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THE CHANGING SCENARIO OF SOLUBILITY ENHANCEMENT TECHNIQUES: AN UPDATE

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ABSTRACT

Drug discovery and development plays an important role. From all of the routes, oral route is the most desirable and preferred route of administering therapeutic agents for their systemic effects, but low solubility of drug is major challenge for formulation scientist. Solubility is the process of dissolution of solid in liquid phase to give a homogenous form. About 40% of orally administered drugs suffer from formulation problems related to their water insolubility. As most of the parameters like dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility of the drug. On the basis of solubility, drugs are divided into four classes of the BCS classification. The major solubility challenges are faced in the Class II and Class IV of the BCS system. There are different techniques which are used to enhance aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for drugs. The various solubility enhancement methods which are mainly used to improve the aqueous solubility of drug includes micro-ionization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The main aim of this article is to describe the solubilization process and various techniques for increasing the solubility and bioavailability.

1. INTRODUCTION:

Solubility of low water soluble drugs is a major encountered challenge in screening studies of a new chemical entities as well as in formulation design and development. Any drug to be absorbed in the systemic circulation must be present in the form of an aqueous solution at the site of absorption. As solubility & permeability are the deciding factor for the *in vivo* absorption of the drug these can be altered or modified by various techniques. A number of methodologies can be adapted to improve solubilisation of poorly water soluble drugs and further to improve its bioavailability. The techniques generally employed include micronization, chemical modification, hydrotrophy etc. As the term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more ingredients to form a homogenous molecular dispersion. Quantitatively it is defined as the concentration of the solute in a saturated solution at certain temperature and solubility of a drug is represented through a various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction[1].

The Pharmacopoeia lists solubility in terms of number of millilitres of solvent require to dissolve 1g of solute. If exact solubility is not known, The Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in (Table 1)

Table 1: Expressions for Approximate Solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

2. Biopharmaceutical Classification System:

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with *in vitro* dissolution parameters of the drug product, the BCS generally depends on the three major factors: solubility, intestinal permeability and dissolution rate, all of which determine the rate and extent of oral drug absorption from IR solid oral dosage form[2]. It classifies drug into four classes (Table. 2).

CLASS I	CLASS II
HIGH SOLUBILITY, HIGH PERMEABILITY	LOW SOLUBILITY, HIGH PERMEABILITY
CLASS III	**CLASS IV**
HIGH SOLUBILITY, LOW PERMEABILITY	LOW SOLUBILITY, LOW PERMEABILITY

Table 2: A typical representation of the biopharmaceutical classification system.

The drug with low water solubility often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges. The poor solubility and low dissolution rate of poorly water soluble drugs in aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutical Classification Systems (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. Considerations of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even vary poorly soluble compounds might be improved to minimize the limitations to oral availability[3-5].

$dC/dt = AD.(Cs-C.)/h$ .....(1)

Where,

dC/dt is the rate of dissolution,

A is the surface area available for dissolution,

D is the diffusion coefficient of the compound,

Cs is the solubility of the compound in the dissolution medium,

C is the concentration of drug in the medium at time t,

h is the thickness of the diffusion boundary layer adjacent to the surface to the dissolving compound.

The main possible ways for improving dissolution characterstics according to this determination are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and to improve the apparent solubility of the drug under physiologically relevant conditions. Larger the surface area, greater will be the dissolution rate. Since the surface area increases with decreasing particle size, which can be accomplished by conventional methods like trituration, grinding, ball milling, fluid energy micro-ionization, salt formation and controlled precipitation.

Although these conventional methods have been used commonly to increase dissolution rate of drug, there are practical limitations with these techniques as the desired bioavailability enhancement may not always be achieved. Therefore, different formulation approaches are being explored to increase

bioavailability of poorly soluble drugs. One of such useful formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion.

3. PROCESS OF SOLUBILISATION

The process of solubilisation involves the breaking of inter-ionic and intermolecular bonds of the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute , interaction between the aqueous phase and the solute phase molecule or ion[6].

