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AN OVERVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY SOLUBLE DRUGS AND SOLID DISPERSION AS AN EMINENT STRATEGIC APPROACH

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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.

INTRODUCTION: Almost more than 90% drugs are orally administered . Drug absorption sufficient and reproducible bioavaiblity, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.

More than 90% of drugs approved since 1995 have poor solubility [1]. It was estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble and not well absorbed after oral administration [2, 3] which can distract from the drugs inherent efficacy [4-6].

Drug absorption, sufficient and reproducible bioavaiability and/or pharmacokinetic profile in human are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the model list of essential medicines of the World Health Organization (WHO) are assigned BCS classification on the basis of data available in the public domain. Of the 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable and 6 (10%) to class IV (Poorly soluble, poorly permeable). The rate and extent of absorption of class II and IV compounds is highly dependent on the bioavailability which ultimately depends on solubility [7].

The BCS is a scientific framework for classifying a drug substance based on aqueous solubility and intestinal permeability. When combined with the *in-vitro*

dissolution characteristics of the drug product the BCS takes into account 3 major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid-oral dosage form .[8] The BCS has proven to be an extremely useful guiding tool for the prediction of *in-vivo* performance 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 (**Fig. 1**).

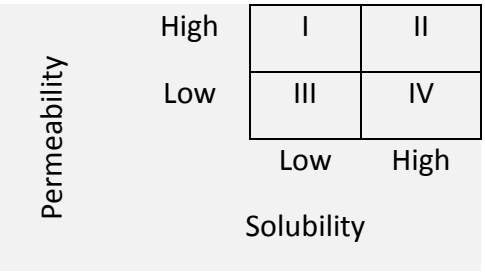

FIGURE 1: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

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 [9].

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 [10].

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. These descriptive terms are listed in **Table 1**.

TABLE 1 : EXPRESSION FOR APPROXIMATE SOLUBILITY [11]

Descriptive terms	Relative amounts of solvents to dissolve 1 parts of solute
Very soluble	< 1`
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10000
Insoluble or practically insoluble	> 10000

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; enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs [12]. Poor aqueous solubility is caused by two main factors [13].

1. High lipophillicity
2. Strong intermolecular interactions which make the solubilization of solid energetically costly.

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 [13].

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 following major headings [14, 15];

I. Chemical modification
    1. pH adjustment
    2. Salt formation
    3. Co-crystallization
    4. Co-solvency
    5. Hydrotropic
    6. Solubilizing agents
    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
    4. 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 [16-19].

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.

Commercial Products: Phenytoin injection (Epanutin® ready mixed, Pfizer) 50 mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na^+ per 5 ml ampoule).

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 [20]. 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

Disadvantages:

- High reactivity with atmospheric carbondioxide and water resulting in precipitation of poorly water soluble drug, epigastric distress due to high alkalinity.

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 [21]. 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 [14].

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. [22]. 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 [23-26]. 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 [27-29].

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.

Commercial products: Nimodipine intravenous injection (Nimotop ® Bayer) and Digoxin elixir Pediatric (Lanoxin ®, GSK).

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 – soluble drugs [30].

   Rasool *et al*., [31] 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.

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. In place of using large conentration of one hydrotrope a blend of say 5 hydrotropes are used in $1/5^{th}$ concentration reducing their individual toxicities [32].

Mechanism of Hydrotope Action: Hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. They do not have a critical concentration above which self aggregation starts to occur (as found for micelle) instead they aggregate in a stepwise self - aggregation process, gradually increasing aggregation size [33].

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 [34]. 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 [36];

- Milling
- Homogenization in water (wet milling as in a colloid mill).
- Homogenization in non-aqueous media or in water with water-miscible liquids.
- Precipitation.
- Cryo-vaccum method.

Nanomorph: The nanomorph technology is to convert drugs substances with low water solubility from a course crystalline state into amorphous nanoparticles without any physical milling or grinding procedures. Here the suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent.

This leads to precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth [37].

Nanosuspension: These are colloidal dispersion of nanosized drug particles stabilized by surfactants. They are biphasic systems consisting of pure drug particles dispersed in an aqueous vehilcle in which the diameter of the suspended particle is less than 1 µm in size [38].

