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Chemical Modification: A unique solutions to Solubility problem

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ABSTRACT

Almost 40% of the new chemical entities at present self find out poorly water soluble drugs. Badly water soluble drugs have solubility and dissolution related bioavailability problems. Solubility is one of the most important parameter to give desired concentration of drug in systemic circulation to get its pharmacological response. Orally administered drugs obtained completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs perform an valuable role in the process of formulation development. Enhancement of solubility of drug is the most challenging job in drug development process. Solubilization may be affected by co solvent water interaction, micellar solubilization, reduction in particle size, inclusion complexes, solid dispersion, and change in polymorph. This review highlight various techniques of solubility enhancement with special emphasis on Chemical modification methods like Salt formation, Co-crystallization, Co-solvency, Hydrotropy, use of novel solubilizer etc along with physical modification techniques.

Keywords: Salt formation, Co-crystallization, Solubility, particle technologies, Milling solubility enhancement, Cosolvent, physical and chemical methods.

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Introduction

Definition:-

Solubility is defined in quantitative terms as the concentration of solute in saturated solution at a certain temperature, qualitatively; it is defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development[1].

Drug Solubility and Bioavailability Expressions

The Indian Pharmacopoeia lists the solubility of drugs as the number of milliliters of solvent in which 1 gm of solute will dissolve. Solubility can also be expressed as molality, Mole fraction and percent by weight and percent weight in volume. Increase in solubility their increase in bioavailability of drug.[2,3]

Table 1 Descriptive Terms of Solubility[4,5]

Descriptive Terms	Parts of Solvent Required for 1 Part of Solute
Very Soluble	Less than 1
Freely Soluble	1 to 10
Soluble	10 to 30
Sparingly Soluble	30 to 100
Slightly Soluble	100 to 1000
Very Slightly Soluble	1000 to 10000
Practically Insoluble or Insoluble	More Than 10000

Factors affecting solubility·

1. Particle Size
2. Temperature
3. Pressure
4. Nature of the solute and solvent
5. Molecular size
6. Polarity
7. Polymorphs[6,7,8]

BCS classification of drugs [9]

Bcs class	solubility	permeability	absorption pattern
1	low	low	poorly absorb
2	low	high	well absorb
3	high	high	well absorb
4	high	low	variable

Importance of solubility determination:-

Drug absorption requires that molecules be in solution at the absorption site. Dissolution of solid dosage forms in gastro intestinal fluids is a prerequisite to the delivery of a drug to the systemic circulation following oral administration[5]. The improvement in oral bioavailability be able to attain by decrease the hepatic first pass metabolism. That's related difficulties by means of conventional dosage form are able to reduce by some appropriate novel drug delivery systems like use of self-emulsifying microemulsion drug delivery system, lipids nanoparticles and microemulsion etc.[9] Dissolution in turn depends on the solubility of the drug substance in surrounding medium. For drugs absorbed by passive diffusion, those exhibiting low aqueous solubility tend to have a slower oral absorption rate than those exhibiting high aqueous solubility. [10,11,12]

Techniques of solubility improvement[13,14,15]

As Solubility and Permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like,

A) Physical modifications

a) Particle Size Reduction

1) Micronization

2) Nanosuspension

3)Sonocrystallisation

4) Supercritical fluid process

5)Spray drying

b) Modification of the crystal habit

c) Drug dispersion in carriers

d) Complexation

1) Staching Complexes

2) Inclusion Complexes

e) Solubilization by surfactants

1) Microemulsions

2) Self microemulsifying drug delivery systems

f)Novel drug-drug solid dispersion

B) Chemical modifications

1) Salt Formation

2) Co-crystallization

3) Co-solvency

4) Hydrotropy

5) Use of novel solubilizer

6) Nanotechnology

A) Physical modifications

a) Particle Size Reduction:

Particle size reduction increases the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Nanonization techniques are generally employed to improve solubility and dissolution rate of drugs in order to improve its oral bioavailability. [15,16]

