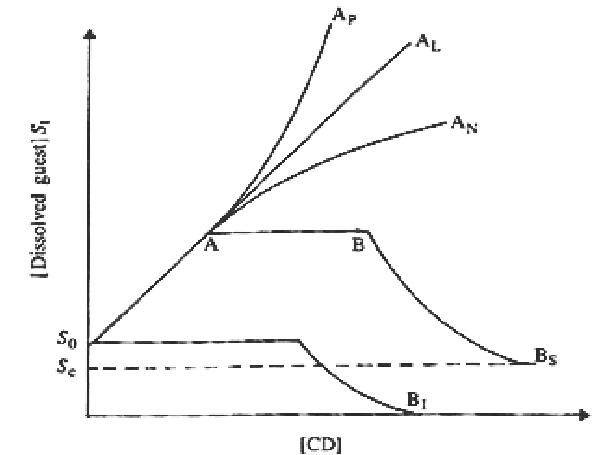
**2. Competitive displacement:** Tokumura *et al*. reported that the β -CD complex of a poorly water-soluble drug, cinnarizine, was more soluble *in vitro* than cinnarizine alone27,28. Based on the *in vitro* dissolution experiments oral administration of the complex showed less bioavailability than expected. It was suggested that cinnarizine was too strongly bound to the CD so that complex dissociation was limiting oral bioavailability. Co-administration of phenylalanine, a displacing agent, improved the bioavailability of cinnarizine from the complex but not from conventional cinnarizine tablets.

**3.** **Protein binding:** Drug binding to plasma proteins may be an important mechanism by which the drug may be released from a drug-CD complex. It is evident that proteins may effectively compete with CDs for drug binding and thus facilitate the *in vivo* release of drugs from drug-CD complexes. Dilution alone may be effective in releasing free drugs from weak drug-CD complexes but when the strength of the binding between the drug and CD is increased, a mechanism such as competitive displacement is at work. Frijlink *et al*. studied the effect of CD on the displacement of both naproxen and flurbiprofen29 from plasma binding sites *in vivo*. They found that tissue distribution of flurbiprofen and naproxen was higher when CD-drug solution was administered compared to drug solution in plasma, 10 minutes after parenteral dose, which indicates that more drugs were free from CD solution to distribute into the tissues than from the plasma solution.

**4. Drug uptake by tissue:** Drug uptake by tissue is one of the potential contributing mechanisms for drug release from CD. When the drug is lipophilic and has access to tissue, and is not available to the CD or the complex, the tissue then acts as a sink, causing dissociation of the complex based on simple mass action principles. This mechanism is more relevant for strongly bound drugs or when the complex is administered at a site where dilution is minimal, e.g., ocular, nasal, sublingual, pulmonary, dermal or rectal sites. For example, CD has been used in ophthalmic delivery of poorly water-soluble drugs to increase their solubility and/or stability in the tear fluid, and in some cases to decrease irritation25,31.

**STUDY OF CD-COMPLEXATION**

The phase solubility method described by Higuchi and Connors is the most widely used approach to study inclusion complexation which examines the effect of a solubilizer, i.e., CD or ligand, on the drug being solubilized, i.e., the substrate. Phase solubility diagrams are categorized into A and B types; A type curves indicate the formation of soluble inclusion complexes while B type suggest the formation of inclusion complexes with poor solubility. A BS type response denotes complexes of limited solubility and a BI curve indicates insoluble complexes. A-type curves are subdivided into AL (linear increases of drug solubility as a function of CD concentration), AP (positively deviating isotherms), and AN (negatively deviating isotherms) subtypes. β -CD often gives rise to B-type curves due to their poor water solubility whereas the chemically modified CDs like HP- β -CD and SBE- β -CD usually produce soluble complexes and thus give A-type systems



**Figure 1.3.2: Theoretical phase solubility diagram**

The most common type of cyclodextrin complexes is the 1:1 drug /cyclodextrin complex (D/CD) where one drug molecule (D) forms a complex with one cyclodextrins molecule (CD)

D +CD K (1:1) D/CD (1)

The value of the stability constant (K1:1) is used to compare the affinity of drugs for different cyclodextrins or cyclodextrin derivatives. The total solubility of drug (St) in aqueous cyclodextrin solution will then be:

St =So+ { K1:1 So / 1+ K1:1 So}[CD]t (2)

Where, S0 is the intrinsic solubility of the drug, i.e. the solubility when no cyclodextrin is present, and [CD]t is the total concentration of cyclodextrin in the aqueous medium.

