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REVIEW ARTICLE

Solubility Enhancement by Solid Dispersion - A Review

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ABSTRACT

The use of poorly soluble drugs has a number of drawbacks such as increasing the dosage, administration frequency and the resultant occurrence of side effects. Furthermore, the rate-limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastro intestinal fluids rather than the rapidity of their diffusion across the gut wall; it is however, important to improve the oral bioavailability of poorly water soluble. A lot of research has been carried out in this area and for better clinical efficiency, some improvements in solubility and dissolution rate has to be made generally.

Key words: poorly soluble drugs, oral bioavailability, solubility and dissolution rate.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specific temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solution or hydration if the solvent is water [1].

Table 1.1: Solubility definitions

Definition	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 – 10,000
Insoluble	>10,000

Techniques of solubility enhancement [3]

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

1) Physical Modifications

A. Particle size reduction

a. Micronization
b. Nanosuspension
c. Sonocrystalisation
d. Supercritical fluid process

B. Modification of the crystal habit

a. Polymorphs
b. Pseudopolymorphs

C. Drug dispersion in carriers

a. Solid dispersions

D. Complexation

a. Use of complexing agents

E. Solubilization by surfactants:

a. Microemulsions
b. Self microemulsifying drug delivery systems

2) CHEMICAL MODIFICATIONS

3) OTHER METHODS

a. Cocrystalisation
b. Cosolvency
c. Hydrotrophy
d. Solvent deposition
e. Selective adsorption on insoluble carrier
f. Use of soluble prodrug
g. Functional polymer technology
h. Porous microparticle technology
i. Nanotechnology approaches

PHYSICAL MODIFICATIONS

A. Particle size reduction

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

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a. 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 [4]. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [5].

b. 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. Techniques for the production of nanosuspensions include Homogenization and 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 [6]. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone.

B. Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture and stability. 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. Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates for further interaction with water. On the other hand, the organic solvates have greater solubility than the nonsolvates. Some drugs can exist in amorphous form. Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is Amorphous >Metastable polymorph >Stable polymorph Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

C. Drug dispersion in carriers

a. Solid dispersions

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognized in 1961 [6]. 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 method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion [7]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. 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 [8]. 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 and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier [9]. The techniques of production of solid dispersion include Hot Melt method, Solvent Evaporation Method, Hot-melt Extrusion and Melting –solvent method [10].

D. Complexation

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

a. 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 [11]. Some compounds that are known to form staching complexes are as follows.Nicotinamide32, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene.

b. 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. Three naturally occurring CDs are α-Cyclodextrin, β- Cyclodextrin, and γ-Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility.35 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 A etc. with cyclodextrins improves the solubility of particular drugs [12].

Approaches for making inclusion complexes are
Physical blending method
Kneading method
Co-precipitation technique
Solution/solvant evaporation method
Neutralization precipitation method
Milling/co-grinding technique
Atomization/spray drying method
Freeze drying technique

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.55 When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.

a. Microemulsion

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 and Labrafil 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 [13].

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. 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 constant60 of the solvent by the use of co-solvents rather than the pH of the solvent. The use of salt forms is a well known technique to enhanced dissolution profiles.61 Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water [17].

3) Other methods

a. Cocrystalization

A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces. 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 recognized 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. 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.

b. cosolvency

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[14]. 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.

c. Solubilizing agent

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.

d. Hydrotrophy

Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. Hydrotropes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules.

e. Solvent deposition In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose

f. Selective absorption in insoluble carriers

A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the

rapid release of drugs from the surface of clays are– the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media.

g. Use of soluble prodrug

physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. prodrug of established drugs has been successfully used to improve water solubility of corticosteroids, vitamins and benzodiazepines.

h. Functional polymer technology

Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, "Resinate", can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from the resinate on exposure to the physiological fluids.

i. Porous microparticle technology

In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology applied as HDDSTM (Hydrophobic Drug Delivery System). These drug particles provide large surface area for increased dissolution rate. The solid form has a proprietary spray drying technology that allows the size and porosity of the drug particles to be engineered as desired.

j. 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 and the next step taken was Nanonisation [15].

PREPARATION OF SOLID DISPERSION

The fusion (melt), solvent evaporation, spray drying, lyophilization (freeze drying), hot-melt extrusion, electrostatic spinning method, coating on sugar beads using fluidized bed-coating system, supercritical fluid technology, are the methods reported for the preparation of solid dispersions and these methods are discussed below.