Advantages:

- It is useful for molecules with poor solubility, poor permeability or both.
- The reduce particle size helps in intravenous administration of poorly soluble drugs without blockade of the blood capillaries.
- The nanosuspension can be lyophilized or spray dried and also incorporated in a solid matrix.

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 [39];

$$\text{Log } S/ S_0 = 2 \gamma V/ 2.303 RTr$$

Where, S = solubility of infinitely\ large particles, S_0 = 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 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 [40].

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.

Advantages [41]:

- 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.
- Technically development of sterile intravenous formulation is even more challenging.

Commercial products: Rapamycin (Rapamune, 1 mg and 2 mg tablets, Wyeth). Sometimes sonocrystallization techniques is also used for particle size reduction [42]

2. **Modification of Crystal Habit:**

a. Polymorphs: depending upon the internal structure, a solid can exist either in a crystalline or amorphous form (**fig. 2**). When a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as polymorphism. Polymorphs are of two types:

- **Enantiotropic** is the one which can be reversibly changed into another form by altering the temperature and pressure *eg*. Sulphur.
- **Monotropic** is the one which is unstable at all temperatures and pressure *eg*. Glyceryl stearates. The polymorphs differ from each other with respect to their physical properties such as solubility, melting point, density, hardness and compression characteristics (Fig. 2).

