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SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY WATER-SOLUBLE DRUGS: A REVIEW

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ABSTRACT
One of the important parameters to achieve desired concentration of drug in blood is drug solubility. A success of formulation development is depending on how effectively it makes drug available for absorption. Among all newly and existing drug candidate about 40 % drugs are lipophilic in nature and fails to reach therapeutic range due to poor aqueous solubility and ultimately it shows slow dissolution and low bioavailability. Selection of solubility enhancement technique depends on drug properties, site of absorption and required dosage form characteristics. This review article covers the area of different conventional and novel approaches of solubility enhancement for poorly water-soluble drugs.

KEYWORDS: Drug solubility, Solubility enhancement, Solid dispersion, Fluidized bed processing.

INTRODUCTION
Despite many advanced dosage forms, the tablet remains the most widely used dosage forms owing to its stability, dose uniformity and user acceptability. Drugs having poor aqueous solubility are one of the major challenges in the dosage form designing. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability. (Patel et al., 2012).

Solubility is defined in quantitative terms (Table 1) 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 interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is 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. (Kumar and Murtaza, 2012).

Table 1: Pharmacopeial standards description of solubility.

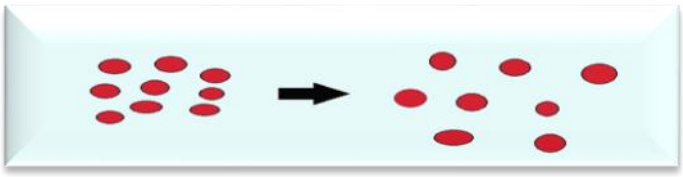
Descriptive term	*Part of solvent required per part of solute as per Indian Pharmacopeia*	*Approximate volume of solvent in milliliter per gram of solute as per British Pharmacopeia*
Very soluble	Less than 1	Less than 1
Freely soluble	From 1-10	From 1-10
Soluble	From 10-30	From 10-30
Sparingly soluble	From 30-100	From 30-100
Slightly soluble	From 100-1000	From 100-1000
Very slightly soluble	From 1000-10000	From 1000-10000
Practically insoluble	10000 or more	More than 10000

Process of Solubilization
The progression of solubilization comprises the breaking of inter-ionic or intermolecular bonds in the solute, providing space in the solvent for separating the molecules of the solvent, intercommunication between the solvent and solute molecules or ions.

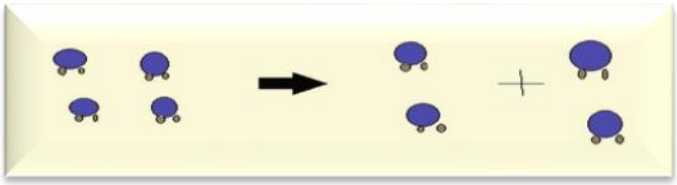
Solubilization process (Fig. 1) takes place by breaking of intermolecular bonds in solute and separation of the molecules of the solvent to provide space in the solvent for the solute.

Process of solubilization takes place in three stages: (Patel et al., 2017)

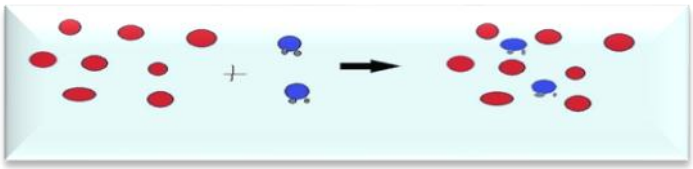
- ✓ Holes open in a solvent
- ✓ Molecules of the solid breaks away from the bulk
- ✓ The freed solid molecule is integrated into the hole in the solvent.



Step: 1 Holes open in a solvent.



Step: 2 Molecules of the solid breaks away from the bulk.



Step: 3 The freed solid molecule is integrated into the hole in the solvent.

Fig 1: Process of Solubilization.