A plot of St versus [CD]t, according to Eq. (2) (i.e. a phase-solubility profile), will give a straight line with a slope, {K1:1 So/ 1+ K1:1 So } [CD]t less than unity and an intercept (Sin t) equal to S0.

Then K1:1 is calculated from the slope and S0 values from the following formula:

K1:1= Slope/ S0 (1-slope)

However, thus determined K1:1 value is strongly affected by accuracy of the intercept. The feasibility of using cyclodextrins in pharmaceutical formulations can be calculated from K1:1 and S0 25, 31.

**Advantages of complexation**

1. Enhance solubility
2. Enhance bioavailability
3. Enhance stability
4. Simplest to formulate
5. Convert liquids and oils to free-flowing powders
6. Reduce evaporation and stabilize flavours
7. Reduces bad odours and bitter tastes
8. Reduce haemolysis
9. Prevent admixture incompatibilities31,32.

**Disadvantages of complexation**

1. Laborious and expensive methods of preparation
2. Reproducibility of physicochemical characteristics
3. Difficulty in incorporating into formulation of dosage forms
4. Scale-up of manufacturing process and
5. Stability issues31,32.

**APPLICATIONS OF CYCLODEXTRINS**

A few applications of cyclodextrins are summarized in **Table 1.3.2** with examples31,32.

**Table 1.3.2: Applications of cyclodextrins**

|  |  |
| --- | --- |
| **Application** | **Examples** |
| Stabilisation of light- or oxygen-sensitive substances. | Curcumin and β cyclodextrins are used for improvement of water solubility and hydrolytic phytochemical stability of curcumin. |
| Improvement of solubility of substances. | Piroxicam is poorly soluble drug to increase the solubility β cyclodextrins are added. By using steam aided granulation technique. Increased surface area of piroxicam and exposed to dissolution medium |
| Cyclodextrins as permeation enhancers | CDs can also be used a membrane permeability enhancer and stabilizing agents. The permeability through biological membrane is enhanced by the presence of cyclodextrins. |
| Modification of liquid substances to powders | Inclusion complexes between the cinnamomum oil and cyclodextrins were prepared by co precipitation method in different ratios and convert the liquid substances into powders. |
| Protection against degradation of substances by microorganisms | Photochemical Photochemical stability of naproxen and niflumic acid in their liquid inclusion complexes with β- cyclodextrin. Cyclodextrins are used to increase their stability and avoid degradation. |
| Masking of ill smell and taste. | Famotidine is complexed with cyclodextrin to improve the taste of the drug, including polymer like hydroxy propyl cellulose. |

#### MARKETED CYCLODEXTRIN PRODUCTS

#### Availability of many pharmaceutical formulations in market using cyclodextrin as a functional excipient demonstrates the utility of cyclodextrins33 and they are shown in Table 1.3.3.

#### Table 1.3.3: Examples of marketed products containing cyclodextrin

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Route of administration | Trade name | Market |
| β- CD products | | | |
| Benexate HCl | Oral | Ulgut, Lonimel | Japan |
| Dexamethasone | Dermal | Glymesasan | Japan |
| Iodine | Topical | Mena gargle | Japan |
| Nicotine | Sublingual | Nicorette | Europe |
| Nimesulide | Oral | Nimedex, Mesulid | Europe |
| Nitroglycerin | Sublingual | Nitropen | Japan |
| Omeprazol | Oral | Omebeta | Europe |
| PGE2 | Sublingual | Prostamon E | Japan |
| Piroxicam | Oral | Brexin | Europe |
| Tiaprofenic acid | Oral | Surgamyl | Europe |
| HP-β-CD PRODUCTS | | | |
| Cisapride | Rectal | Propulsid | Europe |
| Hydrcortisone | Buccal | Dextocort | Europe |
| Indomethacin | Eye drops | Indocid | Europe |
| Itraconazole | Oral, IV | Sporanox | Europe, USA |
| Mitomycin | IV | Mitozytrex | USA |

