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SOLID DISPERSION: A REVIEW

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ABSTRACT

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability range of hydrophobic drugs. In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble. Among all newly discovered chemical entities most of the drugs are lipophilic and fail to reach market due to their poor water solubility and not achieving their full potential. The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs. These reviews encompasses the basic concept about solid dispersion, their advantages, disadvantages, limitations, various types of solid dispersion, criteria of solvent selection, criteria of carrier selection, methods of preparation, characterization, applications and various types of marketed preparations.

1. INTRODUCTION

Administration of drug by oral route is the most common and preferred method of delivery due to convenience and ease of taking drug. From a patient's point of view, swallowing a dosage form is a comfortable and a familiar means of administrating dosage form. As a result, patient compliance and hence drug treatment is typically more effective with orally administered dosage form as compared with other routes of administration, for example, parenteral. Although the oral route of drug administration is preferred, but for many drugs, it can be a problematic and inefficient mode of delivery for a number of reasons. Inadequate drug absorption gives poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route.

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When taking an active agent orally, it must first dissolve in GI fluid before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with low aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two points focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. There are various factors responsible for solubilization of drug such as partical size, temperature, pressure, nature of solute and solvent, molecular size, polymorph etc.

Numerous solid dispersion methods have been demonstrated in the Pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as solvent evaporation, melt granulation technique, use of surfactant(s) and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, each of these techniques have its own limitations. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. The list of poorly water soluble drugs and their solubility profiles as given in Table No. 1.1.

Table No 1.1: List of Poorly Water Soluble Drugs, Category and Solubility Profile

Sr. No.	Drugs	Category	Solubility profile
1.	Ibuprofen	Anti-inflammatory, Analgesic	Ibuprofen is very slightly soluble in water. Less than 1 mg of Ibuprofen dissolves in1 ml of water (<1 mg/ml).
2.	Furosemide	Diuretics	However, it is much more soluble in Alcohol/ water mixtures.
3.	Gliclazide	Anti-diabetic	Soluble in Acetone, sparingly soluble in Ethanol (95%).
4.	Glipizide	Anti-diabetic	Slightly soluble in Ether and Ethanol (95%). Sparingly soluble in Dichloromethane.
5.	Aceclofenac	Anti-inflammatory, Analgesic	Practically insoluble in water, freely soluble in Acetone, soluble in Ethanol (95%).
6.	Indomethacin	Anti-inflammatory, Analgesic	Soluble in Chloroform, sparingly soluble in Ethanol (95%).
7.	Ketoprofen	Anti-inflammatory, Analgesic	Freely soluble in Ethanol (95 %), Chloroform and Ether.
8.	Diclofenac	Anti-inflammatory	Freely soluble in Methanol, Ethanol (95%), sparingly soluble in water and Glacial acetic acid.

This review focuses on the solid dispersion technique of solubilization for the attainment of effective absorption and improved bioavailability. For solubility enhancement solid dispersion is one of the most promising approaches.

The Biopharmaceutical Classification System (BCS) defines four classes of drug substances on the basis of their solubility and permeability characteristic are as fallows.

Class	Permeability	Solubility
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

Solid dispersion technologies are the most promising for improving the oral absorption and bioavailability of BCS Class II drugs.

In solid dispersion drug disperse in the matrix generally a hydrophobic drug is dispersedin a hydrophilic matrix , which forms a solid dispersion. When the solid dispersion is interact with gastrointestinal fluid, the carrier or the polymer which enhance solubility of drug it first dissolves and the drug releases as fine colloidal particles. This results in enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs.[1-8] It also sustained the release of drugs, altered solid state properties, enhance release of drugs from ointment and suppository bases and improved solubility and stability.[9]

1.1 Advantages of Solid Dispersions[10]

The improvement of solubility of poorly water-soluble drug by solid dispersion technology by many way, such as:

1.1.1 Particles with reduced size

Molecular dispersions, as solid dispersion, represent the particle size reduction and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. Due to high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug.

1.1.2 Particles with improved wettability

Enhancement of the drug solubility is related to the drug wettability improvement verified in solid dispersion.

1.1.3 Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. Utilization of linear structure of polymer produces larger and more porous particle as compared with solid dispersions that prepared with reticular polymers. Dissolution rate is higher more the porous nature of the particle.