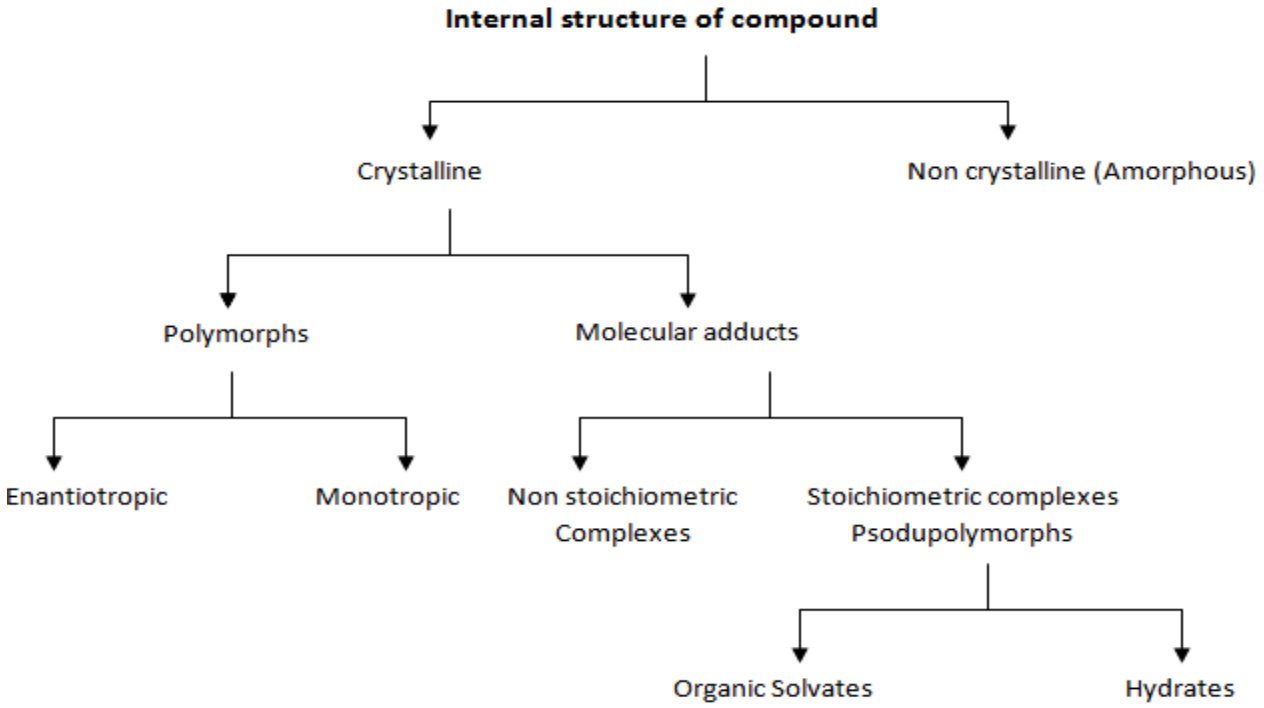

FIG. 2: CLASSIFICATION OF INTERNAL STRUCTURE OF A COMPOUND

Polymorphs can further be stable or metastable. Metastable polymorphs have high energy state, lower melting points and higher aqueous solubility as compared to stable and so are more preferred in formatulation since they have better bioavailability eg., of the three polymorphic forms chloramphenicol Palmitate A, B and C, B shows best bioavailability.

The amorphous forms have greater aqueous solubility than the crystalline form because energy required to transfer a molecule from crystal lattice is greater than that required for noncrystalline solid eg., amorphous novobiocin is 10 times more soluble than crystalline. Thus, the order for dissolution of different solid forms of drugs is Amorphous > metastable polymorph > stable polymorph. Melting followed by rapid cooling or recrystallisation from different solvents can produce metastable forms of a drug.

a. **Pseudopolymorphs:** The stoichiometric type of adducts where the solvent molecules are in corporate in the crystal lattice of the solid are called are the solvates and the trapped solvent as solvent of crystallization. The solvates can exist in different crystalline forms called as pseudopolymorphs and the phenomenon is called as pseudopolymorphism. When the solvent in association with the drug is water, the solvate is known as hydrate.

   Generally, a solvate has grater aqueous solublility than the hydrate because the hydrate the less energy for crystal break up in comparison to solvate eg,. anhydrous form of theophylline and ampicillin have higher aqueous solubilities then their monohydrate and trihydrate focus respectively. On the other the hand, the organic solvate have greater aqueous solubility than the non solvates [43, 44].

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 agents (**Table 2**).

TABLE 2: LIST OF COMPLEXING AGENTS

Types	Examples
Inorganic	I_B^-
Coordination	Hexamine Cobalt (III) Chloride
Chelates	EDTA, EGTA
Metal - Olefin	Ferrocene
Inclusion	Cyclodextrins, Choleic acid
Molecular Complexes	Polymers

Staching Complexation: These are formed by the overlap of the planar regions of aromatic molecules. Non polar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This cause some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favoured by large planar non polar regions in the molecule stached complexes can be homogenous (self association) or mixed (complexation) eg., Nicotinamide, Anthracene, Pyrene, Methylene Blue [45].

Inclusion 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 [46]. The most commonly used host molecules are cyclodextrins. Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes can be formed simply by adding the drug and the excipient together, resulting in enhanced drug solubilization. Cyclodextrins are a group of structurally related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface.

Cyclodextrin consisting of 6, 7 and 8 D-glucopyranosyl units connected to α-1, 4 glycosidic linkage are known as α, β, γ cyclodextrins, respectively. Hydrophilic cyclodextrins are non toxic in normal doses while lipophilic may be toxic, methyl, hydroxyl propyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use [46]. Derivatives of β- cyclodextrin (HP – β-CD) are most commonly used in pharmaceutical formulation. Cyclodextrin complexes have shown to increase the stability, wettability and dissolution of many lipophillic drugs [47]. Cyclodextrins can also be used as membrane permeability enhancer and stabilizing agents [48].

Approaches to make Inclusion Complexes:

- Physical blending method
- Kneading method [49]
- Co-precipitation technique
- Solution/ solvent evaporation
- Neutralization precipitation method
- Milling/ cogrinding technique [50]
- Atomization / spray drying method [51]
- Lyphilization [52]
- Microwave irradiation method [53]
- Supercritical antisolvent technique [54]

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.

    a. **Microemulsions:** The term microemulsion was first used by Jack H. Shulman in 1959. A. microemulsion is a four component system composed of external phase, internal phase, surfactant and co-surfactant. The addition of surfactant in the internal phase unlike the cosurfactant results in the formation of and optically clear, isotropic , thermodynamically stale emulsion. It is termed as microemulsion because of the internal or dispersed phase < 0.1 µ droplet diameter. The surfactant and co-surfactant alternative each other and form a mixed film at the interface, which contributes to the stability of the microemulsion [55]. Non ionic surfactants, such as tweens and labrafil with high hydrophilic-lipophilic balances are often used to ensure immediate formation of o/w droplets during production.