Factors Affecting on Solubilization

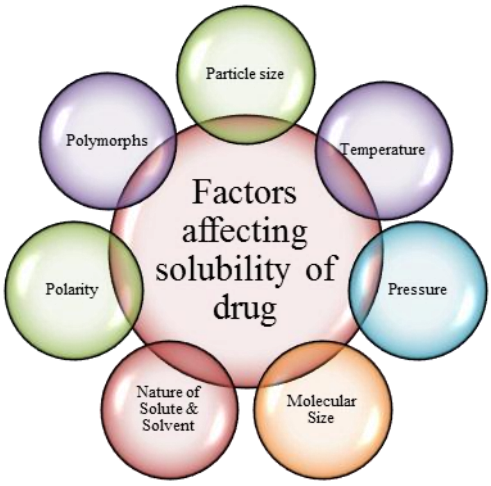


Fig 2: Factor affecting solubility of drug.

Particle size

Solubility is influenced by the size of the particle. As the particle becomes smaller the surface area to volume ratio increases, this allows a greater interaction of the solute with the solvent. (Fig-2).

Temperature

With the increase in the temperature of the solution there is an increase in the solubility of a solid solute.

Pressure

This parameter acts according to the state of the solute; where in- for gaseous solute an increase in pressure increases solubility and vice versa, the changes in pressure has practically no effect on solubility for solid and liquid solutes.

Molecular size

The larger the molecular size or the higher its molecular weight leads to less solubility of the substance. Since it is

difficult for the solvent molecules to surround the larger molecules in order to solvate then substance. The amount of carbon branching in organic compound will increases the solubility. Since more branching will decreases the size (or volume) of the molecule hence making easier to solvate the molecules with solvent. (Vemula et al., 2010).

Nature of the solute and solvent

The result of the differences in the nature of lead chloride and zinc chloride leads to dissolution of only 1 gm of lead chloride in 100 grams of water at room temperature, whereas 200 grams of zinc chloride in the same consideration. (Savjani et al., 2012).

Polarity

Solubility will be greatly affected by the polarity of the solute and solvent molecules. The solubility will be facilitated by the phenomenon 'like dissolves likes' where in non-polar solute will dissolve in non-polar solvent and polar solute in polar solvent. This is driven by the inter molecular forces known as dipole-dipole interaction. Wherein, the positive end that a polar solute pass is attracted by the negative end of the solute and positive end of solvent. The weaker intermolecular forces that all the molecules have than the other forces are called as London dispersion forces. (Jain et al., 2010).

Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism.

Importance and Need of Solubility

One of the most important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown is solubility. The main cause for low bioavailability is attributed to poor solubility and low permeability. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water-soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. There are various approaches enlisted in literature to enhance the solubility of a poorly water-soluble drug. (Table-2) The techniques or approaches to enhance solubility is selected on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. (Thorat and Kadam, 2013).

Table 2: BCS Classification System with examples of different drug is discussed in following table.

Class	Description	Examples
I	High solubility High permeability	B-blockers propranolol, Metoprolol, Cyclophosphamide, Doxycycline, Fluconazole, Levonorgestrel etc.
II	Low solubility High permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine, Paliperidone, Dapsone, Ibuprofen, Nitrofurantoin etc.
III	High solubility low permeability	B blockers, atenolol, H2 antagonist Ranitidine, Abacavir, Allopurinol, Cimetidine, Acyclovir, Hydrochlorothiazide etc.
IV	Low solubility Low permeability	Diuretic Hydrochlorothiazide, Furosemide, Famotidine, Acetazolamide, Ritonavir, Indinavir etc.

