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Review Article

TECHNIQUES TO IMPROVE THE ABSORPTION OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solubility is essential for the therapeutic effectiveness of the drug, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Solubilization may be affected by cosolvent water interaction, micellar solubilization, reduction in particle size, inclusion complexes, solid dispersion, and change in polymorph. Some new technologies are also available to increase the solubility like microemulsion, self emulsifying drug delivery system and supercritical fluid technology. This review focuses on the recent techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Keywords: solubility, solubility enhancement techniques.

Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system[1].

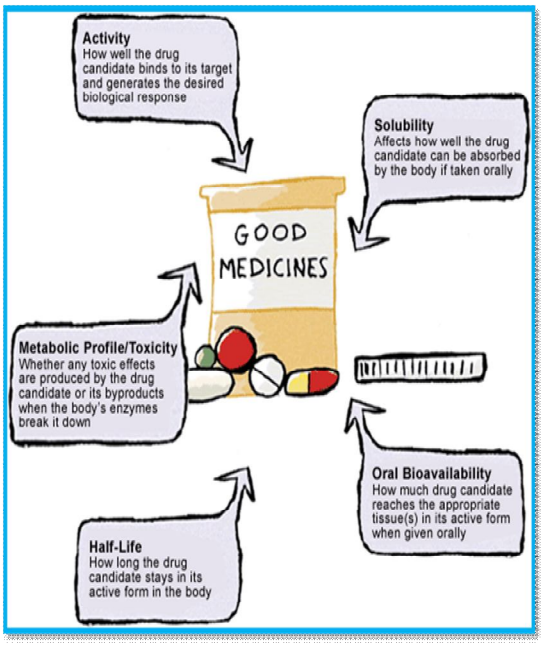
1. Particle size
2. Temperature
3. Pressure
4. Nature of the solute solvent
5. Molecular size
6. Polarity
7. Polymorphs

Factors affecting the rate of solution:

Rate of solution

The rate of solution is a measure of how fast substance dissolve in solvents.

1. Size of the particle
2. Temperature
3. Amount of solute aiready dissolved
4. Stirring



TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are[2]

I. PHYSICAL MODIFICATIONS

1. Particle size reduction
a. Micronization
b. Nanosuspension
2. Modification of the crystal habit
a. Polymorphs
b. Pseudopolymorphs
3. Drug dispersion in carriers
a. Eutectic mixtures
b. Solid dispersions
c. Solid solutions
4. Complexation
a. Use of complexing agents
5. Solubilization by surfactants:
a. Microemulsions
b. Self microemulsifying drug delivery systems

I. PHYSICAL MODIFICATIONS

1. Particle size reduction

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

a. Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improve 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 micronisation is used to increased surface area for dissolution[3]

b. Nano suspension

Nano suspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants[4]. The advantages offered by nano suspension 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.

Techniques for the preparation of nano suspensions[4]

a) Homogenization

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles.

Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors[5].

b) Wet milling

Active drug in the presence of surfactant is defragmented by milling.

Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. The nano suspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one[2, 6]. Drying of nano suspensions can be done by lyophilisation or spray drying.

Other techniques for reduction of the particle size

1. Sonocrystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation.

Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API)[7]. Most applications use ultrasound in the range 20 kHz-5 MHz[8].

2. Supercritical fluid process

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes[9]. A supercritical fluid (SF) can be defined as a dense noncondensable fluid[10]. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). Through manipulation of the pressure of SCFs, the favorable characteristics of gases-high diffusivity, low viscosity and low surface

tension may be imparted upon liquids to precisely control the solubilisation of a drug with a supercritical fluid. SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determine its solvents power. Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes. A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter.

The most widely employed methods of SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas antisolvents recrystallisation (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCF due to its favourable processing characteristics like its low critical temperature (Tc = 31.1-C) and pressure (Pc = 73.8 bar)[11].

RESS involves solubilising a drug or a drug-polymer mixture in SCF and subsequently spraying the SCF solution into a lower pressure environment via a conventional nozzle or capillary tube. The rapid expansion undergone by the solution reduces the density of the CO_2, correspondingly reducing its solvent power and supersaturating the lower pressure solution. This supersaturation results in the recrystallisation and precipitation of pure drug or drug-polymer particles of greatly reduced size, narrow size distribution and high purity. The solubility of nifedipine has been improved by RESS[12].

GAS processing requires the drug or drug-polymer mixture be solubilised via conventional means into a solvent that is then sprayed into an SCF; the drug should be insoluble in the SCF, while the SCF should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles.

2. Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an 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. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

3. Drug dispersion in carriers

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961[13].The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method[14]. Novel additional preparation techniques have included rapid precipitation by freeze drying[15] and using supercritical fluids and spray drying , often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion[16]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone[17, 18] polyethylene glycols[19], Plasdone-S630[20]. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used[20].

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.The eutectic combination of chloramphenicol/urea[21] and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

1. Hot Melt method

Sekiguchi and Obi [14] used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the

drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

2. Solvent Evaporation Method

Tachibana and Nakumara[22] were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 C. The solid dispersion of the 5-lipoxygenase/cyclooxygenase inhibitor ER-34122 shown improved in vitro dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation. These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

3. Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient[23]. The process has been useful in the preparation of solid dispersions in a single step.

4. Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

4. 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. There are many types of complexing agents and a partial list can be found in below table.

List of Complexing Agents

S.No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

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 as follows:

Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc.

Higuchi and Kristiansen[24] proposed a model according to which the compounds capable of undergoing stacking can be classified into two classes (classes A and B) based on their structure. The compounds in class A have higher affinity for compounds in class B than for those in class A and vice versa[25].

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). 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.The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility[26]. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

The kinetics of cyclodextrin inclusion complexation has been usually analyzed in terms of a one-step reaction or a consecutive two-step reaction involving intracomplex structural transformation as a second step. Cyclodextrins is to enhance aqueous solubility of drugs through inclusion complexation. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold. Complex formation of rofecoxib, celecoxib, clofibrate, melarsoprol, taxol, cyclosporin etc. with cyclodextrins improves the solubility of particular drugs.

E. Solubilization by surfactants:

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic[27]. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.

Microemulsion

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 cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability, and less inter- and intra-individual variability in drug pharmacokinetics[28].

II. CHEMICAL MODIFICATIONS

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. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard)[29] of the solvent by the use of co-solvents rather than the pH of the solvent.

Other techniques

1. Co-crystallisation

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[30].

Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of subtherapeutic amounts of drug substances such as aspirin or acetaminophen. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals[31]. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

2. Cosolvency

The solubilisation of drugs in co-solvents is an another technique for improving the solubility of poorly soluble drug[79]. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization[32]. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone[33].

3. Hydrotrophy

Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute.Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

4. Solubilizing agents

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

5. Nanotechnology approaches

Nanotechnology will be used to improve drugs that currently have poor 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.

CONCLUSION

A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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