**1.4.** **DRUG PROFILES**

**1.4.1. CLOPIDOGREL BISULPHATE**

**Drug name:** Clopidogrel bisulphate

**IUPAC name:** Methyl (2S)-2-(2-chlorophenyl)-2-{4H, 5H, 6H, 7H-thieno [3, 2-c] pyridin-5-yl}acetate

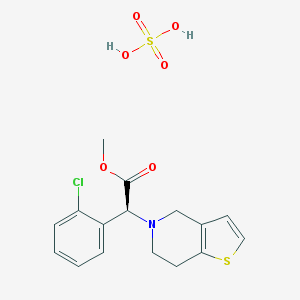
**Molecular formula:** C16H16ClNO2S

**Molecular weight:**  321.822 g/mole

**Category:** Inhibition of platelet aggregation.

**BCS classification:** Class II

**Chemical structure**



**Figure 1.4.1.1: Chemical structure of clopidogrel bisulphate**

**Typical properties**

Melting point: 1580C

Solubility: 0.0118 mg/mL

pKa: 5.14

**Mechanism of action**

Clopidogrel, an inhibitor of platelet aggregation, selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

**Dose:** 75mg, 300mg

**Pharmacokinetics**

**Absorption:** Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. CBS is a prodrug and it is metabolized in liver into inactivated carboxylic acid derivative which is highly protein bound. Active metabolite is a thiol derivative but it has not been identified in the human plasma35, 36.

**Distribution:** Clopidogrel and the main circulating inactive metabolite bind reversibly to human plasma proteins.

**Metabolism:** Hepatic, extensive and rapid, by hydrolysis to the main circulating metabolite, a carboxylic acid derivative, which accounts for approximately 85% of the circulating drug-related compounds. A glucuronic acid derivative of the carboxylic acid derivative has also been found both in plasma and urine. Neither the parent compound nor the carboxylic acid derivative has a platelet inhibiting effect34, 36.

**Elimination:** CBS and its metabolites are excreted in urine and in faeces; after C14 labelled clopidogrel oral administration, about 50% of the drug is eliminated through urine and about 46% from feaces35.

**Side effects:** Dizziness, nausea, constipation, dyspepsia, abdominal pain, nose bleed.

**Contraindications:** Active bleeding**,** hypersensitivity reaction

**1.4.2. DOLUTEGRAVIR SODIUM**

**Drug name:** Dolutegravir sodium

**IUPAC name:** (3S, 7R)-N-[(2,4-difluorophenyl)methyl]-11-hydroxy-7-methyl-9,12-dioxo-4-oxa-1,8- diazatricyclo [8.4.0.0^{3,8}]tetradeca-10,13-diene-13-carboxamide

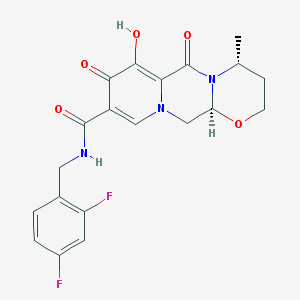
**Molecular formula:** C20H18F2N3NaO5

**Molecular weight:** 441.367 g/mol

**Category:** Anti retroviral drug

**BCS Classification:** Class II

**Chemical structure**



**Figure 1.4.2.1: Chemical structure of dolutegravir sodium**

**Typical properties**

Melting point: 190-193 0C

Solubility: 0.0922 mg/mL

pKa: 8.2

**Mechanism of actions**

DTG is a newly developed human immune deficiency virus (HIV-1) integrase inhibitor; it binds to the active site, blocking the strand transfer step to retroviral DNA integration. This is an essential step of the HIV replication cycle and will result in an inhibition of viral activity37.

**Dose:** 10 mg, 25 mg and 50 mg (once daily)

**Pharmacokinetics**

**Absorption:** DTG is absorbed within 2 to 3 hours post dose and it is increased with co-administration of food. Dosing separation is needed when DTG is to be given together with polyvalent cation containing drugs including cation-based antacids, oral iron supplements, oral calcium supplements, and buffered medication due to DTG’s chelation with polyvalent cations. DTG should be taken 2 hours before or 6 hours after the dose of polyvalent cation-containing drugs38, 39 .

**Distribution:** DTG is highly bound to human plasma proteins and the apparent volume of distribution is 17.4 L41.

**Metabolism:** DTG is highly metabolized through three main pathways and it forms no long-lived metabolites. The first pathway is defined by the glucuronidation by UGT1A1, the second pathway by carbon oxidation by CYP3A4 and the third pathway is what appears to be a sequential oxidative defluorination and glutathione conjugation. The main metabolite found in blood plasma is the ether glucuronide form (M2) and its chemical properties disrupt its ability to bind metal ions, therefore, it is inactive38, 39.

**Elimination:** DTG has a terminal half-life of approximately 14 hours and an apparent clearance of 1.0 L per hour based on population pharmacokinetic analyses41.