Technique for Solubility Enhancement

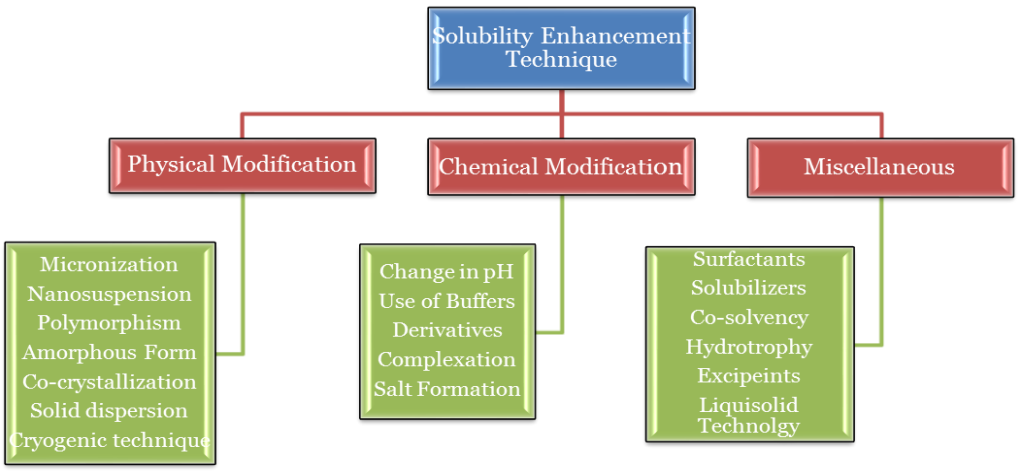


Fig 3: Technique for solubility enhancement.

1. Physical Modifications

Solubility is a phenomenon which is related to particle size and surface area thus it becomes important to reduce the particle size of the drug thereby increasing its surface area and thus enhancing its solubility. There are conventional techniques to reduce the particle size, few of which include comminution and spray drying. These techniques rely upon mechanical stress to disaggregate the active compound. However due to mechanical stress of communition and thermal stress of spray drying the drug substance may undergo degradation in both the cases and if thermo labile then spray drying would cause a problem. Thus, using some of these conventional and traditional approaches solubility may not be enhanced up to the desired level. (Fig-3)

Micronization

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. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The Micronization is used to increased surface area for dissolution.

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. (Fig-4) Nanosuspensions can be produced by different techniques, the "Bottom-up", "Top-down" and "combination" techniques. (Singh et al., 2010)

Bottom-up techniques

Bottom-up techniques are usually referred to as "precipitation techniques" and based on the controlled precipitation or crystallization of drug from a supersaturated solution. Hydrosol technique was the first precipitation technique to obtain drug nanocrystals, whereby the lipophilic drug is first dissolved in an organic solvent followed by precipitation i.e. adding an anti-solvent that is miscible with the organic solvent, usually water, then the solvents can be removed by evaporation or lyophilization to obtain drug nanocrystals.

Top-down techniques

Top-down techniques involve breaking down larger particles via media milling or high-pressure homogenization (HPH). In media milling the particles are grinded using high shear forces generated by the movement of the milling beads/pearls, whereas, in high pressure homogenization (HPH) the particles are forced to pass through a tiny gap with high velocity causing the particle size reduction by cavitation.

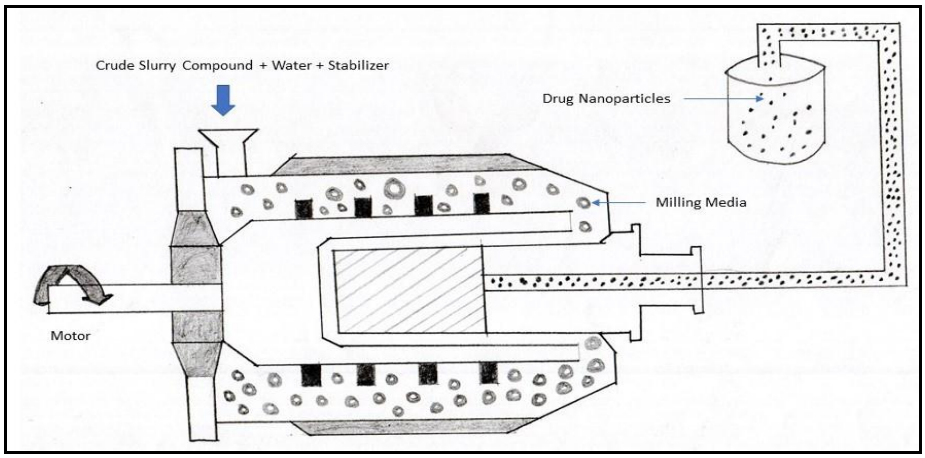


Fig 4: Schematic drawing of wet-milling process for nanosuspensions preparation.

