International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 191-202 www.ijprajournal.com ISSN: 2249-7781

Solubility Enhancement of Drugs

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Submitted: 01-01-2022 Accepted: 10-01-2022

ABSTRACT
Solubility is an important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Among all newly discovered chemical entities most of the drugs are lipophillic and fail to reach market due to their poor water solubility. The solubility behavior remains one of the most challenging aspect informational development. Hence various techniques are used for the improvement of solubility of poorly water soluble drugs which include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency micellar solubilization, hydrotrophy etc. Of all these approaches solid dispersion have attracted tremendous interest as an efficient means of improving the dissolution rate and hence the bioavailability to arrange of hydrophobic drugs. This article reviews the various preparation techniques and types of solid dispersion based on molecular arrangement. Finally some of the practical aspects have also been considered for the preparation of dispersions.

Keywords: Solubility, Need of solubility enhancement ,Solubilization, techniques of solubility enhancement,bioavailability.

I. INTRODUCTION

Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable.

The BCS is a scientific framework for classifying a drug substance based on aqueous solubility and intestinal permeability. When combined with the in-vitrodissolution characteristics of the drug product the BCS takes into account 3 major factors:

a. solubility,
b . intestinal permeability
c. dissolution rate

all of which govern the rate and extent of oral drug absorption from solid-oral dosage form .

The BCS has proven to be an extremely useful guiding tool for the prediction of in-vivoperformance of drug substances and development of new drug delivery system to suit the performance of drug in the body as also for the regulation of bioequivalence of drug product during scale up and post approval. It classifies the drug into four classes.

high permeability high solubility class 1	high permeability low solubility class 2

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low permeability high solubility class 3	low permeability low solubility class 4

Class	Solubility	Permeability	Absorption Pattern	Examples	Challenges in Drug Delivery
I	High	High	Well absorbed	Diltiazem Propranolol Metoprolol	No major challenges for immediate release forms but CR forms need to limit drug release or dissolution since absorption of released drug is rapid.
II	Low	High	Variable	Nifedipine Carbamazepine Naproxen	Formulations are designed to overcome solubility or dissolution problems by various means (see later sections of this chapter).
III	High	Low	Variable	Insulin Metformin Cimetidine	Approaches are employed to enhance permeability (see later sections of this chapter).
IV	Low	Low	Poorly absorbed	Taxol Chlorthiazide Furosemide	Combination of strategies used for Class II and Class III drugs are employed to improve both dissolution and permeability.

Class V drugs: are those that are metabolically or chemically unstable thus limiting their bioavailability. The various approaches to overcome these problems are aimed at enhancing their stability by use of methods such as –

- Prodrug design.
- Enteric coating (protection from stomach acid).
- Enzyme inhibition or lymphatic delivery (to prevent presystemic metabolism).
- Lipid technologies.

Due to this major reason solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility .

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous in interaction of two or more substances to form a homogenous molecular dispersion. The saturated solution is the one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality. Volume fraction and mole fraction. Drug solubility is the maximum contraction of the drug solute dissolved in the solvent under specific condition of the temperature, pH and pressure. The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate.

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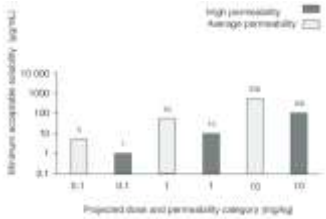
Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over



The pharmacopoeia lists solubility in terms of number of millilitres of solvent required to dissolve 1 gm of solute. If exact solubilties are not known, the pharmacopoeia provides general terms to describe a given range.

Need of Solubility Enhancement:

Drug absorption from the gastrointestinal tract can be limited by a variety of factors, most significant contributors being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally it must first dissolve in gastric and / or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation.

Hence, two areas of pharmaceutic research that focus on improving the oral bioavailability of active agents include;

1. enhancing solubility and dissolution rate of poorly water-soluble drugs
2. enhancing permeability of poorly water soluble drugs poor aqueous solubility is caused by two main factors .