1) Micronization:

Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Micronization of drugs can be done by milling techniques using jet mill, rotor stator colloid mills, etc. However, it is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[17]

2) Nanosuspension:

Another approach used to reduce the particle size is nanonization which generally results in formation of nanosuspension- a sub-micron colloidal dispersion of pure particles of drug stabilized by surfactants. It increases dissolution rate due to larger surface area exposed to gastrointestinal fluid. The numerous of compound having improve the dissolution rate and bioavaibility of various drug are badly soluble in water. The another methods are used in nanonization like spray drying, pear milling, wet milling, homogenization etc.[18]

3) Sonocrystallisation:

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz. [19]

4) Supercritical fluid process:

Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallized at greatly reduced particle sizes.[20,21]

5) Spray dried solid dispersion technology

Spray drying technology can be defined as a unit operation in which a liquid stream is constantly divided into very fine droplet into a glass compartment where they come in contact with hot gas and get dried into fine particles, which are further separated from the drying gas using a cyclone or a bag-filter. Spray driers can operate in open cycle mode for

aqueous based or in closed-loop mode for organic based system.[22,23]

6) Self-nanoemulsifying drug-delivery systems

Self-nanoemulsifying drug-delivery systems have emerged as an effective delivery system due to their proven ability to enhance bioavailability of lipophilic drugs. Self nano emulsifying drug-delivery systems is a thermodynamically stable isotropicmixture of oil, surfactant, co-surfactant and drug that form a spontaneous oil-in-water nanoemulsion with a droplet size less than 100 nm when introduced into an aqueous medium under gentle agitation. Several potential advantages of SNEDDS include their ability to present drug in a solubilized form inside the gastrointestinal lumen, thus providing greater interfacial area for drug absorption, providing greater chemical and enzymatic stability, inhibiting P-glycoprotein mediated drug efflux, enhancing lymphatic transport.[24]

7) Pharmaceutical particle technologies

Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration.[25,26]

8) Milling techniques for improving the solubility

Milling involves the application of mechanical energy to physically break down coarse. A myriad of milling techniques and equipment are now available for particle size reduction of drugs, with many capable of scaling up and adaptable to consistent and continuous manufacturing. The mechanisms by which milling enhances drug dissolution and solubility include alterations In the size, specific surface area and shape of the drug particles as well as milling induced amorphization and/or structural disordering of the drug crystal.[26]

9) Solubility and Dissolution Enhancement by Spherical Crystallization

Spherical crystallization technique combines crystallization followed by agglomeration to generate spherical crystals with improved micromeretic properties, thus obviating need for further processing by agglomeration and granulation.[27]

10) Nanostructured lipid carriers for oral bioavailability enhancement

Nano particulate carrier systems. Polymeric and solid lipid nanoparticles are two varieties of such Nano carrier systems. Polymeric nanoparticles suffered with some drawbacks like toxicity and unavailability of some good techniques for production of nanoparticles at large scale.

11) Microwave Irradiation

This method is developed for rapid organic synthesis and reactions, which require shorter reaction time and higher aim product.

12) Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Polymorphs of a drug are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Based on the thermodynamic properties, polymorphs can be classified as enantiotropes and monotropes. In enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. [28]

13) Drug dispersion in carriers:

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products. Eutectic dispersions are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers. In the solid solution form, the drug could be partially or completely soluble in the dispersing matrix.[28]

14) Complexation:

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

15) Staching Complexation:

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. Some compounds that are known to form staching complexes are Nicotinamide, Anthracene, Benzoic acid, Salicylic acid, etc.