Combination techniques

The combination techniques have been developed to improve the particle size reduction effectiveness, e.g. to obtain a very small nanocrystals below 100 nm, or to overcome the drawbacks of standard nanosuspension processes, e.g. to reduce the number passes through the homogenizer. NANOEDGE is the first combination technology and was developed by Baxter healthcare company, it combines a microprecipitation step (a solvent-antisolvent technique) followed by a high-energy process. H42 is another combination technology where spray-drying and high-pressure homogenization are combined. Moreover, H96 combination technology which combines lyophilization and high-pressure homogenization, and it considers as the most effective combination technique to produce nanocrystals with particle sizer smaller than 100 nm.

Polymorphism

The comminution techniques can produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Thus, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit,

crystal form (crystalline or amorphous), surface nature, and surface energy. If the crystallizing conditions are modified or manipulated (by using different solvents or change in the stirring or adding other components to crystallizing drug solution), it then becomes possible to make crystals with different packing arrangement; such crystals are called as polymorphs. Thus, polymorphs for the same drug differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability.

Polymeric Alteration

Unlike crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

Co-crystallization

This is one of the new approaches available for the enhancement of drug solubility. It includes application of co-crystals also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular and electrically neutral species held together by noncovalent forces. These co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Three of the co-crystallizing agents are classified as generally regarded as safe (GRAS) includes saccharin, nicotinamide, and acetic acid limiting the pharmaceutical applications. (Pathak and Patole, 2014).

Solid Dispersion

Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, (Fig- 5) generally a hydrophilic matrix and a hydrophobic drug. There are different approaches which can be used for increasing the dissolution of the poorly soluble drugs. Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"; they classified solid dispersions (Table-3) into the following representative types. (Singh, Kurmi, Kaur, 2012).

Table 3: Types of solid dispersion.

Components	Eutectic mixture	Amorphous precipitation	Solid solution	Glass suspension		Glassy solid solution
Drug	Crystalline	Amorphous	Molecular dispersed	Amorphous	Crystalline	Molecular dispersed
Carrier	Crystalline	Crystalline	Crystalline	Amorphous	Amorphous	Amorphous
Phases	2	1	2	2	2	1

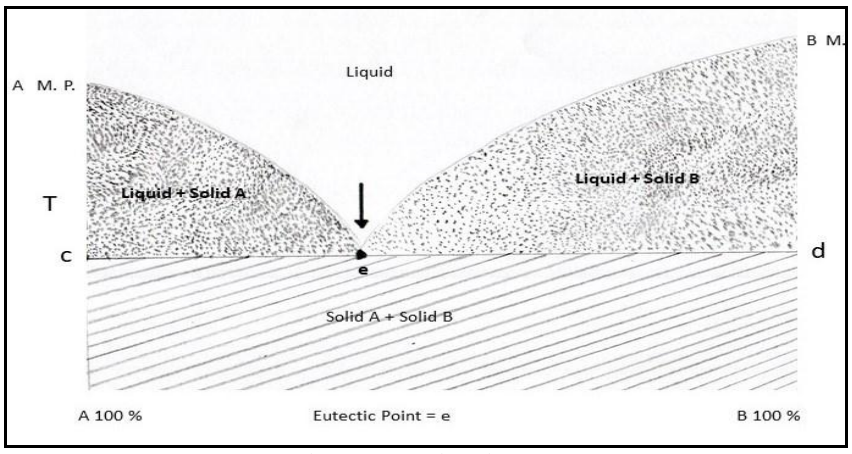


Fig 5: Eutectic mixture.