1.1.4 Drugs in amorphous state

When poorly water-soluble crystalline drugs is in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because during the dissolution process no energy is required to break up the crystal lattice.

1.2 Disadvantages of Solid Dispersions

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes incrystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility. Deteriorating effect

of moisture and temperature have more on solid dispersions than on physical mixtures. In Some cases problem occurred in solid dispersion to easy handling because of tackiness.

1.3 Limitations of Solid Dispersions[11]

The major limitation in the development of solid dispersions is the lack of suitable manufacturing techniques that could be scaled up to commercial production. Problems of solid dispersion involve (i) reproducibility of its physical and chemical properties, (ii) poor stability of dosage form, (iii) aggregation, agglomeration and air adsorption during formulation (iv) decrease in dissolution rate with aging ford (v) difficulty in pulverization and sifting because of their tacky and soft nature.

1.4 Classification of Solid Dispersions[12]

1.4.1 Eutectic Mixtures

Eutectic mixtures differ from solid solutions in that the fused melt of solute-solvent shoe complete miscibility but negligible solid-solid solubility i.e. such systems are basically intimately blended physical mixture of two crystalline components. A phase diagram of two component system is shown in Figure no. 11. When eutectic mixture is exposed to water, the soluble carrier dissolves leaving the in a microcrystalline state which solubilizes rapidly.

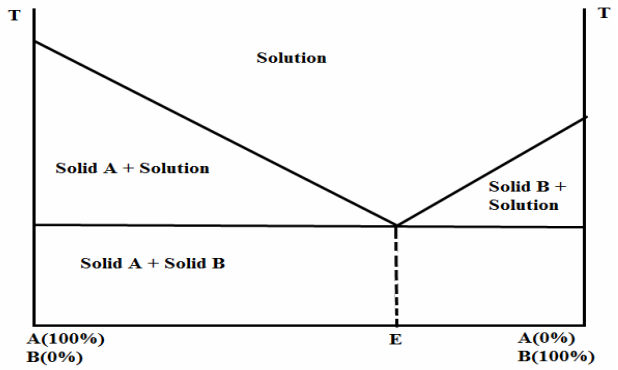

Figure No. 1.1: Simple binary phase diagram showing Eutectic point E. The eutectic composition at point E of substances A and B represents the one having lowest melting point. T_A and T_B are melting points of pure A and pure B respectively.

Examples of eutectic include paracetamol-urea, griseofulvin-urea, griseofulvin-succinic acid, etc. Solid solutions and eutectics, which are basically melts, are easy to prepared and economical with no solvents involved. The method however cannot be applied to:

- drugs which fail to crystallize from the mixed melt,
- thermolabile drugs, and carriers such as succinic acid that decompose at their melting point. The eutectic product is often tacky, intractable or irregular crystals.

1.4.2 Solid Solutions

As per their miscibility of two types of solid solution are classified such as,

i) Continuous Solid Solutions

In that the components are miscible in all proportions. It means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. The schematic diagram of continuous solid solutions is as given in Figure No. 1. 2.

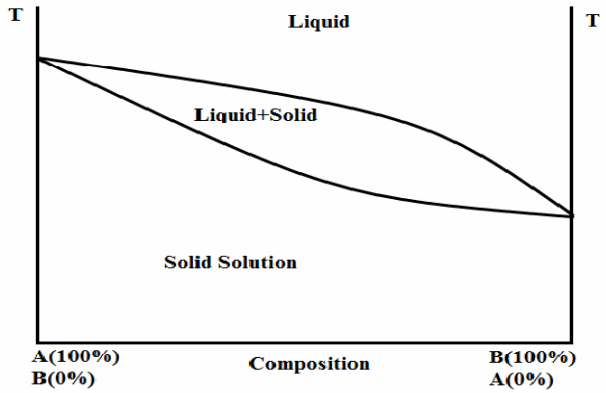

Figure No. 1.2: Hypothetical Phase Diagram of a Continuous

ii) Discontinuous Solid Solutions

In discontinuous solid solutions, the solubility of each of the components is limited in the other component. A typical phase diagram of discontinuous solid solutions as shown in Figure No. 1.3 shows the regions of true solid solutions.