1. High lipophillicity
2. Strong intermolecular interactions which makethe solubilization of solid energetically costly.
3. Solubility of active pharmaceutical ingredients (API's) has always been a concern for formulators, since inadequate aqueous solubility may hamper development of products and limit bioavailability of oral products.

Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across the biological membrane, the main pathway for drug absorption is a product of permeability and solubility.

Among the five key physicochemical screens in early compound screening pKa, solubility, permeability, stability and lipophillicity, poor solubility tops the list of undesirable compound properties. Currently only 8% of new drug candidates have both high solubility and high permeability

SOLUBILISATION

The process of solubilization involve the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Various Techniques for Solubility Enhancement:

Various technologies have arisen to meet the challenge posed by insoluble compounds and these technologies have made a different too. The techniques that are used to overcome poor drug solubility are discussed under

I. Chemical modification

1. pH adjustment
2. Salt formation
3. Co-crystallization
4. Co-solvency
5. Hydrotropic
6. Solubilizing agents

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7. Nanotechnology

II. Physical modifications:
1.Particle size reduction
a. Micronization
b. Nanosuspension

2. Modification of the crystal habit
a. Polymorphs
b. Pseudopolymorphs

3. Complexation
a. Use of complexing agents

Solubilization by surfactants
a. Microemulsions
b. Self microemulsifying drug delivery system

5. Drug dispersion in carriers.
a. Solid solution
b. Solid dispersion

I. Chemical Modification:

1. pH Adjustment: Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parental administration. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compounds types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophillic poorly soluble compounds .

Advantages:

- Simple to formulate and analyse .
- Simple to produce and fast track .
- Uses small quantities of compound .
- Amenable to high throughput evaluations.

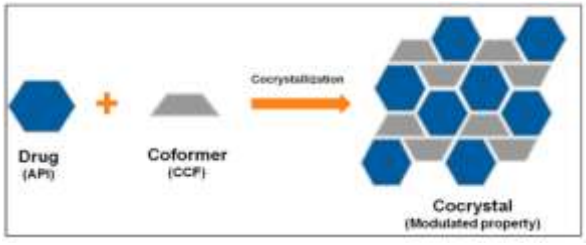
Disadvantages:
Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously it may lead to emboilli, orally it may cause variability.
The selected pH may accelerate hydrolysis or catalyze other degradation mechanism.

2. Salt Formation:
It is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drugs converted in salt having more solubility than respective drugs eg., Aspirin, theophyline, Barbiturates.

It is generally accepted that a minimum difference of 3 units between the pKa value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are water soluble than parent drugs

3. Co-Crystallisation:
It is also referred to as molecular complexes. If the solvent is an integral part of the network structure and forms at least 2 component crystal then it may be termed as co-crystal. A co-crystal may be defined as crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. Only three of the co-cystallizing agents are classified and generally recognized as safe. It includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical application.

Co-crystallisation between two active pharmaceutical ingredients has also been reported such as aspirin or acetaminophen. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals.



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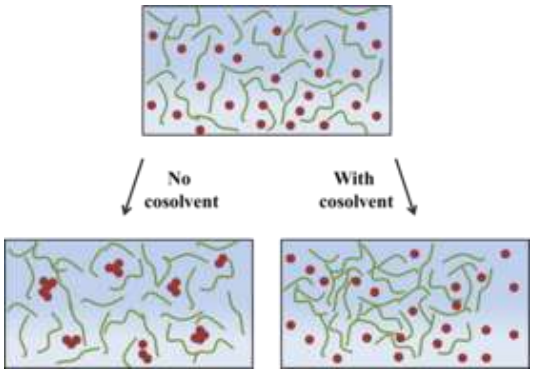
Co-crystals
can be prepared by evaporation of heteromeric solution, sublimation, growth from the melt, and slurry preparation. It is an alternative to salt formation, particularly for neutral compounds .