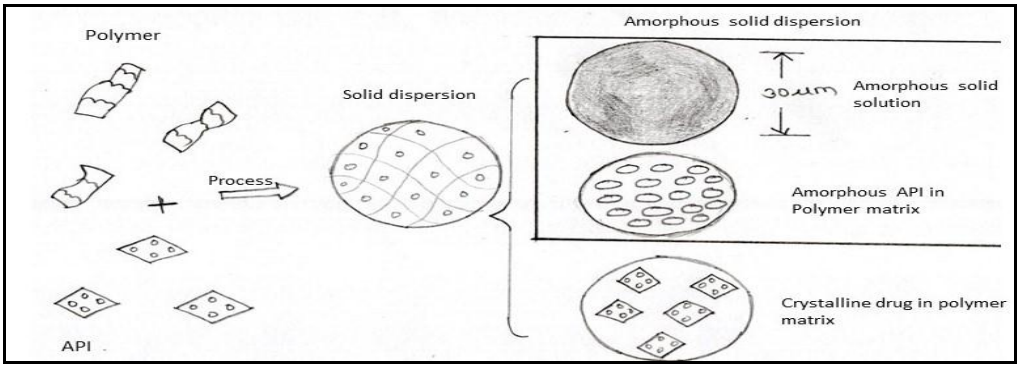


Fig 6: Amorphous type solid dispersion.

Definition of solid dispersion:

Solid dispersion states to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (Fig-6) or in crystalline particles. Consequently, based on their molecular arrangement, six different types of solid dispersions can be notable. Solid dispersions should preferably be designated rendering to their molecular arrangement. (Lingam et al., 2009).

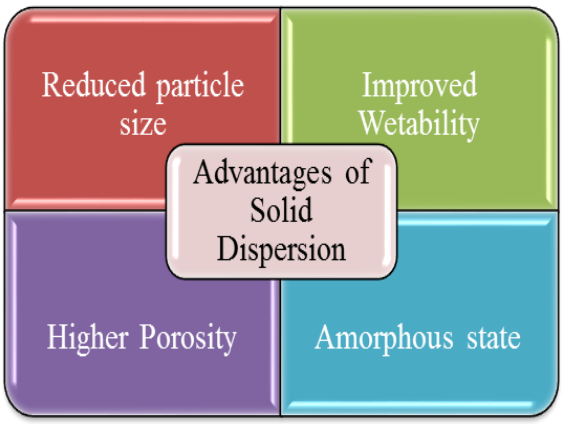


Fig 7:Advantages of solid dispersion.

Advantages of Solid Dispersions:

- **Particles with reduced particle size**

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water-soluble drug and highly soluble carriers. (Fig- 7) A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

- **Particles with improved wet ability**

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

- **Particles with higher porosity**

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

- **Drugs in amorphous state**

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a meta stable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them. (Argade et al., 2013)

Disadvantages of Solid Dispersion

- ✓ Solid dispersion has limitation of poor scale up for purposes of manufacturing
- ✓ SD obtained by some technique may not offer them to easy handling because of its tackiness.
- ✓ Parameters like moisture and temperature influencing on properties of SD than its physical mixture.
- ✓ Crystallinity changes, SD decline in dissolution with aging (Kurmi et al., 2016)

The list of marketed products followed by solid dispersion as shown in table- 4 and different carriers

used in the preparation of solid dispersion shown in table- 5.

Table 4: List of some marketed products utilizing solid dispersion technology.

Drug	Brand Name	Carrier	Manufacturer
Itraconazole	Sporanox	HPMC	Janssen Pharmaceuticals
Tacrolimus	Prograf	HPMC	Astella Pharma
Lopinavir	Kaletra	PVP	Abbot Lab
Nabilone	Casamet	PVP	Meda Pharmaceuticals
Nimodipine	Nimotop	PEG	Bayer Ltd
Finifibrate	Fenoglide	PEG/ Poloxamer	Santarus
Etravirine	Intelence	HPMC	Janssen Therapeutics
Everolimus	Intelence	HPMC	Novartis
Vemurafenib	Zelboraf	Hypromellose acetate succinate	Roche
Nifedipine	Afeditab	Poloxamer	Elan
Rosuvastatin	Crestor	HPMC	Astrazeneca

Table 5: Carriers Used in the Preparation of Solid Dispersion.