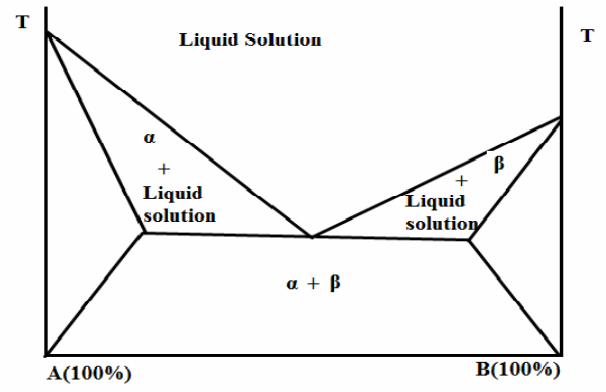

Figure No. 1.3: Hypothetical Phase Diagram of a Discontinuous Solid Solution

In these regions, one of the solid components is completely dissolved in the other solid component. The mutual solubility's of the two components start to decrease, below a certain temperature.

iii) Substitutional Crystalline Solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which in the crystal lattice the solute molecules substitute for solvent molecules. The schematic diagram of substitutional solid solution is shown in Figure No.1.4.

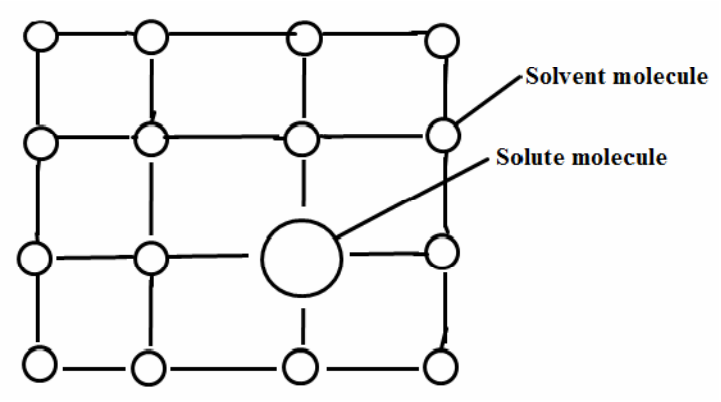

Figure No. 1.4: Substitutional Solid Solution

In that molecules substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

iv) Interstitial Crystalline Solid Solutions

In case of interstitial solid solutions, the interstitial spaces between the solvent molecules in the crystal lattice occupy by the dissolved molecules. The schematic diagram of interstitial crystalline solid solution is as shown in Figure No. 1.5.

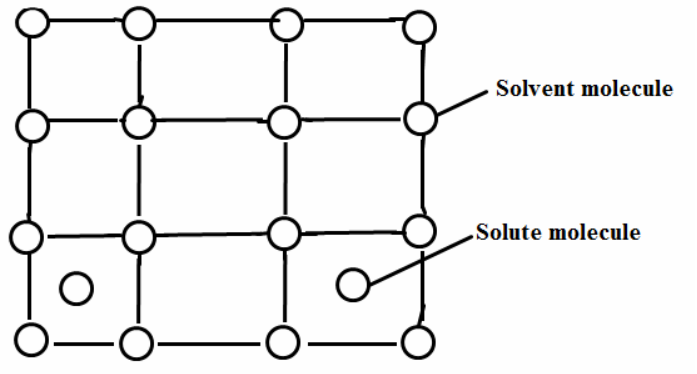

Figure No. 1.5: Interstitial Solid Solution

In interstitial crystalline solid solutions, there is a limit for solute molecule according to solvent molecule, is that molecular diameter of solute molecules is not larger than 0.59 of the solvent molecule's molecular diameter and the volume of the solute molecules should be less than 20% of the solvent.

1.4.3 Amorphous Solid Solutions

In case of amorphous solid solution, within the amorphous solvent the solute molecules are dispersed molecularly but irregularly. The schematic diagram of amorphous solid solution is as shown in Figure No. 1.6.