4. Co-Solvency: The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has a good solubility known as cosolvents.
Cosolvents are mixtures of water and/ or more water miscible solvent used to create a solution with enhanced solubility for poorly soluble compounds eg., of solvents used in co-solvent mixture are PEG 300, propylene glycol or ethanol .



Dimethyl sulfoxide (DMSO) and dimethyl acetonamide (DMA) have been widely used as cosolvent because of their large solubilization capacity of poorly soluble drugs and their relatively low toxicity .

Advantages:
Simple and rapid to formulate and produce.

Disadvantages:
As with all the excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size.
As with all solublized forms, the chemical stability of the insoluble drug is worse than in a crystalline state

5. Hydrotropy:
Hydrotropy is a solublization
phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solution of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium nitrate have been observed to enhanced the aqueous solubilities of many poorly water – solubledrugs.

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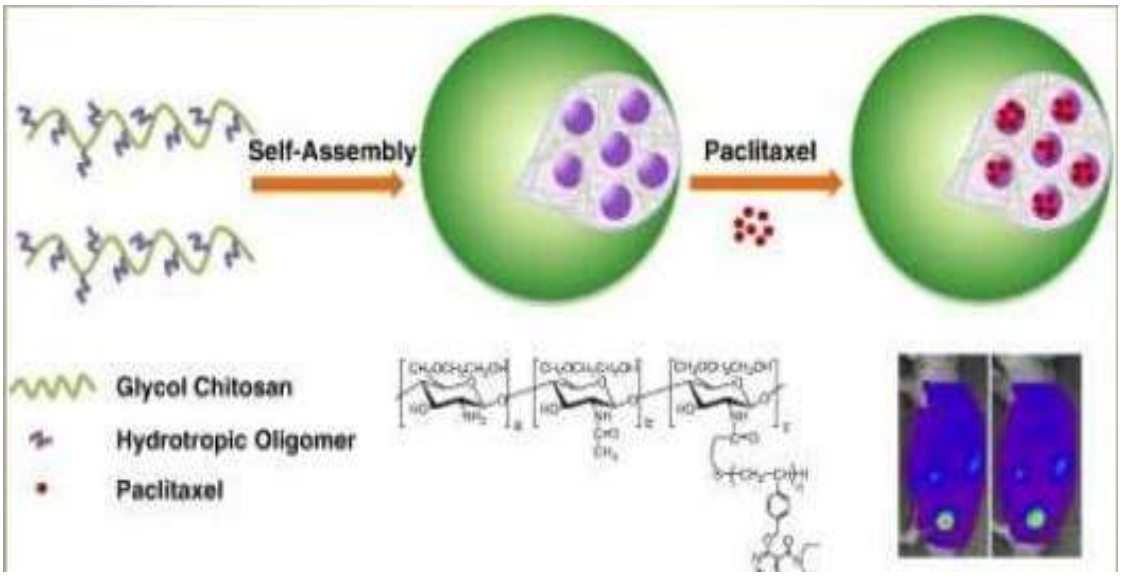

enhanced the solubility of five poorly water soluble drugs, diazepam, griseofulsin, progesterone-17-estradiol and testosterone, in the presence of nicotinamide and related compounds.
All solubilities were found to increase in a non-linear fashion as a function of nicotinamide concentration.

a. Mixed Hydrotrophy:
It is a phenomenon to increase the solubility of poorly water soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosages form of water insoluble drugs and to reduce concentration of individual hydrotropic agents to minimize the side effects.

Advantages:
It is superior to other solubilization methods such as miscibility, micellar solubilization, cosolvency and salting in because the cosolvent character is independent of pH, has high selectivity and does not require emulsification.
It only requires mixing the drug with the hydrotrope in water.
It does not require chemical modification of hydrotropic drugs, use of organic solvents, or preparation of emulsion system.

6. Solubilizing Agents:
The solubility of poorly soluble drug can also be improved by various solubilizing materials ex. PEG 400 is improving the solubility of hydrochlorthiazide.