    b. **Self Microemulsifying Drug Delivery Systems** (**SMEDDS**): SMEDDS are anhydrous system of microemulsion. It has also been referred to as microemulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. This agitation comes from stomach and intestinal motility [56]. The surfactant can be non ionic like poly oxyethylene surfactants eg., Brij. or sugar esters like sorbitan mono-oleate (span 80), cationic or anionic like alkyl trimethyl ammonium bromide and sodium dodecyl sulphate, or zwitteronic such as phospholipids like lecithin.

    Lecithin is popular because it exhibits excellent biocompatibility. Combination of ionic and non ionic surfactants are also very effective [57]. Most self emulsifying drug delivery system are limited to administration in liquid filled soft or hard shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shall and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the campus shell [58]. Emulsion droplet size is a major factor influencing bioavailability of drugs form emulsion formations, since SMEDDS contain high concentration of surfactants , they should be limited to short term oral administration due to potential of causing diarrhea [59].

Advantages:

- The pre-concentrates are easy to manufacture.
- Optimal bioavailability and reproducibility and be expected without co-administration of food if microemulsion are well developed.

Disadvantages:

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- These formulation are challenging to validate.
- Tolerability of formulations may be poor in cases where long term chronic administration is intended.

Eg., of some poorly soluble compounds that use micro-emulsion pre-concentrates are HIV Protease inhibitor tipranavir (Aptivus® capsules, Bochringer Ingel Hein Gm BH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral® Capsules, Novartis AG) [60].

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 dispersion.

   a. **Solid solution:** A solid solution is a binary system comprising of a solid solute moleculary dispersed in a solid solvent. Since, the two compartments crystallize together in a homogenous 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 [61].

   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 [62]. Chiou and 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 [63].

The concept of solid dispersion was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of sulfonamide drug and a water soluble carrier in early 1960s [64]. Solid dispersion represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosages forms. They may be also called as solid state dispersions as first used by Mayersohn and Gibaldi or as co-precipitates.

No review of solid dispersion would be complete without a brief description of eutectic mixtures. A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (**Fig. 3**)

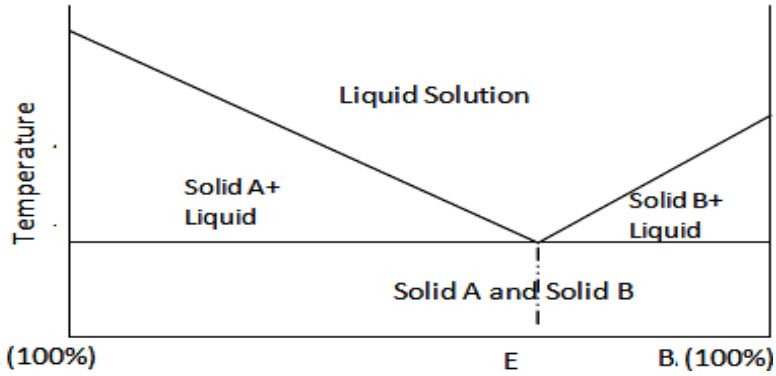

FIGURE 3: PHASE DIAGRAM OF A SIMPLE EUTECTIC MIXTURE WITH NEGLIGIBLE SOLID SOLUBILITY

When a mixture of A & B with composition E is cooled, A and B crystallize out simultaneously, whereas when other composition are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a component of the two compound in order to obtain a physical mixture of very fine crystals of the two component. When a mixture with composition E, consisting of slightly soluble drug and an inert highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing the very fine crystals of the drug resulting in enhanced dissolution rate and improved bioavailability.

Classification [65]**:** Solid dispersion are classified as shown are classified in **Fig. 4**.

