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ASPECTS OF SOLUBILISATION: A REVIEW

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ABSTRACT

Many water soluble drugs are present in the BCS class Π category, which are characterized by low solubility and high permeability. By increasing the dissolution rate, the solubility of drug can be easily enhanced. Various solubility enhancement techniques are available for increasing the solubility as well as permeability of drugs like micronization, complexation, cosolvent addition, conservation and soli dispersion. As oral route is one of the most desirable and preffered method for drug administration, thus solubility of drug is a major challenge in formulation designing. About 40% of the orally administered drugs are having solubility problems. Thus, because of these solubility problems, the bioavailability of drugs also gets affected. This makes the solubility enhancement of drugs necessary. In this review we concentrate on the solubility and various problems related to the solubility and various techniques which can be used to enhance the solubility.

KEYWORDS: Solubility, Bioavailability, Dissolution.

INTRODUCTION

The therapeutic effectiveness of any drug and any new chemical entity depends upon its bioavailability and thus ultimately upon the solubility of those drug molecules. Solubility is one of the key parameter to achieve the desired concentration of drug in the systemic circulation to show its pharmacological response.[1] The solubility of a solute is defined as the maximum quantity of solute that can dissolve in a certain amount of solvent at a specific temperature.[2] The solubility can also be defined as the ability of one substance to form a solution with another substance.[3] The substance which is to be dissolved is called the solute and the fluid or the dissolving fluid in which that solute dissolves is called the solvent. Solute

and solvent together form a solution. Thus, the process of dissolving the solute into the solvent is called as solution. If the solvent is water, this process is known as hydration.[4]

The solubility of a drug is generally represented via various concentration expressions such as the molarity, molality, parts, percentage, volume fraction, mole fraction. Also the pharmacopoeia lists the solubility in terms of the number of millilitres of the solvent required to dissolve 1g of the solute. The Indian Pharmacopoeia presents some general terms to describe a given range. These descriptive terms are given in table1.[5] Solubility is an essential physical property referring to the total strength of a given substance or the solute to get dissolve in a solvent.

SOLVENT

It is the component which forms the main constituent of a solution and it is also capable of dissolving another substance to form a consistently disperse mixture at a molecular level.

SOLUTE

It is a substance which is present in small quantity and dissolves in the solvent.[2]

Table 1. Definition of solubility

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

PROCESS OF SOLUBILISATION

The process of solubilisation involves three steps:-

- The separation of solvent molecules to provide the space in the solvent for solute.
- The breaking of the intermolecular bonds or inter-ionic bonds in the solute.
- The interaction between the separated solvent molecules and the broken solute molecules or ion.[2,6]

NEED FOR SOLUBILITY

According to the recent estimates, approximately 40-50% of the new chemical entities are being rejected because of there poor solubility; as solubility is one of the key parameter to achieve the desired concentration of drugs or active ingredient in the systemic circulation.

Because the therapeutic effectiveness of any drug molecule depends upon the solubility as well as on the bioavailability of that drug molecule.[7]

Bioavailability can be defined as the rate and extent of the therapeutically active drug that reaches to the systemic circulation in the unchanged form and is available at the site of action.[2] The absorption of drugs from the GI tract can be affected by various factors, most significantly by poor aqueous solubility and by the poor membrane permeability of the drug molecule. Thus, when any drug or an active agent is administered orally, it must first get dissolved in the gastric or in the intestinal fluids before it get permeated through the membranes of the GIT to reach the systemic circulation. Thus, to improve the oral bioavailability of drugs or active agents, there is a need to increase the solubility and dissolution rate of poorly water soluble drug candidates.

According to BCS classification of drugs, class II and IV drugs are poorly water soluble drugs and thus dissolution of these drugs is the rate limiting step when administered. The BCS classification of drugs is described in table 2.[8,9]

Table 2. BCS Classification

Class I High Permeability, High Solubility Example: β blockers, metaprolol	**Class II** High Permeability, Low solubility Example: NSAIDS, neteglinide
Class III Low Permeability, High Solubility Example: H2 antagonist, cimetidine	**Class IV** Low Permeability, Low Solubility Example: Diuretics, Hydrochlorthiazide

FACTORS AFFECTING SOLUBILITY

The solubility of any drug or other components depends upon given points:-

- Nature and composition of the solvent medium
- Physical form of the solid
- Temperature and pressure of system

There are a lot of other factors which affects the process of solubility like:-

1. Particle Size

The size of the solid particles affects the solubility because with the decrease in particle size, the surface area to volume ratio increases. The larger surface area of solute molecules allows more interaction with the solvent. The effect of particle size on solubility can be described by.[4,10]