7. Nanotechnology :
refers broadly to the study and use of materials and structures at the nanoscale level of approximately, 100 nanometers (nm) or less 35, Nanonisation is a process whereby the drug powder is converted to nanocrystals of size 200-600 nm eg. Amphotericin

B. the basic technologies currently in use to prepare nanoparticles are
a. Milling
b. Homogenization in water (wet milling as in a colloid mill).
c. Homogenization in non-aqueous media or in water with water-miscible liquids.
d. Precipitation.
e. Cryo-vaccum method.

II. Physical Modification:
1. Particle Size Reduction:
The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The effect of particle size on solubility can be described by .;
Log S/ S0 = 2 V/ 2.303 RTr
Where,
S = solubility of infinitely\ large particles
S0 = solubility of five particle, V = molar volume,
g = Surface tension of the solid,
r = radius of fine particle.

Particle size reduction can be achieved by

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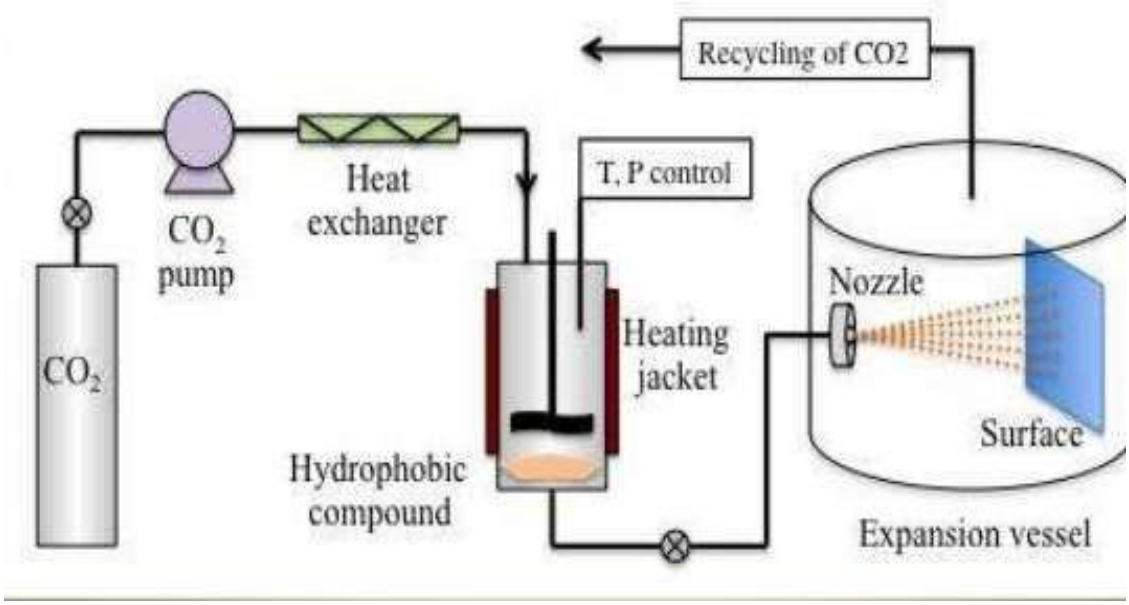
micronisation and nanosuspension.

a. Micronisation: In micronisation, the solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug micronization is done by milling techniques using jet mill, rotor, stator, colloid mills etc., micronisation is not suitable for drugs having a high dose number because a does not change the saturation solubility of the drug .

b. Nanosuspension: Is another technique to achieve particle size reduction and have been employed for drug including tarazepide, atovaquone, amphotericin-B, paclitaxel and bupravaquon. Nanosuspensions are prepared by homogenization and wet milling process.

c. Supercritical fluid process:

A supercritical fluids are dense non-condensable fluid whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp) allowing it to assume the properties of both a liquid and a gas. Through manipulation of the pressure of SCFs, the favourable characteristics of gases - high diffusivity, low viscosity and low surface tension may be imparted upon the liquids to precisely control the solubilisation of a drug with a supercritical fluid.