**Side effects:** Difficulty falling asleep, headache, stomach pain, gas, diarrhoea 40.

**Contraindications:** Hypersensitivity reaction, co administration with dofetilide 41.

**1.5. CYCLODEXTRIN PROFILES**

**1.5.1. BETA CYCLODEXTRIN**

**Non-proprietary name:** Beta cyclodextrin

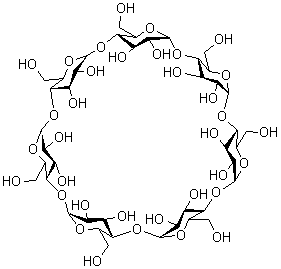
**Synonyms:** β -cyclodextrin, beta-cycloamylose; betadex; betadextrin

**Molecular formula:** C42H70O35

**Molecular weight:** 1134.98 g/mole

**Category:** Stabilizing agent, solubilising agent

**Chemical structure**



**Figure 1.5.1.1: Chemical structure of β-cyclodextrin**

**Description**: Crystalline, non-hygroscopic

**Typical properties**

**Density:** 1.44 gm/ cm3

**Melting point:** 255-264 º C

**Solubility:** Soluble in 200 parts of Propylene glycol, 1 in 50 parts of water at 20 º C, practically insoluble in acetone.

**Stability and storage conditions:** Stable in the solid state and should be kept away from high humidity

**Safety:** β- CD is considered to be nontoxic when taken orally i.e., through tablet and capsule formulations but should not be used in parenteral formulations since it is nephrotoxic42.

**Applications in pharmaceutical technology**

It is widely used to form inclusion complexes with a variety of drug molecules resulting primarily in improvements to dissolution and bioavailability due to enhanced solubility and improved chemical and physical stability. To mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. In oral tablet formulations β-CD may be used in both wet granulation and dry compression process43.

**1.5.2. HYDROXYL PROPYL BETA CYCLODEXTRIN**

**Non-proprietary name:** Hydroxy propyl beta cyclodextrin

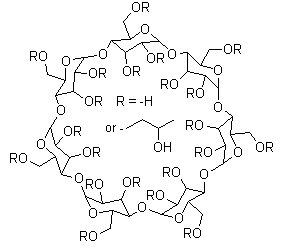
**Synonyms:** 2-Hydroxypropyl beta cyclodextrin, 2-Hydroxypropylether-b-cyclodextrin

**Molecular formula:** [C54H102O39](https://pubchem.ncbi.nlm.nih.gov/search/#query=C54H102O39)

**Molecular weight:** 1375.37 g/mole

**Category:** Stabilizing agent, solubilising agent

**Chemical structure**



**Figure 1.5.2.1: Chemical structure of hydroxyl propyl β- cyclodextrin**

**Description**: Crystalline, non-hygroscopic

**Melting point:** 278 º C

**Solubility:** very soluble in water (> 500 mg/mL at room temperature compared to 18 mg/Ml for β-cyclodextrin).

**Stability:** Stable in bases and weak organic acids, but gets hydrolyzed by strong acids44.

**Safety:** HP-β- CD is also considered to be nontoxic and it does not exhibit nephrotoxicity unlike β-CD42.

**Applications in pharmaceutical technology:** HP-β-CD, like β-CD and other derivatives of β-CD are suitable for molecular encapsulation of a variety of poorly water soluble compounds to enhance the aqueous solubility of the encapsulated compounds. In addition to increase the solubility, the stability of the guest compound can be enhanced and the volatility can be reduced43.

It can be used in oral, rectal, dermal, ocular, and parenteral formulations.

**1.6.** **POLYMER PROFILES**

**1.6.1. POLY VINYL PYROLIDINE K30**

**Non-proprietary name:** Poly vinyl pyrolidine K30

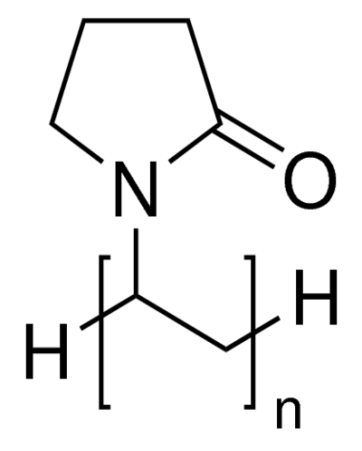
**Synonym:** Plasdone, povidone

**Molecular formula:** (C6H9NO) n

**Molecular weight:** 40,000 g/mole

**Category:** Disintegrant, dissolution aid, suspending agent and tablet binder

**Chemical structure**



**Figure 1.6.1.1: Chemical structure of PVP K30**

**Description:** White crystalline powder

**Typical properties**

**Density:** 1.69 g/cm3

**Melting point:** 150-1800C

**Solubility:** Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

**Stability and storage:** Stable up to 110– 130 °C and darkens at 150 °C, with a reduction in aqueous solubility. Should be stored in an airtight container in a cool and dry place.