Class	Examples
Acids	Citric Acid, Tartaric acid, succinic acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer Material	Polyvinyl Pyrrolidone, PEG 4000, PEG 6000, Sodium Alginate, Carboxy Methyl cellulose, Guar gum, Xanthum gum, Methyl Cellulose
Surfactant	Polyoxyethylene Stearate, Poloxamer, Deoxycholine Acid, Tweens, Spans,

Solid Dispersion Techniques

Solvent Evaporation Method

Basic process of preparing solid dispersion consists of dissolving the drug and the polymeric carrier in a common solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some cases, large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. To minimize the volume of organic solvent required, some investigators have reported the use of cosolvents. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, solvent methods show many disadvantages such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form. (Wairkar et al., 2013).

Fusion Method / Melting Method

The fusion method is sometimes referred to as the melt method. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it gets melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg et al. and Chiou and Riegelman. The solidified masses were often found to require storage of 1 or more days in desiccators at ambient temperatures for hardening and ease of powdering. The fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. (Kamalakkannan et al., 2010).

Hot Melt Extrusion

Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces result in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage

forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. (Fig-8) High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials. (Gaikwad and Chhaprel, 2012).

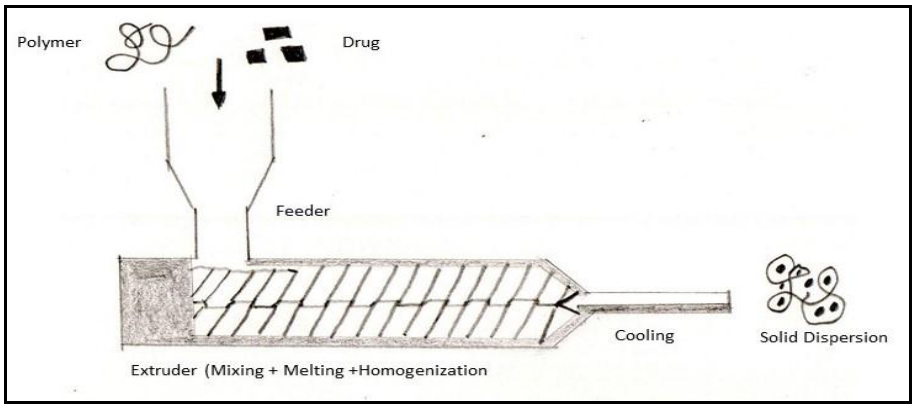


Fig 8: Hot melt extrusion.

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. (Fig-9) Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. Carbon dioxide is the most commonly used SCF because it is chemically inert, non-toxic and non-flammable. (Vadlamudi et al., 2016).

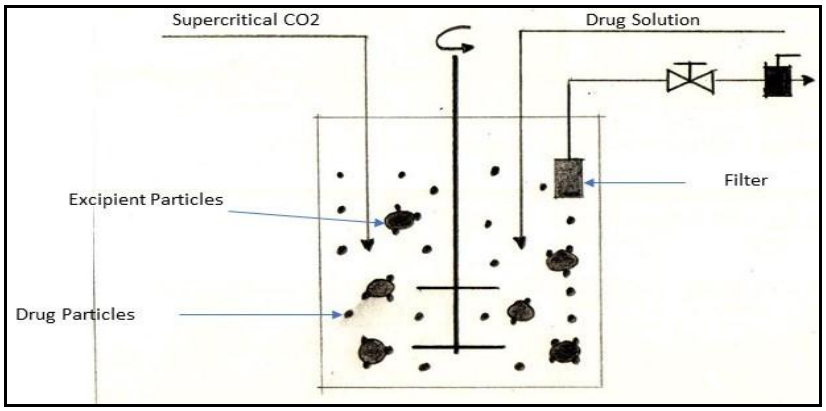


Fig 9: Supercritical fluid technology.