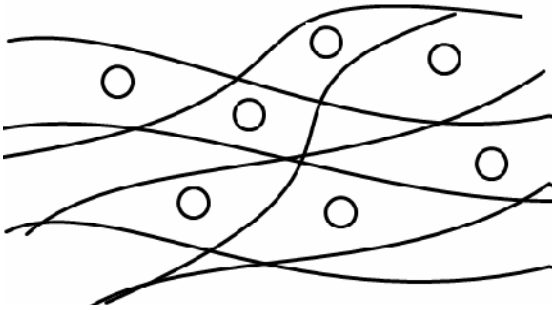

Figure No. 1.6: Amorphous solid solution

Improvement of drug's dissolution properties using Griseofulvin in Citric acid, was the first report about the formation of an amorphous solid solution. Other carriers Sugars such as Sucrose, Dextrose and Galactose, Urea, various Cellulose derivative, organic polymers such as Polyvinylpyrrolidone (PVP), Polyethylene Glycol have been utilized for this purpose.

1.4.4 Glass Solutions and Glass Suspensions

In case of glass solution or the glass suspensions, a homogenous glassy system in which a solute molecules dissolves in a glassy solvent. The meaning of the term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The schematic diagram of variation of enthalpy with temperature is as shown in Figure No. 1.7.

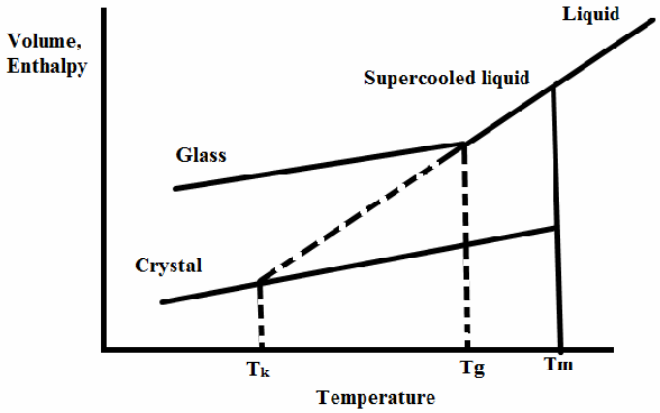

Figure No. 1.7: Schematic Picture of the Variation of Enthalpy with Temperature

By an abrupt quenching of the melt the glassy or vitreous state is usually obtained, characterized by transparency and brittleness below the glass transition temperature.

1.5 Solvents[13]

Solvent used for the preparation of solid dispersion should have the following criteria:

1. Both drug and carrier must be soluble in that particular solvent.
2. Due to the risk of residual levels after preparation toxic solvents to be avoided.
   For example, Dichloromethane and Chloroform
3. Because of the less toxic nature of Ethanol it is used as an alternative.
4. Water based systems are preferred.
5. Care must be taken in to consideration when surfactants are used to create carrier drug solutions because it can reduce glass transition temperature.

1.5.1 Class I Solvents (Solvents to be avoided)

Because of their deleterious environmental effects solvents included in this class are not to be taken in to use. For example, Carbon tetrachloride, Benzene etc.

1.5.2 Class II Solvents (Solvents to be limited)

Theses solvent should be limited used in Pharmaceutical products because of their inherent toxicity. For example, Chloroform, Chlorobenzene etc.

1.5.3 Class III Solvents (Solvents with low toxic potential)

Solvents included in this class may be regarded as less toxic. For example - Acetic acid, Acetone etc, and have the low risk to human health.

1.5.4 Class IV Solvents

(Solvents which have no adequate toxicological data was found)

For the manufacturers of excipients, drug substances or drug products some solvents may also be of interest. For example, Isopropyl ether, Petroleum ether etc.

1.6 Carriers[14]

The physical and chemical nature of the carrier have the major influence on the dissolution profile of the dispersed drug. A carrier should have the following criteria to meet to be suit for increasing the dissolution rate of drug.

Selection of a carrier

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

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. In solvent method solvent should besoluble in a variety of solvents and pass through a vitreous state upon solvent evaporation.

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 drug.

a) First Generation Carriers

Example: Crystalline carriers: Organic acids,Urea, Sugars,.

b) Second Generation Carriers

Example: Polyethylene glycols (PEG), Povidone (PVP), and Polymethacrylates, Cellulose derivatives, such as Ethylcellulose or Hydroxypropylcellulose, Hydroxypropylmethylcellulose (HPMC) or Starch derivates, like Cyclodextrins.

c) Third Generation Carriers

Example: Surface active self emulsifying carriers: Gelucire 4, Poloxamer 408 and Tween 80.

1.7 Methods of Preparation[15-23]

Numerous manufacturing methods for solid dispersions have been reported in literature are as follows.