**Incompatibilities**

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals 45.

**Safety**

Povidone is nontoxic and non-irritant when absorbed from the gastrointestinal tract or mucous membranes and has no irritant effect on the skin and causes no sensitization47.

**Applications in pharmaceutical technology**

Povidone solutions are used as binders in wet-granulation processes. As a solubilizer in oral and parenteral formulations and to enhance the dissolution of poorly soluble drugs. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspensions and solutions46.

**1.6.2. POLY ETHYLENE GLYCOL 6000**

**Non-proprietary name:** Poly ethylene glycol 6000

**Synonym:** Polyoxyethylene glycol, Macrogol, Polyoxyethylene ether

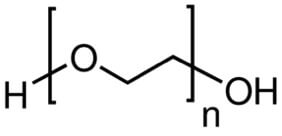
**Molecular formula:** C2nH4n+2On+1

**Molecular weight**: 6000 g/mole

**Category:** Lubricating agent; solubilising agent; coating agent

**Description:** White, waxy or paraffin-like

**Chemical structure**



**Figure 1.6.2.1: Chemical structure of PEG 6000**

**Typical properties**

**Density:** 1.2 g/ cm3

**Melting point:** 58-630C

**Solubility:** Soluble in water, aromatic hydrocarbons and slightly in aliphatic hydrocarbons.

**Stability and storage:** Chemically stable in air and in solution. Should be stored in well closed container in a cool and dry place (≤30ºC).

**Incompatibilities**

PEG exhibits some oxidizing activity due to the two terminal hydroxyl groups45.

**Safety**

They are generally considered as nontoxic and non-irritant materials. However the most serious effects associated with polyethylene glycols are hyperosmolarity metabolic acidosis following the topical use of polyethylene glycols in burn patients48.

**Applications in pharmaceutical technology**

PEGs are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycols liquids are useful as plasticizer in transdermal films45.

**1.6.3. SOLUPLUS**

**Non-proprietary name:** SOLUPLUS

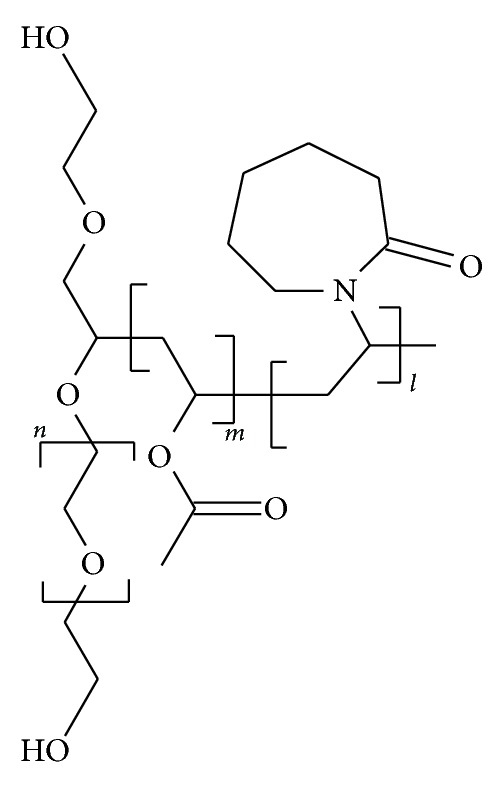
**Chemical name:** Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer

**Molecular weight:** 90,000-1, 40,000 g/mole

**Category:** Solubilizer

**Description:** Free flowing white to slight, yellowish granule with a faint characteristic odour.

**Chemical structure**



**Figure 1.6.3.1: Chemical structure of soluplus**

**Typical properties**

**Density:** 1.08 g/ mm3

**Melting point** : > 58ºC

**Solubility:** Freely soluble in water. Soluble in acetone, methanol, dimethylformamide and ethanol (up to 25%).

**Stability and storage:** The product is stable and it should be stored in a tightly closed container50.

**Incompatibilities**: Incompatible with atmospheric moisture49.

**Application in pharmaceutical technology**

Due to its bifunctional character, it acts as matrix polymer for solid solutions. It is also capable of solubilising poorly soluble drugs in aqueous media.

Used as binder in wet granulation or as a dry binder in direct compression for poorly soluble drugs50.