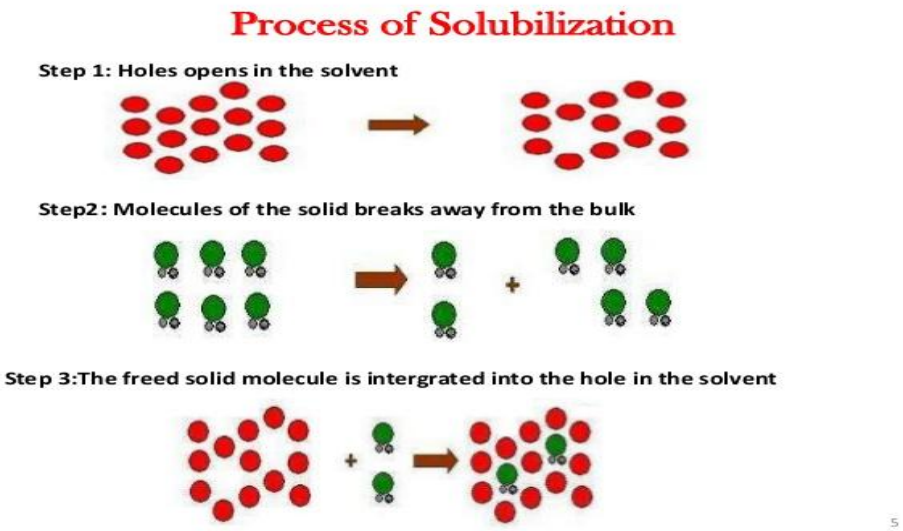

Figure 1: Process of solubilization

4. TECHNIQUES OF SOLUBILITY ENHANCEMENT

4.1 Cosolvancy

4.2 Reduction of particle size

4.2.1 Micro-ionization

4.2.2 Nanosuspension

4.2.3 Homogenization

4.2.4 Wet milling

4.2.5 Sonocrystallization

4.2.6 Spray drying

4.2.7 Supercritical fluid process

4.3 Hydrotrophy

4.4 Complexation

4.5 Use of salt form

4.6 Solid dispersion

4.6.1 Simple eutectic mixture

4.6.2 Hot melt method

4.6.3 Solvent evaporation

4.7 pH adjustment

4.8 Micro-emulsion

4.9 Modifications in the crystal habit

4.9.1 Polymorphs

4.9.2 Pseudopolymorphs

4.1 Cosolvancy

Cosolvancy refers to the technique of using co-solvents to increase the solubility of poorly water-soluble substances; it is also commonly referred to as solvent blending. Co-solvents are defined as water-miscible organic solvents that are used in liquid drug formulation to increase the solubility of poorly water-soluble substance or to enhance the chemical stability of a drug. This technique has been used as an approach for preparing liquid drug preparations throughout the history of drug formulation. Certain drugs of botanic origin were known to be poorly soluble in water and required formulation in water-ethanol mixtures in order to deliver an adequate dose of drug in a small volume of preparation [7].

A common example of a class of formulation containing co-solvents is the elixir, which by definition is sweetened, hydrochloric solution intended for oral use. Tincture which generally contain the higher amount of alcohol, are another classic example of liquid dosage form containing a co-solvent. The need to employ co-solvents in the formulation of new drugs are solution for oral, parenteral and topical use remain high, especially with the increasing structural complexity of new therapeutic agents. In many cases, co-solvency can increase the solubility of non-polar drug up to several order of magnitude above the aqueous solubility.

The primary disadvantage of co-solvency include the potential for biological effects and the potential for drug that have been solubilized using co-solvents to precipitate upon dilution with aqueous fluid. In addition, precipitation of drug upon dilution with aqueous media or during injection or application to mucous membrane must always be considered in deciding if a co-solvent can be used as a vehicle for poorly water-soluble drugs[8].

4.2 Reduction of Particle Size

The bioavailability is intrinsically related to drug particle size; decreasing the particle size increases the surface area and hence improves the dissolution properties. Reduction in particle size can be achieved by following techniques-

4.2.1 Micro-ionization

Increases the dissolution rate of drugs through increased surface area; it dose not increase equilibrium solubility. This is done by milling techniques using jet mill, rotor stator colloid mills etc. Also not suitable for drugs having a high dose number because it dose not change the saturation solubility of the drug.

4.2.2 Nanosuspension

This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles innanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.The nanosuspension approach has been employed for drugs including tarazipide, atovaquone, amphotericin B, paclitaxel and bupravaquone [9].

4.2.3 Homogenization

The suspension is forced under pressure through a value that has been nano aperture. This causes bubble of water to form which collapses as they come out of valves. This mechanism cracks the particle. Conventional homogenizers used are sonicators and high shear fluid processors.

4.2.4 Wet milling

The drug which is in active form in the presence of surfactant is defragmented by milling. Other techniques involves the spraying of drug solution in a volatile organic solvent into a head aqueous solution. Rapid rate of solvent evaporation produces drug precipitation in the presence of surfactants.