Advantages :
Low excipient to drug ratio is required. Generally crystal forms are chemically and physically more stable than amorphous particles. \ Formulations are well tolerated provided that strong surfactants are not required for stabilization.

Disadvantages:
Due to high surface charge on the discrete small particles, there is a strong tendency for particle agglomeration.
Developing a solid dosages form of high pay load without agglomeration is difficult.

2.Modifications of crystal habit.

Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form on drug is always more suited than crystalline form due to higher energy associated and increased surface area. The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

- They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is Amorphous > metastable polymorph > stable polymorph
- Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

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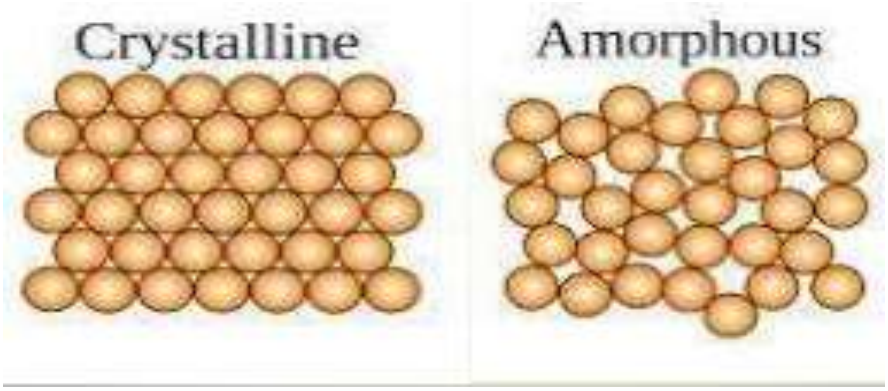
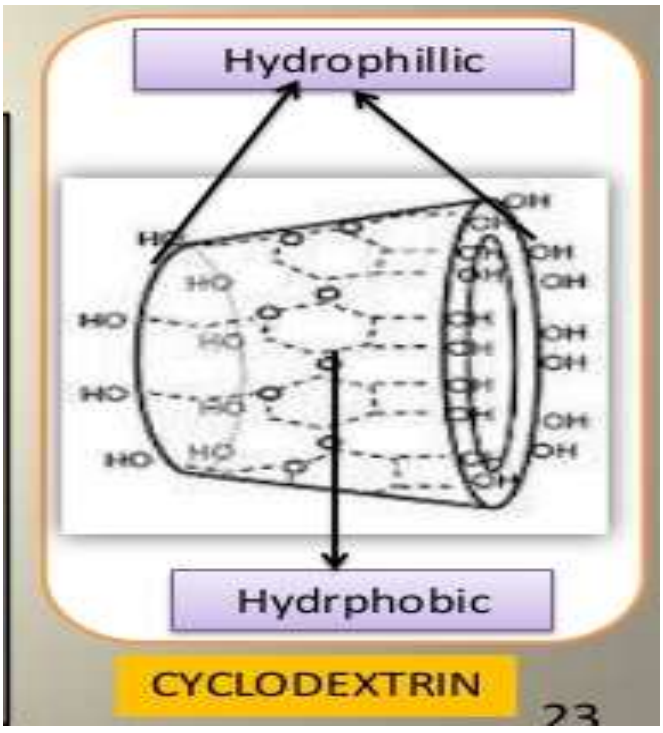


3. Complexation:

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. It relies on relatively weak forces such as London forces, hyd4rogen bonding and hydrophobic interactions. There are many types of complexing agentsInclusion Complexation: These are formed by the insertion of the non-polar molecular or the non polar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The cavity of host must be large enough to accommodate the guest and small enough to eliminate the water.



- The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex. Three naturally occurring CDs are alpha Cyclodextrin, beta Cyclodextrin , and game Cyclodextrin.