**1.7. REVIEW OF LITERATURE**

**1.7.1. RECENT RESEARCH WORK ON CLOPIDOGREL AND DOLUTEGRAVIR**

**1. Srinivas M *et al.,*** **(2017)** developed dolutegravir (DTG) sustained release 200mg matrix tablets. Six formulations of DTG 200mg were formulated by direct compression technique using different hydrophilic polymer grades such as carbopol 971G, HPMC K 100M were used as rate controlling polymers in different concentrations and other ingredients are micro crystalline cellulose, talc, sodium stearyl fumarate, before the formulation the granules are evaluated by pre-compression studies. The obtained tablets were evaluated with different post-compression parameters like hardness, friability, thickness, weight variation, drug content and *in vitro* dissolution studies. The formulation F4 was selected as an optimized formulation because it gives best results in terms of *in vitro* drug release in a sustained release manner and best fitted to first order model with R2 value of 0.999. Short time stability studies indicate no appreciable changes in drug content and *in vitro* drug release of optimized formulation of F4 51.

**2. Dahima R, (2016)** prepared self-emulsifying drug delivery system (SEDDS) to improve the oral bioavailability of antiretroviral drug dolutegravir (DTG), a BCS Class II molecule. The SEDDS formulation consisted of DTG, capmul MCM, labrasol, tween 20, propylene glycol & transcutol HP. The saturation solubility study of DTG was conducted in different oils, surfactants and co-solvents. The pseudo-ternary phase diagrams were drawn to identify the self emulsifying regions. The formulation was characterized for droplet size analysis, zeta potential, poly-dispersibility index, and assay, impurities and *in vitro* dissolution behaviour 52.

**3. Masthanamma S K *et al*.,** **(2015)** performed studies to solubilise the poorly water-soluble anti retroviral drug, dolutegravir (DTG) with hydrotropic solubilisation technique. Determination of solubility of the drug in 8 M urea hydrotropic solution and distilled water was carried out at room temperature. There was more than 50-fold enhancement in aqueous solubility of DTG with 8 M urea (as compared to aqueous solubility). Thus, hydrotropic solutions can be used in place of organic solvents (which are pollutants, toxic and give error due to volatility) 53.

**4. Wardhana Y W K *et al.,* (2015)** performed studies to improve solubility and dissolution rate of clopidogrel bisulphate by solid dispersion with various PEG densities (PEG-4000, 6000) and different grade of HPC (HPC-SL & SSL, LHPC-11 & 21). All matrices were prepared by solvent evaporation method and were characterized by FTIR, PXRD, and SEM. Improvement in the solubility was shown by all the matrices, mixed PEG (1:1) has shown the highest solubility than the individual whereas only HPC-SL gave the highest solubility from its different grades54.

5. **Zainab E J *et al*.,** **(2014)** performed studies to enhance the dissolution rate of clopidogrel bisulfate by the preparation of the nanoparticles using antisolvent-precepitation method employing different stabilizers at drug :stabilizer ratio 1:2 alone and in combination and characterized for particle size, drug entrapment efficiency (DEE), dissolution testing, scanning electron microscopy imaging and atomic force microscopy (AFM). Lyophilized nanoparticles were compressed into tablets by direct compression method and later they were evaluated by different methods. Compatibility studies- FTIR, DSC, and PXRD were also done. Amongst all formulations F13,stabilized with PVPK-30 and PVA, showed complete drug dissolution i.e.100% at the end of 10 minutes in both media 0.1N HCL (pH 1.2) and phosphate buffer solution (pH 6.8) and characterized by short disintegration time, high hardness, low friability and produced higher dissolution rate in comparison with the marketed tablet 55.

**6. Jain Aarti M *et al*.,** **(2013)** performed studies to enhance the solubility & dissolution rate of the drug by preparing its complex with PVP K-30, PEG 4000 and HP-β-CD by kneading method. The inclusion complexes were further formulated into tablets by direct compression technique using superdisintegrants like crosspovidone, cross carmellose sodium and sodium starch glycolate. The prepared inclusion complex were characterized using FTIR, DSC and PXRD & finally the prepared tablets were evaluated for various pharmaceutical characteristics viz. hardness, friability, weight variation, drug content and *in vitro* dissolution profiles56.