1.7.1 Solvent Evaporation Method

In this method drug and carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, dried the obtained mass in a dessicator over anhydrous Calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized and sieved through a suitable mesh number sieve. The main advantage of the solvent method is in that the drugs or carriers can be prevented from thermal decomposition. Because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as,

- Higher cost of preparation.
- Complete removal of liquid solvent is difficult.
- On the chemical stability adverse effect of traces of the solvent.
- Common volatile solvent is required.

1.7.2 Fusion /Melting Method

The fusion process is technically the less difficult method of preparing dispersions provided in the molten state the drug and carrier are mixed. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, the sample are poured onto a metallic plate immediately after fusion and it is kept at ice bath. In that process modification is carried out involves spray congealing from a modified spray drier onto cold metal surface. fusion time and rate of cooling is affected by decomposition it should be

avoided. Another way of modification on the above method by closed melting point method wherein solid dispersions of Troglitazone-Polyvinylpyrrolidone (PVP) K-30 have been prepared. In this method controlled mixing of water content to physical mixtures of Troglitazone PVP K-30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. To produce solid dispersion with 0% apparent crystallinity this method is reported.

1.7.3 Lyophillization (Freeze-drying) Technique

In freeze-drying technique transfer of heat and mass to and from the product under preparation. Lyophillization is a technique of molecular mixing where the drug and carrier are co-dissolved in that solvent in which both drug and polymer is soluble, frozen and sublimed to obtain a lyophilized molecular dispersion.

1.7.4 Hot Melt Extrusion

Hot-melt extrusion (HME) process has been used since 1930 in plastic industry. Extrusion can be simply defined as the process of forming a new material by forcing it through an orifice or die under controlled conditions, such as feed-rate, pressure, temperature, and mixing. Utilization of HME technique in the formulation development of poorly water soluble because of the enhanced dissolution properties, absorption and therapeutic efficacy. The main advantage of this technique include no requirement of solvent polymers itself act as binders.

1.7.5 Coating on Sugar Beads using Fluidized Bed-Coating System

This method involves a fluidized bed-coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. Coating on sugar beads using fluidized bed-coating system can be applied for both controlled and immediate-release solid dispersions. For example, Itraconazole (Sporanox oral capsules).

1.7.6 Electrostatic Spinning Method

In this technology, solid dispersion technique is used in combination with Nanotechnology. In this method, a liquid stream of drug/polymer solution is exposed to a potential of 5-30 Kv. The fibres of submicron diameter are formed and the formed fibers are collected on the screen after evaporation of the solvent.

This technique is mostly used because it is simple and cheap, has potential for the preparation of nanofibres and is utilized for the preparation of solid dispersion in future. The limitation of this method is that it is less economical for all drugs and carriers.

1.7.7 Spray Drying

It is one of the most widely used techniques in the preparation of solid dispersion. Th1 drug and carrier are dissolved or suspended and the solvent is removed by spraying it into a stream of heated air. Van Drooge prepared a solution of Diazepam and Povidone and then sprayed into liquid nitrogen and then lyophilized. As compared to freeze-drying this technique is 40-50 times less expensive, so it is cost-effective and simple.

1.7.8 The use of Surfactant

The interest to use surface active agent and self emulsifying carriers for the solid dispersion of poorly soluble drugs increased in recent years. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension because of this unique property surfactants have attracted the attention of investigators for preparation of solid dispersions. Gelucires a new class of surfactant was recently introduced which identify by melting points and HLB values, it consisting of Mono-, Di- and Triglycerides and of Mono and Di Fatty acid esters of Polyethylene glycol (PEG) derived from natural vegetable Fatty acids and having amphiphilic character and it is widely used in the formulation of semi solid dispersions.. Low HLB value of Gelucire can be employed to decrease the dissolution rate of drugs and higher HLB ones for instant release. Gelucire 50/13 and Gelucire 44/14 are two examples of this synthetic group where 14 and 13 represent HLB values while 44 and 50 represent melting point of Gelucire respectively. A commonly used surfactant, results in improvement of dissolution and bioavailability of poorly water soluble drug attributed to solubilization effect of surface active agent is Polysorbate 80, it also ensures complete release of drug in metastable finely dispersed state having large surface area.