16) Inclusion complexation

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). Cyclodextrins and their derivatives have been employed as host for inclusion complex to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery. [29]

e) Solubilization by Surfactants:

Surfactants are molecules with distinct polar and nonpolar regions in which hydrocarbon segment is connected to a polar group which may be anionic, cationic, zwitterionic or nonionic. The presence of surfactants may lower the surface tension and increase the solubility of the drug. Microemulsions and SEDDS are drug delivery systems based on this concept. [29]

17)Microemulsion

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm.These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. [29]

18) Novel drug-drug solid dispersion

The drug-drug solid dispersion is defined as the it is the solubility enhancement method in the category of solid dispersion with use of two drug in which insoluble drug are dispersed in soluble drug without physiological inert carrier

and soluble drug it self act as carrier for solubility. By using this we can give combination of drug any which contain poor & highly soluble drug because fixed dose combination of drug become rule for combating many clinical disorder so it is very beneficial and we are convert the fixed dose combination having the soluble insoluble combination into the solid dispersion form etc. The drug-drug solid dispersion are the novel approach to enhanced the solubility to avoiding the physiological inert carrier.[30]

B) Chemical modifications[31,32]

1) pH Adjustment:

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.Furosemide (pKa of 3.9) is unstable at an acid pH, but is very stable under alkaline conditions. In dogs, the oral bioavailability is approximately 77%.

2) Salt formation:

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. It can lead to changes in solubility and permeability of the parent molecule, which can lead to improved bioavailability. The use of salt forms is a well known technique to enhance dissolution rates. Generally, an alkaloidal base is slightly soluble in water, but if the pH of medium is reduced by addition of acid, the solubility of the base is increased as the pH continues to be reduced. **Example:** Rosiglitazone maleate, Pioglitazone HCl, Atropine sulphate

3) Co-crystallisation:

Co crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. Cocrystallization is a flourishing research field with direct application to the pharmaceutical industry.The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystal, 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 non-covalent forces.[23] Different techniques for co crystallization 1)Solvent evaporation 2)Grinding 3)Slurry Co - Crystallization 4)Solvent drop grinding (Modification of Grinding) 5)High throughput co-crystallization 6)Hot melt extrusion 7) Sonocrystallization Method. Few example of research work done cocrystal formation Flurbiprofen, Itraconazole ,Carbamazepine etc.

Co Crystals Characterization Parameters 1) Solubility 2) Maximum wavelength 3) Stability 4) Intrinsic dissolution 5) Bioavailability 6) Melting Point 7) Melt (Hot stage microscopy) 8) DSC 9) XRD 10) Vibrational spectroscopy.

4) Cosolvency:

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 good solubility known as cosolvents. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterals. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Commonmly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, n-Octanol are the commonly used cosolvents.

Ideal behaviour of Cosolvents

- It should be easily available and sufficiently pure.
- It should be non-toxic, non-irritating, and nonsensitizing.
- It also must exert no pharmacologic activity of its own.
- It should be stable under normal conditions of pharmaceutical use.
- It should not adversely affect the action of the medicament.
- Ideal solvent should not be affected by acids or alkalies.
- The viscosity of solvent should be as such so as to allow ease of administration.
- It should remain fluid over a wide temperature range[31].

5) Hydrotropy:

Hydrotropy is a solubilization 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 observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

Significance of Hydrotrophy

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency 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 hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.
- Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.

6) Use of novel solubilizer:

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap,Soluplus Povacoat, dendrimers, is improve the solubility of hydrophobic API.

7) Nanotechnology approaches:

Nanotechnology can be used to improve solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation.[32]

Conclusion

From the above article we conclude that the solubility of the drug is the most critical factor in the formulation development that controls the therapeutic efficacy of the drug. The various techniques described above can be used to enhance the solubility of the drug. The choice of the method will be based on its effectiveness as well as safety in terms of biocompatibility of the excipient used. A lot of research has been carried out in this area and some improvements in solubility and dissolution rate has to be made generally. Researcher working on solubility enhancement may use following techniques Chemical modification methods like Salt formation, Co-crystallization, Co-solvency, Hydrotropy, use of novel solubilize etc along with physical modification techniques & try to remove drawbacks of individual technique.

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