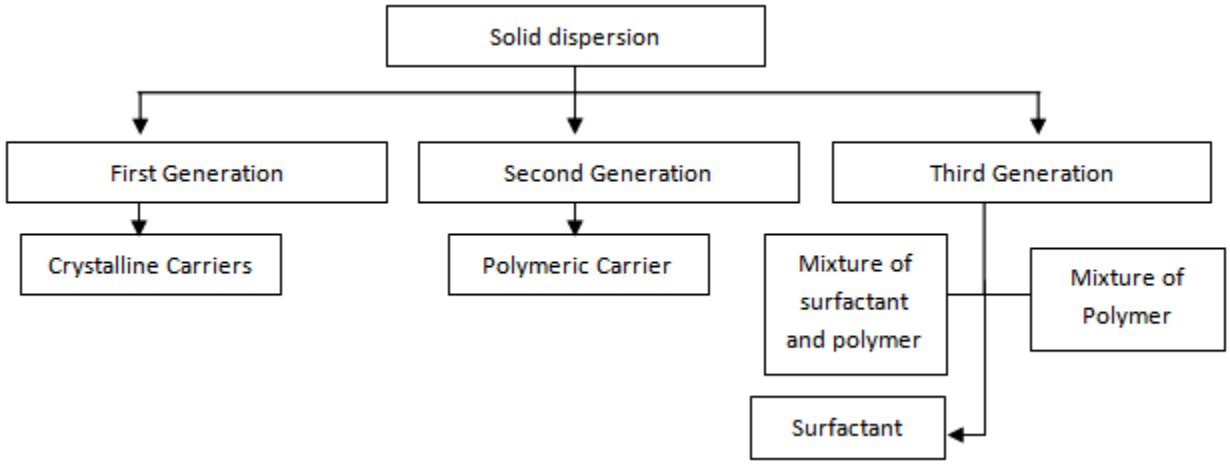

FIG. 4: CLASSIFICATION OF SOLID DISPERSION

Manufacturing Process: Melting and solvent evaporation methods are the two major processes of preparing solid dispersions [66].

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 [67].

Meltrex™ 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 [66].

Advantages [67]:

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

Disadvantages [67]:

- 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

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 [68].

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

Melt Solvent Evaporation Method [67]: This method includes the addition of given amount of drug into fixed amount of solvent taken, then the solution is incorporated into the melted form of polyethylene

glycol below 70°C. This method can be used for thermolabile drugs with high melting points. But it is limited to drugs with a low therapeutic dose, below 50mg.

Alternative approaches to prepare Solid Dispersions:

Melt Extrusion Method: The drug-carrier mixture is typically processed with a twin screw extruder. This mixture is melted and homogenized simultaneously and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. The advantage of this method is that the mixture is only subjected to an elevated temperature for about one minute which is good for thermolabile drugs [69].

Lyophilisation Technique: It involves transfer of heat and mass to and from the product under preparation. In this method drug and carrier are codissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [70].

Melt Agglomeration Process: In this technique the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipient 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) by using a high shear mixer [71].

Spraying on Sugar Beads using Fluidized Bed Coating: This method has been used for both controlled and immediate released solid dispersions. It includes the spraying of drug carrier solution onto the granular surface of excipients or sugar surface to produce granules ready for tableting eg., Itraconazole coated on sugar sphere, is made by layering onto sugar beads a solution of drug and HPMC in an organic solvent of ethanol and dichloromethane [72].

Electrospinning method: This technology is used in the polymer industry and combined solid solution/ dispersion technology with nanotechnology [73]. In this process, a liquid stream of a drug or polymer solution is subjected to a potential between 5 and 30 kv and when the electric forces overcome the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are formed. As the solvent evaporates the fibres can be collected on a screen or a spinning mandril. The fibre diameters depend on surface tension, dielectric constant, feeding rate and electric field strength [74].

Surface Active Carriers: Two of the important surface active carriers are Gelucire 44/14 and vitamin ER-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). A commonly used surfactant, polysorbate 80 mixed with solid PEG has also been used as alternative surface active carrier [75].