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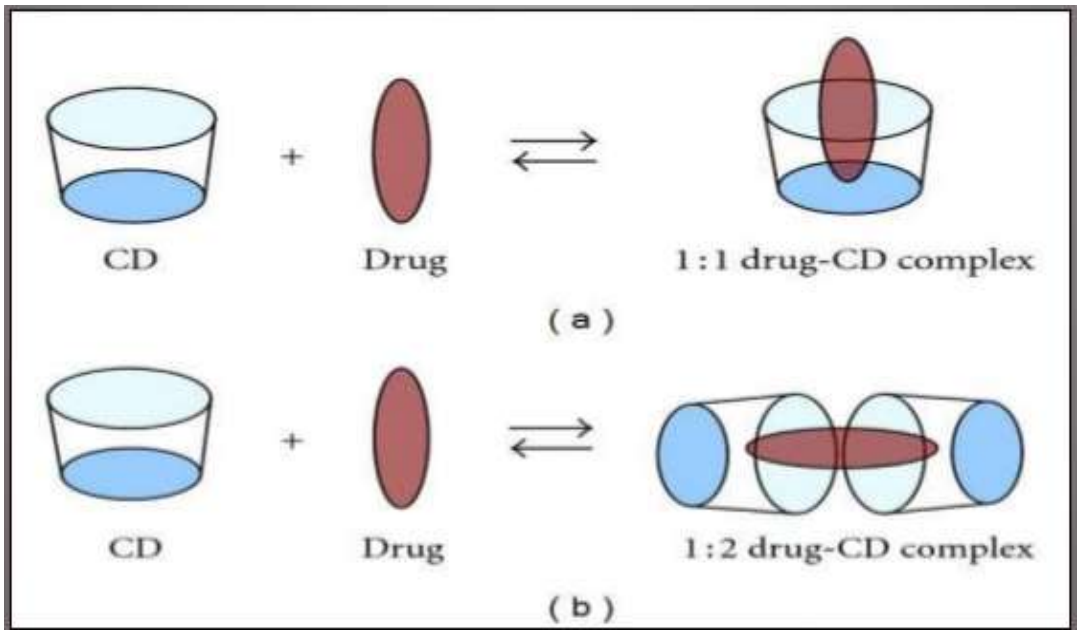
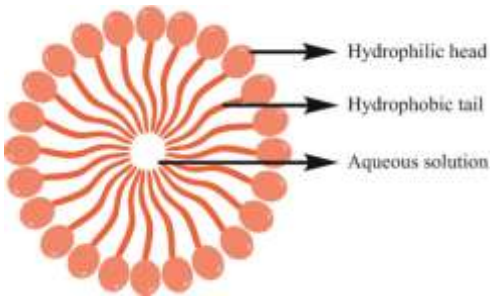


4. Solubilization by surfactants: Surfactants are very useful as absorption enhancer and enhance both the dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.



- Microemulsion : A micro emulsion is a four-component system composed of external phase, internal phase, surfactant and co surfactant . The addition of surfactant, which is predominately soluble in the internal phase unlike the co surfactant, results in the formation of an optically clear, isotropic thermodynamically stable emulsion. It is termed as micro emulsion because of the internal phase SO1 micron droplet diameter
- The surfactant and the co-surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages:

- Ease of preparation due to spontaneous formation.
- Thermodynamic stability,
- transparent and elegant appearance,
- enhanced penetration through the biological membranes,
- increased bioavailability and
- less inter- and intra-individual variability in drug pharmacokinetics.

5. Drug dispersion in Carriers:

The three means by which the particle size of a drug can be reduced to submicron level are use of solid solution, use of eutectic mixture, use of solid

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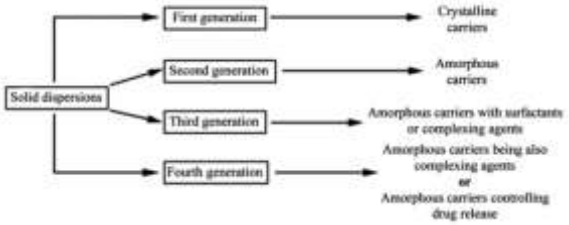
dispersion.

a. Solid solution: A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since, the two compartments crystallize together in ahomogenous one phase system – solid solution are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solution show greater aqueous solubility and faster dissolution than eutectic and solid dispersion. They are generally prepared by fusion method. Such system prepared by fusion are called as melts. These systems are classified as continuous solid solutions, substitutional solid solutions and interstitial solid solutions .

b. Solid Dispersion: Solid dispersion refers to a group of solid products consisting at least two components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline amorphous. The drug can be dispersed molecularly in amorphous particles (cluster) or in crystalline particles . Rigelman in their classic review, defined these system as the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method.