4.2.5 Sono-crystallisation

It involves re-crystallization of poorly soluble materials using liquid solvents and anti-solvents. It utilizes ultra sound power characterized by frequency range 20-100 kHz for inducing crystallization. It is not only enhance the nucleation rate but also an effective means of size reduction and controlling size distribution of the API. Most applications are ultrasound in the rage 20 kHz-5 MHz.

4.2.6 Spray drying

It involves drying a liquid feed through a hot gas. The liquid feed varies according to the material being dried and it is not limited to food or pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is one step rapid process and eliminates additional processing.

4.2.7 Supercritical fluid process

Those fluids are referred to as supercritical fluids which are having temperature and pressure greater than its critical temperature and critical pressure so as they are acquire properties of both gas and liquid. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and

allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug [10].

4.3 Hydrotropy

Hydrotrophy is a solubilisation phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been determined for increasing the water solubility of many poorly water-soluble drugs[11].

Advantages of hydrotropic solubilisation technique:

i. It is superior to other solubilisation method, because the solvent character is independent of pH, has high selectivity and does not require emulsification
ii. It is easy method as it require mixing the drug with the hydrotrope in water.
iii. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

4.4 Complexation

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methyleglucamide. They are unique since the increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule. Solid dispersion of nimesulide with PEG-6000 enhanced the solubility of nimesulide by more than 1000%[12].

4.5 Use of salt form

Salts have been employed to improve solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between pKa value f the group and that of its counter ion is required to form stable salts. Alkali metals salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are water-soluble[13].

4.6 Solid dispersion

Sekiguchi and Obi, originally proposed the concept of solid dispersion, who investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions show a useful pharmaceutical techniques for increasing the dissolution, absorption and therapeutic efficacy of drug in dosage forms. The term solid dispersion refered as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent mixtures.

These are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The aqueous

solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier. Thus, the basic difference between solid dispersion and solid solution/eutectics is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter: e.g. amorphous sulphathiazole in crystalline urea. Such dispersion are often called as **co-evaporates** or **co-precipitates.** The method is suitable for thermo-labile substance but has a number of disadvantages like high cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent[14].

The solubility enhancement of glipzide by different solubilisation technique was observed in decreasing order as;

Hydrotropic solubilisation > Solid dispersion > Micellar solubilisation.

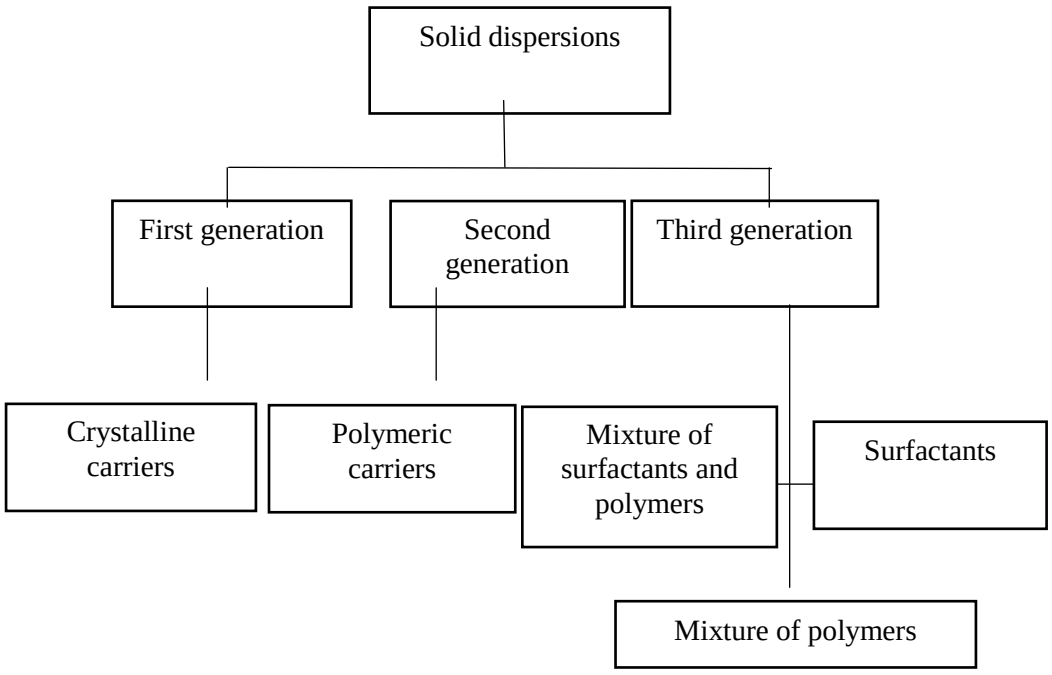

Figure 2: Classification of Solid Dispersion

4.6.1 Dropping method:

A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it 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. Because 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 to a spherical shape [15].