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where, S is the solubility of fine particles

$S_\circ$ is the solubility of infinitely large particles

γ is the surface tension of solid

V is molar volume

r is the radius of fine particle

2. Molecular Size

The molecular size will affect the solubility of the drug as larger the molecule or higher the molecular weight of the drug, less is the solubility of that substance. In organic compounds, the amount of carbon branching increases the solubility because more branching will reduce the size of molecule and also make it easier for the solvent to solvate the molecules.[11]

3. Temperature

With the increase in temperature the process of solution absorbs the energy and thus the solubility will get increased but if the process of solution releases the energy with the increase in temperature then it will decrease the solubility. Only a few solid solutes are there which are less soluble in warm solutions. In case of gases, the solubility get decreased when temperature of solution is increased.[1]

4. Pressure

In case of solids and liquid solutes, there is no effect of pressure on the solubility but in case of gaseous solutes, when the pressure is enhanced, there is an increase in the solubility and with the decrease in pressure there is a decrease in solubility.[2]

5. Nature of solute and solvent

There is a lot of difference in the solubility of two or more different substances on the basis of their natures. For example: In 100 grams of water at room temperature only 1 gram of Lead(II)chloride can be dissolved where 200 grams of Zinc chloride can be dissolved in same amount of water i.e. 100 grams of water at same room temperature.[3]

6. Polarity

The polarity of solute and the solvent molecules will affect the process of solubility. Generally, the polar solute molecules get dissolved in polar solvent system and nonpolar solute molecules get dissolved in nonpolar solvent system. Thus if the solute molecule is polar in nature it must have both positive and negative ends and if the solvent is also of polar nature then it also consist of both the ends, thus the positive ends of solute molecule gets attracted towards the negative ends of the solvent molecules. These type of attractions are known as dipole-dipole interactions which is a type of intermolecular force.[1]

7. Polymorphs

Solids have a rigid form and a definite shape. The shape or crystal habit of a given solid may vary but angles between the faces remains constant. A crystal is made up of ions, atoms or molecules in a lattice or in a regular geometric arrangement constantly repeated in three dimensions. This repeating arrangement is known as the unit cell. The ability of a substance to crystallize in more than one crystalline form is known s polymorphism. The polymorphs can vary in their melting points. As, the melting point of any solid is related to its solubility, the polymorphs will have different solubility.[10]

8. Rate of solution

The rate of solution can be defined as the measure of how fast the substance dissolves in a solvent. The various factors that affect the rate of solution are:-

- size of particles
- temperature
- amount of solute already dissolved
- stirring.[10]

METHODS FOR SOLUBILITY ENHANCEMENT

There are various techniques which can be used to increase or to overcome the poor drug solubility. These techniques are discussed under the following major headings:-

A. Chemical Modifications:-

1. Change in the pH
2. Use of buffer
3. Derivatization
4. Salt formation

B. Physical Modifications:-

1. Particle size reduction

- Micronisation
- Nanosuspension
- Sonocrystallisation
- Supercritical fluid process

2. Modifications in the crystal habit

- Polymorphs
- Pseudopolymorphs

3. Drug dispersion in carrriers

- Eutectic mixtures
- Solid mixtures
- Solid solutions

4. Complexation

- Use of complexing agents

5. Solubilisation by surfactants

- Microemulsions
- Self microemulsifying drug delivery system

C. Other Methods:-

1. Co-crystallisation
2. Co-solvency
3. Hydrotrophy
4. Solubilizing agents
5. Selective adsorption on insoluble carrier
6. Solvent deposition
7. Functional polymer technology
8. Using soluble prodrug
9. Microparticle technology
10. Precipitation porous
11. Nanotechnology approaches

A. Chemical Modifications

1. Change in the pH

The most effective and the simplest mean of increasing the aqueous solubility of organic solute which is ionisable, is the change in the pH of the system. For example:

- In case of the weakly acidic drugs, at low pH, the solute is in unionised form and thus produces insoluble precipitates where at higher pH it is in ionised form which leads to the more soluble drug.
- In case of weakly basic drugs, at low pH, the solute is in ionised form, thus more soluble drug but when the pH is high then the solute is in unionised form which will result in insoluble precipitation.[2]

2. Use of buffer

Buffers are used to maintain the pH of solution over the time and also used to reduce or to eliminate the potential for the precipitation which may occur upon dilution. When dilution of a solution is done then pH alteration occurs which results in the decreased solubility. When the pH is changed by 1 fold, it increases the solubility by 10 fold and if it changes by the 1 pH unit, then this will decrease the ionization of drug and the solubility decreases by 10 fold.