**1.7.2. RECENT RESEARCH WORKS ON CYCLODEXTRIN AND HYDROPHILIC POLYMERS COMPLEXATION**

**1. Harmanpreet Singh *et al.,* (2017)** performed studies to prepared cinnarizine (CNZ)–β-CD complexes by the kneading, co-precipitation and co-evaporation methods with and without the addition of hydrophlilic polymers (HPMC E5-LV,HPMC- K4M and PVP K-25 & K-30), and to determine the polymers influence on enhancing the CNZ solubility. The presence of hydrophilic polymers in ternary complex system did produce irregular-shaped but smooth-surfaced particles while binary complex system did not. The ternary complexes prepared with HPMC K4M, β-CD and CNZ showed higher solubility efficiency value compared to other tested hydrophilic polymers to make ternary complex systems57.

**2. Sultana H *et al.,*** **(2016)** studied the preparation and evaluation of ternary inclusion complexes of simvastatin (SV) to improve its aqueous solubility, dissolution rate and oral [bioavailability](https://www.omicsonline.org/bioequivalence-bioavailability.php). The inclusion complexes of SV were prepared by kneading method using β-CD and hydrophilic [polymers](https://www.scitechnol.com/polymer-science-applications.php) (PVP, PEG, and HPMC). The dissolution of SV from inclusion complexes was found to be higher than the pure drug. Other SV-β-CD Complexes prepared along with hydrophilic polymers showed higher dissolution than SV-β-CD Complex. The order of hydrophilic polymers enhancing dissolution rate of β-CD complexes was PVP>HPMC>PEG58.

**3. Alexandre C C V *et al.,* (2015)** performed studies to develop and characterize ternary system of efavirenz (EFZ), M-β-CD and PVP K30. The results showed that the solid ternary system provided a large increase in the dissolution rate which was greater than 80%. The use of the ternary system (EFZ, M-β-CD and PVP K30 1%) proved to be a viable, effective and safe delivery of the drug. The addition of the hydrophilic polymer appeared to be suitable for the development of a solid oral pharmaceutical product, with possible industrial scale-up and with low concentration of CDs 59.

**4. Chowdary K P R *et al*., (2015)** performed the studies to enhance the solubility and dissolution rate of ritonavir (RTV) by cyclodextrin complexation along with soluplus and PVP K30 and to evaluate the effects of β-CD, soluplus and PVP K30 on the solubility and dissolution rate of RTV in a series of 23 factorial experiments. The aqueous solubility of RTV was increased linearly as a function of the concentration of β-CD as well as soluplus and PVP K30. The individual and combined effects of β-CD, soluplus and PVP K30 in enhancing the solubility and dissolution rate of RTV were highly significant (P < 0.01). The dissolution of RTV was rapid and higher in the case of RTV-β-CD complex systems when compared to RTV pure drug. Combination of β-CD with soluplus or PVP K30 resulted in a much higher enhancement in the solubility of RTV. Hence complexation of RTV with β-CD – soluplus and β-CD – PVP K 30 is recommended to enhance the solubility and dissolution rate of RTV60.

**5. Ansari M J *et al*., (2014)** performed studies on complexation of silymarin with β-CD alone and in the presence of hydrophilic polymers (PVP, HPMC and PEG 6000) by phase solubility study and to evaluate the feasibility of enhancing the solubility of silymarin. The aqueous solubility of silymarin was linearly increased as a function of the concentration of β-CD alone and in the presence of hydrophilic polymers. Addition of hydrophilic polymers has markedly enhanced the complexation and solubilising efficiency of β-CD in the order PVP > HPMC > PEG 6000. Hence, a combination of β-CD and hydrophilic polymers is recommended for enhancing solubility of silymarin 61.

**6. Chowdary K P R *et al.,*** **(2014)** performed studies in the optimization of irbesartan tablet formulation employing crospovidone, β-CD and PVP K30 by 23 factorial design for enhancing the dissolution rate of irbesartan. Formulation of irbesartan tablets with NLT 85% dissolution in 15 min employing crospovidone, β-CD and PVP K 30 was optimized by 23 Factorial design. Irbesartan tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, and disintegration time and dissolution rate characteristics. The individual and combined effects of β-CD, crospovidone and PVP K30 on the dissolution rate (K1) of irbesartan tablets are highly significant (P<0.01). The optimized irbesartan tablet formulation gave 86.18 % dissolution in 15 min fulfilling the target dissolution set. The dissolution profile of the optimized irbesartan tablet formulation was similar to that of commercial brand (IROVEL-150). Hence the formulation of irbesartan tablets with NLT 85% dissolution in 15 min could be optimized by 23 Factorial design62.