Dropping Method

The dropping method was developed by Bulau and Ulrich (1977) to facilitate the crystallization of different chemicals. This method is a new procedure for producing round particles from melted solid dispersions. Methodology includes that the solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it get solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation. (Deshmukh et al., 2017).

Electrostatic Spinning Method

This technology is used in polymer industry where in it combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. (Fig-10) And as when the electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameter are formed. After evaporating the solvent, the formed fibers can be collected on a screen. (Gautam et al., 2015).

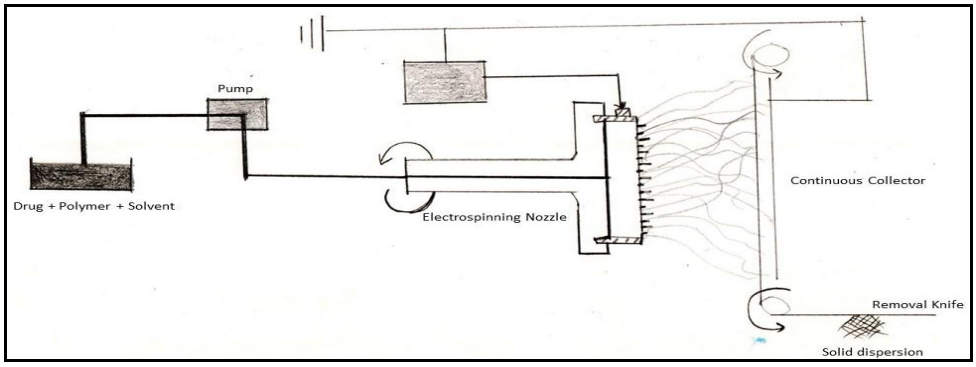


Fig 10: Electrostatic Spinning Method.

Co-precipitation Method

In this method, while during constant stirring, a non-solvent is added drop wise to the drug and carrier solution and the drug and carrier are co-precipitated to get micro particles, and then this micro particle suspension is filtered and dried. (Jain et al., 2012).

Spray Drying

In this type of preparation, the carrier and the active ingredient are dissolved or suspend in a suitable solvent. (Fig-11) This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. (Hart et al., 2013) Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly. (Shah et al., 2015)

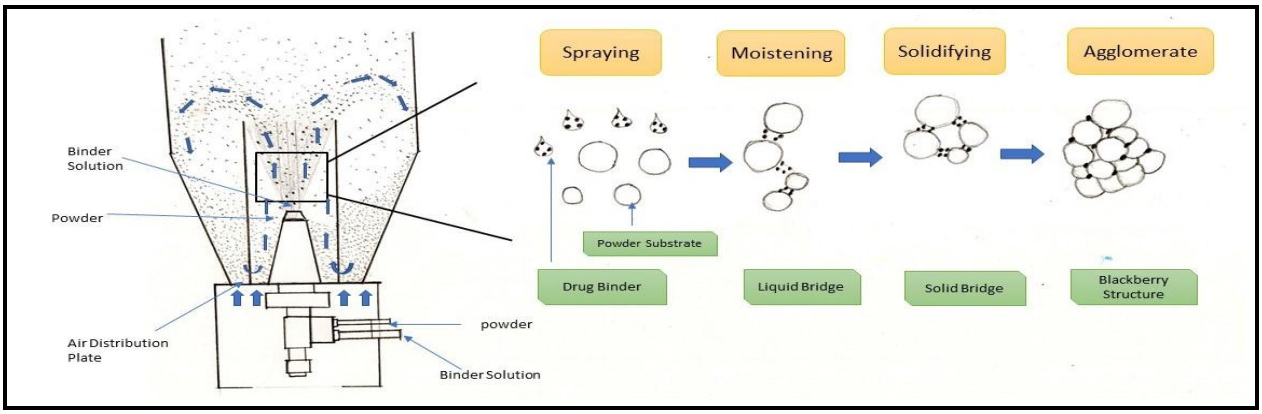


Fig 11: Fluidized bed processing.