3. Derivatization

In this technique a chemical compound is transformed into a product which is of similar structure. This transformed product is called derivative. These derivatives have different solubilities as compared to adduct. It is used for the quantification of the adduct formation of esters and the amide via acyl chlorides.[5]

4. Salt formation

The dissolution rate of different salts is usually different from their parent compounds. The potassium and sodium salts of the weak acids dissolves rapidly than the pure salts. Example, salt form of various drugs like aspirin, barbiturates, theophylline etc. Thus it is the most effective and common method to increase the solubility as well as dissolution rate of any acidic or basic drugs.[2]

B. Physical Modifications

1. Particle size reduction

As discussed earlier, larger the particle size of the solute molecule, lower is its solubility. Thus to enhance the solubility of solute molecules size reduction of the particles is done.[12] It

can be done by various methods like micronization, nanosuspension, sonocrystallisation and super critical fluid process. Each technique requires the different equipment for the reduction of particle size.

- **Micronisation**

The solubility of drug is related to the drug particle size. When particle size is reduced then it will increase the surface area which leads to the improved dissolution properties of the drug. The various conventional methods which are used for particle size reduction like comminution and spray drying depends upon the mechanical stress to break the active compound. The micronization technique is used to enhance the dissolution by increasing surface area but it does not increase equilibrium solubility.[13] Micronization of drugs is achieved by various melting techniques by using jet mill, colloid mill, rotor stator etc. Micronisation is not suitable for those drugs which have a high dose number because micronization does not change saturation solubility of the drugs.[14]

- **Nanosuspension**

A pharmaceutical nanosuspension is a biphasic system which consists nanosized drug particles stabilised by the surfactants. These are used either for oral and tropical use or for parenteral and pulmonary administration. Nanosuspension technology has been developed as an able candidate for the efficient delivery of hydrophobic drugs. This technique is generally applied to those poorly soluble drugs which are insoluble in both water and oils. The average particle size of solid particles in nanosuspensions ranges between 200 and 600nm. The advantage of this technique is the increase the dissolution rate because of layer surface area exposed.[15,16] The various technique for the production of nanosuspension are:-

- **Homogenisation:** homogenizers are generally used for particle size reduction in pharmaceutical and biotechnology industries. Three types of homogenizers which are commonly used are conventional homogenizers, sonicators and high shear fluid processors. In homogenisers, the suspension is forced under a particular pressure through a valve having nanoaperture. This results in bubbles of water to form which then collapses as they come out of valves. This mechanism cracks the particles.[2]

- **Wet milling:** In this technique a drug solution in a volatile organic solvent is sprayed into a heated aqueous solution. Rapid evaporation of solvent produces the drug precipitates in the presence of surfactants. Lyophilisation or spray drying techniques can be used to dry

the nanosuspensions. This technique has been employed for the drugs like tarazepide, atovaquone, paclitaxel, amphotericin B and bupravaquone. All these formulations are in the research stage.[2]

- **Sonocrystallization**

Recrystallization of poorly soluble material by using the liquid solvent and antisolvents has been employed to reduce particle size. Sonocrystallisation is one of the novel approach used for the particle size reduction. It works on the basis of crystallisation by using ultrasound. In this process, the ultrasound power is characterised by frequency range of 20-100 KHz to induce crystallisation. This process not only enhances the nucleation rate but is also an effective mean for size reduction and controlling the size distribution of active pharmaceutical ingredients. Most of the applications use ultrasound in a range 20 KHz-5 MHz.[2, 17]

- **Supercritical fluid process**

A supercritical fluid is a dense non condensable fluid which is having greater temperature and pressure than its critical temperature i.e. T_c and critical pressure i.e. $T_{p.}$ A supercritical fluid (SCF) process allows the micronization of the drug particles within narrow range of the particle size, often to submicron levels. The current SCF processes have revealed the capability to create nanoparticle suspensions of particles having diameter in the range of 5-2000nm.[18] Once the drug particles get solubilised within the SCFs then they may be recrystallized at a greatly are widely particle size. The various methods of SCF processing which are widely employed for micronizing the particles are Rapid Expansion of Supercritical Solutions (RESS) and Gas Antisolvents Recrystallisation (GAS). Both of these methods are used in the pharmaceutical industries. Carbondioxide (CO_2) is used as the SCF because of its favourable processing characteristics such as its low critical temperature (i.e. T_c= 31.1.c) and pressure (P_c= 73.8 bar). In RESS there is solubilisation of a drug or drug-polymer mixture in the SCF and then spraying this SCF solution in a lower pressure environment through a conventional nozzle or capillary tube. The rapid expansion undergone by this solution reduces the density of CO_2, as a result reducing its solvent power and also supersaturating the lower pressure solution. This supersaturation will result in recrystallization and precipitation of the pure drug or the drug-polymer particles of high purity, narrow size distribution and of greatly reduced size.