1. Fusion Method:

The fusion method is sometimes called melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term "fusion method" is preferred. The drug was melted in a carrier and after cooling the dry mass obtained was pulverized and sieved to obtain powder. They prepared the SDs of Sulfathiazole in different carriers (e.g. ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide and urea) by the formation of melt of different drug carrier mixtures. Cooling of the drug-carrier melt was done on ice bath with continuous stirring until the dry mass was obtained. A particular advantage of these carriers for the formation of SDs is Additional attractive features of such carriers include improved compound wettability. This study clearly shows that additions of various hydrophillic carriers like urea, mannitol, PVP and PVP/VA-64 to aceclofenac improves its dissolution rate. Further, all the solid dispersions performed better than the corresponding physical mixtures. The present study also showed that urea, mannitol and PVP/VA-64 yielded solid dispersions with a less improved dissolution rate than PVP as carrier. The melting point of a binary system is dependent upon its composition, i.e., the weight fraction of drug and the carrier present in the system. By proper selection and control, the melting point of a binary system may be much lower than the melting points of its two components. Under such conditions, this melting method can be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point. The main advantages of this method are its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material. Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method is only applied when the drug and matrix are compatible

and when they mix well at the heating temperature. When the drug and matrix are incompatible two liquid phases or suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion and this problem can be prevented by using surfactants. Secondly, another problem may 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. Thirdly, many substances, either drugs or carriers, may decompose during the fusion process at high temperatures [16].

2. Solvent Evaporation Method:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. 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, some disadvantages are associated with this method such as

1) The higher cost of preparation.
2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form [17].

3. Spray Drying:

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing. Polyglycolized glycerides (Gelucire) are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33^{o} and 70°C. Preparation of SDs by conventional spray drying with polyglycolized glycerides has been problematic because a sticky and tacky mass of polyglycolized glycerides is obtained. Therefore, spray drying technique for polyglycolized glycerides has been used with its combination high-melting lipids to solve this problem. Solid dispersion using polyglycolized glycerides creates some problem this can be solved by using silicon dioxide as an adsorbent. Due to presence of surface silanol groups, silicon dioxide is able to form hydrogen bond with drug molecule leading to the increase in wettability and consequently enhanced dissolution rate. SD of glibenclamide with Geluride was successfully prepared using silicon dioxide as an adsorbent by spray drying technique with enhanced dissolution rate. Spray dried dispersions of griseofulvin (GF), poly[N-(2-hydroxypropyl)methacrylate] (PHPMA) and polyvinylpyrrolidone (PVP) were prepared from acetone and water. The glass transition temperature for the ternary solid dispersion (GF, PHPMA, and PVP) shifted from 83°C (acetone/water) to 103°C for the acetone/methanol system. They found that the SDs that was prepared using lower concentrations of drug and polymers in solutions resulted in the formation of particles that display a lower relaxation rate. Their result also supports the hypothesis that the polymer conformation may significantly change the properties of the solid dispersion.

4. Lyophilisation Method:

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase

separation to a minimum .Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration

5. Hot-melt extrusion:

This technology was first utilized predominantly in the plastic industry and to lesser extent in the food industry since 1930's. Many advantages of hot melt extrusion over conventional solid dosage form manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system. This technique employs the uses of extruders which consists of

Conveying system, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder. In this method solvents are not used therefore, it is environmentally friendly, economical and no residual solvent in the final product. Advantage of hot melt extrution technique over melting method is the use of low temperature and short residence time which prevents the drug-carrier mixture from thermal degradation. Another advantage is that production is continuous therefore fewer batches are required and efficient scale-up from laboratory to large-scale production. This method has several disadvantages these are: (i) high shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials, (ii) just like traditional fusion method, miscibility of drug and carrier matrix can be a problem.

6. Electrostatic Spinning Method:

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

7. Coating on sugar beads using fluidized bed-coating system:

This method involves a fluidized bed-coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled- and immediate-release solid dispersions. Itraconazole (Sporanox oral capsules,Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of a drug and hydroxypropylmethylcellulose (HMPC) in a mixture of suitable solvent system comprises a mixture of methylenechloride and preferably ethanol which may be denatured with butanone. As HPMC does not dissolve completely in methylenechloride, at least 10% alcohol has to be added. A solid solution of drug in HPMC is produced upon coating and controlled drying of coated beads is done in a closed Wurster apparatus.

8. Supercritical Fluid Technology:

Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's. A supercritical fluid exists as a single phase above its critical temperature and pressure. The most commonly used supercritical fluids for a variety of applications include supercritical fluid carbon dioxide, nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia. Carbon dioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.1°C) and pressure (Pc = 73.8 bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of CO_2 makes it attractive for processing heat-labile molecules. This technique consists of dissolving the drug and the inert carrier in a common solvent that is

introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods. A variety of supercritical carbon dioxide techniques have been developed with different working principles, such as rapid expansion of supercritical solutions (RESS), gas antisolvent precipitation (GAS), supercritical antisolvent precipitation (SAS), precipitation with compressed fluid antisolvent (PCA), solution enhanced dispersion by supercritical fluids (SEDS), precipitation from gas-saturated solutions (PGSS), etc . Jun et al., in 2005, prepared cefuroxime axetil (CA) solid dispersions with HPMC 2910/PVP K-30 using solution enhanced dispersion by supercritical fluids (SEDS) in an effort to increase the dissolution rate of poorly water-soluble drugs. FTIR analysis demonstrated that the presence of intermolecular hydrogen bonds between CA and HPMC 2910/PVP K-30 in solid dispersions, result in the formation of amorphous or non-crystalline CA. They concluded that an amorphous or non-crystalline CA solid dispersion prepared using SEDS could be very useful for the formulation of solid dosage forms [18].

CONCLUSION

Solubility is a most important parameter for the oral bio availability 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 bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs.

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