2. Chemical Modification:

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. (Rahman et al., 2014) Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. (Chaturvedi et al., 2012).

Salt Formation

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. For solid dosage forms, dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are more water soluble than the parent drug. (Varandal et al., 2013).

Complexation

Complexation is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, and inclusion complexes cyclodextrins.

Inclusion complexes are formed due to the ability of a compound to enclose in another complex. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural

requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. Three naturally occurring CDs are α-Cyclodextrin, β- Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrin is used for enhancement of solubility. (Shukla et al., 2012).

pH Adjustment

Poor water-soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs. (Patil et al., 2013).

Buffers

Buffers are practically used to simply maintain the pH of the system over time. For pH solubilized drugs, another practical use of a buffer is to reduce or eliminate the potential for precipitation of the drug upon dilution. (Badjatya et al., 2011)

Selection of Buffer:

- ✓ In desired pH range the buffer must have adequate capacity.
- ✓ It must be biologically safe for the use intended.
- ✓ There should be no deleterious effect on the stability of the final product.
- ✓ It should permit the use of other excipients like flavoring or coloring agents.

A very small change in pH results in more drug going into the solution. So, by observing the pH solubility profile, it helps in selection of buffer for optimum pH range.

3. Miscellaneous

Hydrotropy

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

Advantages of Hydrotropic Solubilization:

- ✓ Hydrotropy is suggested to be better than other solubilization method, such as miscibility, micellar solubilization, Cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
- ✓ It only requires mixing the drug with the Hydrotropy in water.
- ✓ It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system. (Sarfraz et al., 2017)

Cosolvency

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as Cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility. (Murtaza et al., 2014)

Solubilizing Agents

Solubilizing materials like superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations which increase the solubility and dissolution rate of poorly water-soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water-soluble drug. PEG 400 used to improve the solubility of hydrochlorothiazide. (Nainwal et al., 2011) Modified gum karaya (MGK), a developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug nimodipine. (Zameerruddin et al., 2014).

Self-Emulsifying or Self-Micro Emulsifying Systems

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS), in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS in relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self emulsifying formulations (30-60%) irritates GIT. Most self-emulsifying systems

are limited to administration in lipid filled soft- or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. A Neoral-R is an example of self-micro emulsifying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine-α administered. A Neoral-R could be 174-239% of the bioavailability of cyclosporine-α from Sandimmune-R, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long term use due to the potential of causing diarrhea. (Sapra et al., 2012).

Surfactant / Micellar Solubilization

Use of surfactant is basically a traditional approach to increase solubility. They reduce surface tension and improve dissolution of lipophilic drugs in aqueous medium; by improving wetting of solids and increasing rate of disintegration of solid into finer particles. These are also used to stabilize microemulsions and suspensions into which drugs are dissolved. Micellar solubilization is used by antidiabetic drug like gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.

Liquisolid Technique

The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. (Kumar et al., 2013).

CONCLUSION

Solubility is the most important factor that can control the formulation of drug as well as its therapeutic efficacy, hence it is the most critical factor in the formulation development. Dissolution is the rate determining step for the oral absorption of poorly water-soluble drugs, which can subsequently affect the in vivo absorption of drug. Proper selection of solubility enhancement method is the key to ensure the goals of good formulation like good oral bioavailability, reduce the frequency of dosing and better patient compliance combined with a low cost of production. Because of solubility problem of many drugs the bioavailability of them affected and hence solubility enhancement becomes necessary. The various technique used in alone or in combination to enhance the solubility of poorly water-soluble drug. It is now possible to increase the solubility of poorly water-soluble drugs with the help of various technique.

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