4.6.2 Hot melt method

An important consideration to prepare of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten form. A limitation to the hot melt method is the thermostability of the drug and the carrier. The drug may decompose or evaporate due to high temperature[16].

4.6.3 Solvent evaporation

An important prerequisite for the preparation of a solid dispersion with the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The carrier and the solvent dissolve in the common solvent and then the solvent is evaporated till constant weight of the mixture is obtained[17-18].

4.7 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[19].

Advantages:

i. Simple to formulate and analyse.
ii. Simple to produce and fast track.
iii. Use small quantities of compound amenable to high throughout evaluation.

Disadvantages:

i. Risk of precipitation upon dilution with aqueous media.
ii. Tolerability and toxicity related with the use of a non-physiological pH.
iii. It is less stable chemically compared to formulations crystalline solid.

4.8 Micro-emulsion

A micro-emulsion can be defined as a four component system composed of internal phase, external phase, surfactants and co-surfactants. On the addition of surfactant, which is mostly soluble in internal phase unlike the co-surfactant will result in formation of an optically clear thermodynamically stable, isotropic emulsion. It is having <0.1 micron droplet diameter, thus termed as micro-emulsion. The formation of micro-emulsion does not involve the input of any external energy like in coarse emulsions and is very spontaneous. The surfactants and co-surfactant alternate each other and make a mixed film at the interface, which plays a part in the stability of the micro-emulsion. To ensure the immediate formation of oil-in-water droplets during the production. Some non-ionic surfactants with high hydrophilic-lipophilic balance are often used, such as tweens (polysorbates) and labrafil (polyoxyethylated oleic glycerides) [20].

Advantages of the micro-emulsion over coarse emulsion are:-

i. It is easy to prepare due to spontaneous formation
ii. Transparent and elegant appearance
iii. Thermodynamic stability

iv. Enhanced penetration through biological membranes

v. Increased bioavailability

vi. Less intra and inter individual variability in drug pharmacokinetics[21].

4.9 Modifications in the crystal habit

The ability of any element or compound to crystallize in more than one crystalline form is known as polymorphism. Different polymorphs of the same drug are chemically identical, but they differ in physiochemical properties like melting point, solubility, texture, density, stability etc. Based on their thermodynamic properties, polymorphs can be broadly classified as enantiotropes and monotropes. In enantiotropic system, at a definite transition temperature (below melting point) one polymorphic form can change reversibly into another form. In the case of monotropic system, no reversible transition is possible. When a drug is been characterised under one of these categories, then the further study will involve the detection of the metastable form of crystal. A metastable form is associated with higher energy and thus with higher solubility. In the same way, the amorphous form of a drug is always more suitable than the crystalline form due to the higher energy combined and increased surface area. The anhydrous form of a drug has generally higher solubility than the hydrates. This higher solubility results because of the interaction anhydrate and water. Hydrates require less energy for crystal breakup as compared to the anhydrates which are having thermodynamically higher energy state for the further interaction with water. The non-aqueous or organic solvates have greater solubility than the non-solvates. Thus, the dissolution order of different solid forms of the drug is:

Amorphous> Metastable> Polymorph> Stable polymorph[22].

Table 3: Marketed formulations of drugs by using solid dispersion techniques

Drug	Company	BCS CLASS	Method used	Polymer used
Afeditab (nifedipine)	Elan Corp.	II	Melt/absorb on carrier	Polaxamer or Polyvinylpyrollidone(PVP)
Certican (everolimus)	Novartis	III	Melt or spray drying	Hydroxypropylmethylcellulose(HPMC)
Fenoglide (fenofibrate)	LifeCycle Pharma	II	Spray melt	Polyethylene glycol (PEG)
Ibuprofen	Soliqs	II	Melt extrusion	Various
Intelence (etravirine)	Tibotec	IV	Spray drying	HPMC

Isoptin SRE-240 (verapamil)	Soliqs	II	Melt extrusion	Various
Kaletra (lopinavir and ritonavir)	Abbott Laboratories	II and IV	Melt extrusion	PVP/Polyvinyl acetate
LCP-Tacro (tacrolimus)	LifeCycle Pharma	II	Melt granulation	HPMC
Rezulin (troglitazone)	Pfizer	II	Melt extrusion	PVP
Sporanox (itraconazole)	Janssen	II	Spray layering	HPMC
Torcetrapib	Pfizer	II	Spray drying	HPMC acetate succinate

5. CONCLUSION:

Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

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