**7. Mammudi V *et al*., (2013)** studied the complexation of isradipine (ISD) with HP-β-CD in the presence and absence of hydrophilic polymers (PVP, HPMC, and PEG). Solid inclusion complexes of ISD-HP-β-CD were prepared in 1:1 and 1:2 ratios by the kneading method, with and without the addition of hydrophilic polymers. The solubility and dissolution rate of ISD were significantly improved by complexation with HP-β-CD. The addition of hydrophilic polymers also markedly improved the dissolution rate of isradipine from HP-β-CD complexes in the order HPMC> PEG> PVP 63.

**8. Annamma Devi *et al.*, (2012)** performed studies on the complexation of efavirenz (EFZ) with cyclodextrins, (β-CD) and (HP-β-CD) alone and in the presence of PVP by phase solubility study and to evaluate the feasibility of enhancing the solubility and dissolution rate of EFZ employing the CD’s alone and with PVP. The aqueous solubility of EFZ was linearly increased as a function of the concentration of β-CD and HP-β-CD alone and in the presence of PVP K30 due to the formation of a 1:1 M complex in solution in each case. HP-β-CD gave higher enhancement in the dissolution rate and efficiency when compared to β-CD. Addition of PVP has markedly enhanced the complexation and solubilizing efficiencies of β-CD and HP-β-CD. The solid inclusion complexes of β-CD and HP-β-CD with PVP gave higher rates of dissolution than those of EFZ and its complexes with CDs alone. Hence a combination of CDs (β-CD, HP-β-CD) with PVP K30 is recommended to enhance the solubility and dissolution rate of EFZ, a BCS class II drug64.

**9. Greice S B *et al.*, (2011)** studied to evaluate the effect of different cyclodextrins (β-CD, M-β-CD, and HP-β-CD) and/or hydrophilic polymers (CMC,HPMC, PEG and PVP) on solubility of daidzein in water. The solubility of daidzein in water was significantly enhanced in the presence of cyclodextrins in the order HP-β-CD > M- β-CD> β-CD and the association of daidzein/cyclodextrin complexes to the hydrophilic polymers was able to improve the solubility of daidzein even further. The highest solubilizing effect was obtained for daidzein/HP-β-CD/PVP ternary system65.

**1.7.3. RECENT ANALYTICAL RESEARCH WORK ON DOLUTEGRAVIR**

**1. Masthanamma S K *et al*.,(2016)** developed a simple, accurate, novel, safe, and precise method could for the estimation of DTG. Spectrophotometric measurements were carried out using Schimadzu double beam(UV-1800 model) ultra violet visible spectrophotometer with 10mm matched quartz cells and water as solvent. Linearity for the method was found in the range of 2-14μg/mL (R2=0.997). Tablet formulation was analyzed and % assay for the absorption maxima was found to be 95.6%.The proposed method was validated as per ICH guidelines. Validated studies demonstrated that proposed method is simple, accurate, precise, specific, rapid, reliable, and reproducible66.

**2. Bhavar Girija B *et al*., (2015)** developed a simple, rapid, precise and accurate spectrophotometric method for quantitative analysis of dolutegravir sodium in tablet formulations. The initial stock solution of DTG sodium was prepared in methanol solvent and subsequent dilution was done in water. The standard solution of drug in the water showed maximum absorption at wavelength 259.80 nm. The drug obeyed Beer–Lambert’s law in the concentration range of 5–40 μg/ml with coefficient of correlation (R2) = 0.9992. The method was validated as per the ICH guidelines. The developed method can be adopted in routine analysis of dolutegravir sodium in bulk or tablet dosage form and it involves relatively low cost solvents and no complex extraction techniques67.

**3. Mallikarjuna Rao N *et al*., (2016)** developed a simple, accurate, specific and rugged reverse phase liquid chromatographic method for the simultaneous estimation of lamivudine, tenofavir & dolutegravir in bulk and tablet dosage form. A reverse phase gradient program has been developed to separate the active ingredients. The ingredients present in different concentrations and chromatographic behaviour 0.05M phosphate buffer PH 6.2±0.05 adjusted with diluted potassium hydroxide solution. Acetonitrile was used as mobile phase. A gradient programming has been done on a reverse C18 column (250mm×4.6mm×5 microns) with a flow rate 1ml/min, monitored at 260nm. The mean retention times of lamivudine, tenofavir and dolutegravir were found to be 2.8, 5.2 and 11.5 min respectively. Linearity of lamivudine, tenofavir and dolutegravir was found to be 27-162 μg/mL, 27-162 μg/mL and 4.5-28 μg/mL 68.

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