Manufacturing Process:

Melting and solvent
evaporation methods are the two major processes of preparing solid dispersions .

1. Melting Method (Fusion): The melting or fusion method proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted.

The melted mixture is then solidified rapidly in an ice bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved .

MeltrexTM is a patented solid dispersion manufacturing process, manufactured on the basis of the melting process. This technology makes use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range. This technique is applied to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture.

Advantages :
Simplicity and economy
This method precludes the use of toxic solvent and its subsequent removal

Disadvantages :
Many substances decompose or evaporate at high temperature Thermal degradation or instability at melting point Solid-solid transformation may occur on spontaneous freezing of melting components
Immiscibility of carrier and drugs may lead to irregular crystallization
Evaporation and oxidative degradation can be avoided by heating in a close system under vacuum or inert atmosphere

2. Solvent Evaporation Method: In this method , the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to a constant weight .

Advantages:
Thermal degradation of drugs or carriers can be prevented
High melting carrier can be utilized
Disadvantages:
Higher cost of preparation
Difficulty in completely removing liquid solvent
Selection of common volatile solvent
The possible adverse effect of traces of solvent on chemical stability

3. Melt Solvent Evaporation Method : This method includes the addition of given amount of drug into fixed amount of solvent taken, then the solution is incorporated into the