1.7.9 Inclusion Complexes/Complexation

Complexation is another means of improving the aqueous solubility of insoluble compounds. These are dispersions in which a drug forms a complex with an inert water soluble carrier in the solid state. The release of the drug depends on the solubility and stability constant of the complex and the absorption rate of the drug. The dissolution rate of the drug and oral absorption are believed to be enhanced by formation of a water soluble complex with a high dissociation constant.

Cyclodextrins (CD) are the most frequently used complex carriers in the inclusion complexation technique. Cyclodextrins are cyclic (α-1, 4) linked Oligosaccharides of α-D-Glucopyranose containing a relatively hydrophobic central cavity and hydrophilic exterior surface. The parent molecule of CD consist of 6, 7 or 8 Glucopyranose units and are referred

to as alpha (α-), beta (β-) and gamma (γ-) Cyclodextrin respectively. Cyclodextrin forming a cavity of which the interior is rather hydrophobic, whereas the exterior is highly hydrophilic. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the Cyclodextrin while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water soluble Cyclodextrin-drug complex is formed. By Cyclodextrin-drug complexation solubility of the various poorly water soluble drugs can be increased.

1.7.10 Nano-Suspension

A Pharmaceutical nano-suspension is biphasic systems consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. In nanosuspensions the particle size distribution of the solid particles is usually less than one micron with an average particle size ranging between 200 and 600 nm.

There are various methods for preparation of nanosuspension include, High Pressure Homogenization in non-aqueous media (Nanopure), High Pressure Homogenization in water (Dissocubes), Media Milling (Nanocrystals) and combination of Precipitation. The list of some nanotechnology approaches as given in Table No. 1.2.

Table No. 1.2. Nanotechnology Approaches to Improve the Solubility of Hydrophobic Drugs

Sr. No.	Nanoparticulate Technologies	Description
1.	Nanocrystal	Nanocrystal drug particles (<1,000 nm) produced by wet-milling and stabilized against agglomeration through surface adsorption of stabilizers; applied to NMEs, for example aprepitant/ reformulation of existing drugs, for example Sirolimus.
2.	Biorise	Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilized with biocompatible carriers.
3.	IDD (Insoluble Drug Delivery)	Micro-nm particulate/droplet water-insoluble drug core stabilized by phospholipids; formulations are produced by impaction, high shear or cavitations.
4.	(Calcium Phosphate-based nanoparticles)	To improve oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvant.

1.7.11 Alternative Strategies

Various other approaches also used for the preparation of solid dispersion as given as follows:

- **Physical Mixture Method**

The physical mixture of drug with carrier was prepared by simple mixing with spatula. This resulting mixture was passed through sieve no. 80. The powder was stored in a screw cap container at room temperature.

- **Co-grinding Method**

The mixture of drug with carrier was prepared by grinding the required amount of drug and carriers for 45 min in a mortar with pestle until a homogeneous mixture was obtained. This resulting mixture was sieved through a 85 mesh screen. The powder was stored in a screw cap container at room temperature.

- **Kneading Method**

A mixture of drug and polymer (in different ratios) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar dried this paste under vacuum for 24 hours and passed through sieve no. 60 and stored in a dessicator until further evaluation.

- **Supercritical Fluid Technology (SCF)**

SCF techniques can be adopted for the preparation of solvent free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Super critical fluid is the one where substances existing as a single fluid phase above their critical temperature and pressure. Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. The most commonly used SCF is Carbon dioxide because it is chemically inert, non toxic and non flammable. The supercritical region of hypothetical compound is as given in Figure No. 1.8.

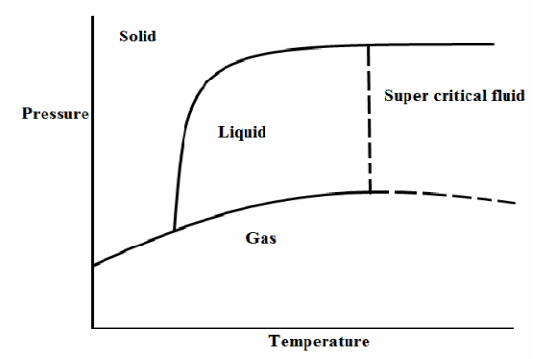

Figure No. 1.8: Supercritical Region of a Hypothetical Compound

1.8 Evaluation and Characterization of Solid Dispersion[24-29]

1.8.1 Physical Appearance

It includes visual inspection of solid dispersions.