Direct Capsule Filling: The filling of semi-solid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. This method helps to avoid grinding induced changes in the crystallinity of the drug. A surfactant must be mixed with the carrier to avoid formation of drug rich surface layer(eg. Polysorbate 80 with PEG, phophatidyl choline with PEG) [76]. The temperature of the molten solution should not exceed 70°C because it might compromise the hard gelatin capsule shell. Triamterene-PEG 500 molten dispersions are filled in hard gelatin capsules using Zanasi LZ 64 capsule filling machine(Zanasi Co., Bologna, Italy) [77]. However, PEG is not a suitable carrier in this method since it dissolves more rapidly than the drug and prevents further dissolution of the drug [78].

Supercritical Fluid Recrystallization: Supercritical fluids (eg., Carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature and pressure, allowing it to assume the properties of both a liquid and a gas. At near critical temperatures, SCFs are highly compressible, allowing moderate changes in the pressure to greatly alter the density and mass transport characteristics of a fluid that largely determines its solvent power. Commonly used SCFs are CO_2, NO, ethylene, propylene, propane, ethanol, ammonia, water, n-pentane.

Advantages:

- It is safe
- It is environmentally friendly
- Economical
- Low operating conditions

Nectar therapeutics and Lavipharm are specializing in particle engineering via SCF technologies [79]. Several methods of SCF processing are precipitation with compressed antisolvents(PCA), gas antisolvent re-crystallisation, rapid expansion of supercritical solutions, precipitation with compressed fluid anti-solvent, solution enhanced dispersion by supercritical fluid, supercritical antisolvant processes(SAS) and aerosol supercritical extraction system(ASES) [80].

Advantages of Solid Dispersions [81, 82]:

- Reduction in particle size results in high surface area resulting in increased dissolution
- Improvement in wettability with carriers with surface activity increases dissolution profile
- Particle with higher porosity are produced and this hastens the drug release profile
- Converts drug from crystalline to amorphous form thus improving the dissolution and bioavailability

Limitations of Solid Dispersions [81, 82]:

- During storage or processing the amorphous state may undergo crystallization
- The method of preparation is expensive and laborious
- Formulation into dosage form is difficult
- Scale up manufacturing process is difficult
- Reproducibility of its physicochemical properties is difficult

Charactersation of Solid Dispersions:

- Powder X-ray diffraction qualitatively detects material with long range order
- Infrared spectroscopy (IR) detects the variation in the energy distribution of interactions between drug and matrix [83]
- Fourier transformed infrared spectroscopy (FTIR) accurately detects crystallinities ranging from 1-99% in pure material [84]
- Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above the glass transition temperature [85]
- Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [86]
- Differential scanning calorimetry is used to detect the amount of crystalline material and the temperatures at which thermal events occur [87]
- Confoccal Raman Spectroscopy, FTIR, IR, Temperature modulated differential scanning calorimetry (TMDSC) are some methods to detect molecular structure in amorphous solid dispersions

Carriers for Solid Dispersions [14]:

Many water soluble excipients are employed as carriers for solid dispersions.

- Acids- Citric Acid, Tartaric Acid, Succinic Acid
- Sugars- Dextrose, Sorbitol, Sucrose, Maltose, Galactose and Xylitol
- Polymeric materials- PEG 4000, PEG 6000, HPMC, CMC, PVP, Guargum, Xanthum Gum, MC, Cyclodextrins, Galactomannon, Sodium Alginate
- Surfactants- Poloxamer, Tweens, Spans, Gelucire 44/14, Deoxycholic Acid, Polyoxyethylene Stearate, Vitamin E TPGSNF
- Miscellaneous- Urethane, Hydroxyalkyl Xanthenes, Pentaerythritol, Urea

Commercially available Solid Dispersion:

1. Gris-PEG (Novartis), griseofulvin in PEG
2. Cesamet (Lily), nabilone in PVP
3. Sporanox (Janssen Pharmaceuticals/ J & J), Itraconazole in HPMC and PEG 20000 sprayed on sugar spheres

4. Solid dispersion of Valdecoxib (NSAID) with PVP by solvent evaporation

5. Terbinafine hydrochloride using PVP K30 by solvent evaporation

6. Surface solid dispersion of Glimepiride using crospovidone, pregelatinised starch, cross-carmellose sodium and avicel PH 101 by solvent evaporation

CONCLUSION : The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Most of the promising newer chemical entities are poorly water soluble 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.

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