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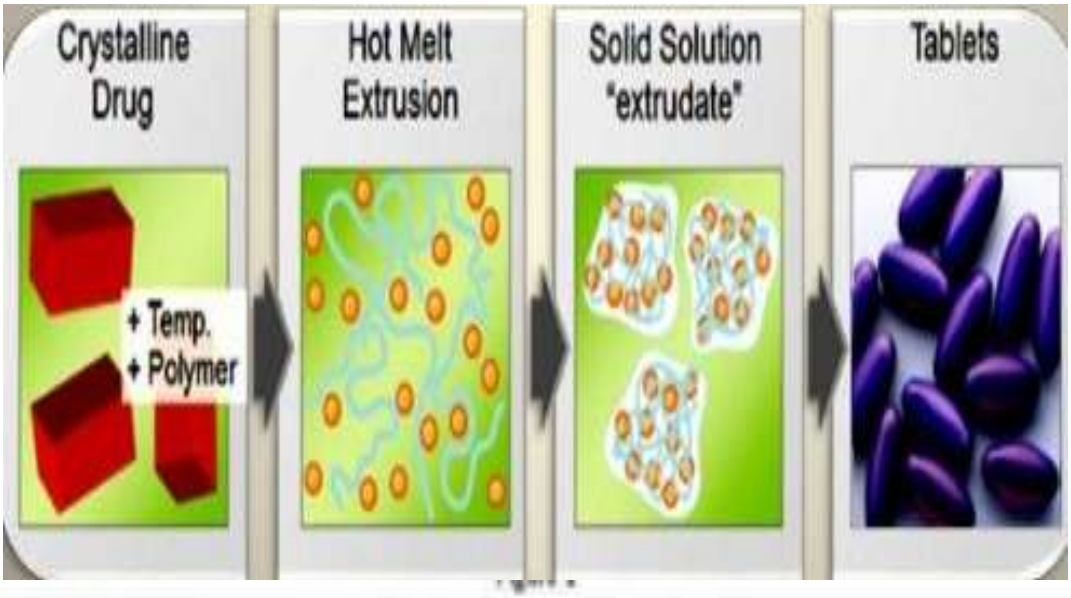
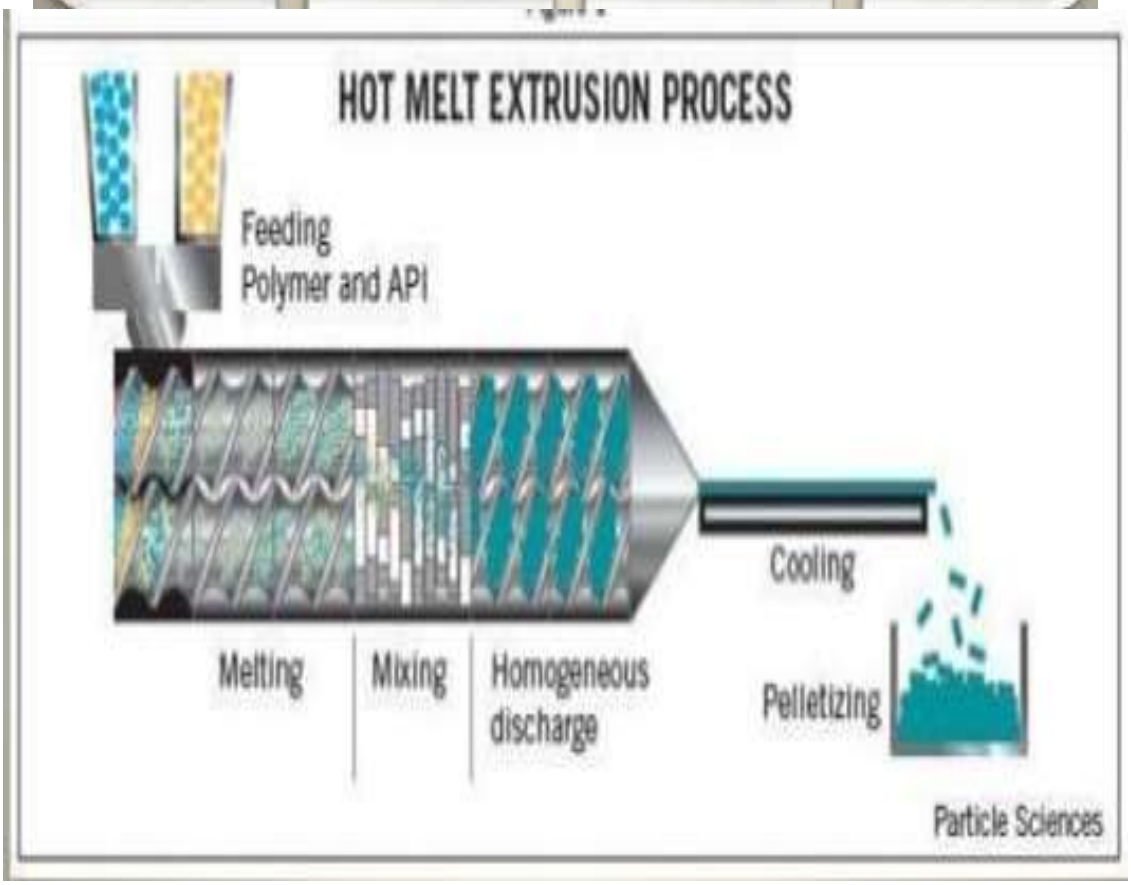
melted form of polyethylene.





II. CONCLUSION :

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the mostchallenging aspects of drug development. Most of the promising newer chemical entities are poorly watersoluble which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersion systems have been

realized as extremely useful tools in improving dissolution properties of poorly water soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been applied to overcome the limitations and make the preparation practically feasible. Although, there are some hurdles like scale up and manufacturing costs to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs. Many techniques are available for solubility enhancement like micronization, Nanonization, supercrystal fluid recrystallization, use of surfactant, evaporation precipitation, Sono-crystallization, Nanomorph technology and solid dispersion. Carriers are plays active role in solid dispersions

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