1.8.2 Percent Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of formulation. Practical yield (PY) can be determined from the following equation by collecting and weighing solid dispersions appropriately,

PY (%) = [Practical Mass (Solid dispersion) /Theoretical Mass (Drug + Carrier)]×100

1.8.3 Drug Content

Analysis of drug content is carried out by taking definite amount of solid dispersion and it dissolved in a suitable solvent in which drug is freely soluble, then after appropriate dilution concentration are measured by UV Spectrophotometry.

1.8.4 Aqueous Solubility Studies

Aqueous solubility studies of drug, was carried out to evaluate the possible solubilizing effect of the carrier by adding an excess of drug to 10 ml of aqueous solutions containing increasing concentrations of polymer, and shaken at 25°C in a temperature controlled bath for 72 hrs. The suspensions were filtered, diluted suitably and drug concentrations were assessed spectrophotometrically. The apparent stability constant (Kc) of the drug-polymer was calculated according to the following equation.

$$Kc=slope/S0\times1-slope$$

1.8.5 Dissolution Studies

The method involves comparing the *in-vitro* dissolution rates of the solute component from a constant surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition. It tells whether the solid dispersion has improved the dissolution rate or not and also tells the degree of crystallinity, if it is carried out under standard conditions. Dissolution studies are the most significant evaluation parameter for any solid dosage form.

1.8.6 Drug Carrier Compatibility

To analyze the interactions drug and carrier interactions this study is performed and also to identify the physical nature of solid dispersions. The methods used for this purposes are as follows,

1.8.6.1 Fourier Transform Infra red (FTIR) Spectroscopy

To rule out drug and carrier interaction infra red studies were carried out in formulation of solid dispersion by Potassium bromide disc method using Infrared spectrophotometer.

1.8.6.2 Differential Scanning Calorimetry

The DSC thermograms were recorded using the instrument differential scanning calorimeter. Within the range of 2-5 mg of each sample was heated in an open aluminum pan from 30-300° C at a scanning rate of 10° C/min under a stream of nitrogen.

1.8.6.3 X-ray diffraction studies

The XRD pattern of pure drug exhibits sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The XRD patterns of the physical mixture are simply a superimposition of each component with respect to the peaks of drug. The lack of sharp peaks in the diffractograms of solid dispersions indicates that the drug is in the amorphous form in these dispersions.

The quantity required for the characterization of solid dispersion by various techniques is as given in Table No. 1.3.

Table No. 1.3: Analytical Method for Characterization of Solid Forms

Method	Material required per sample
Differential scanning Calorimetry	2-5 mg
Infrared spectroscopy	2-20 mg
X-Ray powder diffraction (XRD)	500 mg
Scanning Electron Microscopy	2 mg
Thermogravimetric analysis	10 mg
Dissolution/Solubility analysis	mg to gm

1.9 Applications of Solid Dispersion[30]

The solid dispersion technique may have numerous Pharmaceutical applications, which should be further explored, apart from absorption enhancement. It is possible that such a technique be used:

- In solid state obtaining a homogeneous distribution of a small amount of drug.
- Stabilizing the unstable drug.
- Dispensing a liquid or gaseous compounds in a solid dosage.
- Formulation of a fast release primary dose in a sustained released dosage form.
- Formulation of sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

- By reducing pre-systemic inactivation of drugs like Morphine and Progesterone.
- Conversion of polymorphs into solid solution, isomorphous, eutectic or molecular addition compounds in a given system.

Some of the marketed product which is prepared by solid dispersion as given in Table No.1.4.

Table No. 1.4: Several Marketed and Late Stage Drugs are Designed for Improved Solubility by Solid Dispersion[31]

Name of drug	Technology involved	Year of approved	Brand name	Company name
Griseofulvin	Melt process	1975	Gris-PEG	Wander
Amprenavir	Melt process	2011	Agenerase	Glaxo Smith Kline
Calcitriol	Melt granulation	2009	Rocaltrol	Roche
Cyclosporine	Spray freeze drying	2007	A/I neural	Novartis
Indomethacin	Fusion and mold technique	2009	Indomethacin	Eisai Co

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