While in the GAS processing, the drug or drug-polymer mixture is solubilized through conventional means into a solvent which is then sprayed into an SCF. The drug used should be insoluble in SCF and the SCF used should also be miscible with the organic solvent. The SCF diffuses into spray droplets which causes the expansion of solvent present and the precipitation of drug particles.[19,20]

2. 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 energy state for the further interaction with water. The nonaqueous or organic solvates have greater solubility than the nonsolvates.[16] Thus, the dissolution order of different solid forms of the drug is

Amorphous>Metastable>Polymorph>Stable polymorph.

3. Drug dispersion in carriers

The solid dispersion technique is used to reduce the particle size and thus to increase the dissolution rate of drugs and also to enhance the absorption of drugs. Solid dispersion can be defined as a group of solid products which consist of at least two different components, usually, a hydrophilic matrix and a hydrophobic drug.[7] Also solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier in solid state and can be

prepared by any method or technique of solid dispersion like melting method, solvent method or fusion solvent method.[21] The matrix in a solid dispersion can be either crystalline or amorphous the hydrophilic carriers which are most commonly used for solid dispersions include, polyethylene glycols[22], polyvinyl pyrrolidone[23], plasdone S630.[24] Often, surfactants may also be used in the formation of solid dispersion include sodium lauryl sulphate, tween-80, docusate sodium, pluronic-F68 and myrj-52.[25]

The eutectic mixture combination of sulphathiazole/urea and chloramphenicol/urea are served as the examples for preparation of poorly soluble drug in a highly water soluble carrier.[26]

- **The fusion (melt) method**

The amount of carrier(s) are weighed accurately and are placed in an aluminium pan on a hot plate and are liquefied with the constant stirring at about 60^{o}C temperature. Then the accurately weighed active drug is mixed into the molten carrier(s) with stirring to establish homogeneity. This mixture is then heated until a clear homogeneous melt is obtained. Then, the pan is removed from the hot plate to cool the mixture to room temperature.[7] The limitation of this method is that, at high temperature some drugs may get degraded.[27]

- **The solvent method**

In this method, a weighed amount of active drug and carrier(s) are dissolved in a minimum quantity of chloroform in a round bottom flask. Then this solvent is removed by using a rotary evaporator. The obtained solid dispersion is then transferred on to an aluminium pan and is allowed to dry at room temperature.[7] An important requirement for the manufacture of solid dispersion by the use of this technique is that, both drug and carrier should be completely soluble in the solvent.[2]

- **Dropping method**

A solid dispersion of a molten drug carrier mixture is pipetted and is dropped on to a plate. It then solidifies into round particles. The size and shape of these particles can be affected by factors like the viscosity of the molten mixture and the size of the pipette. As, viscosity is dependent on the temperature, thus it is necessary to adjust the temperature so that when the molten mixture is dropped onto the plate then it solidifies to a spherical shape.[12]

4. Complexation

Complexation is a connection between the two or more molecules to create a non-bonded entity with a definite stoichiometry. Comlexation depends on relatively weak forces such as hydrogen bonding, London forces and hydrophobic interactions. Various examples of the complexing agents include; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrin.[11] Two categories of complexes are:-

- **Stacking complexes**

These are operated or controlled by the association of nonpolar area of drug and complexing agent. This will result in elimination of nonpolar area on contact with water, thus reducing the total energy of the system. Stacking results in clear solution and can be homogeneous or mixed.

- **Inclusion complexes**

These are formed because of the ability of a compound to enclose into another complex. There are no forces involved between them and thus there are no bonds, thus also called as no bond complexes.[18]

5. Solubilisation by surfactants

Surfactants are molecules with different polar and nonpolar regions. Most of the surfactants contain a hydrocarbon portion connected to a polar group. The polar group can be cationic, anionic, non-ionic or zwitter ionic. The presence of surfactants can lower the surface tension and can increase the solubility of the drug within an organic solvent.[17]

- **Microemulsion**

A microemulsion 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 microemulsion.[28] The formation of microemultion does not involve he 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 microemulsion. 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). Advantages of the microemulsion over coarse emulsion are:-

- It is easy to prepare due to spontaneous formation
- Transparent and elegant appearance
- Thermodynamic stability
- Enhanced penetration through biological membranes
- Increased bioavailability
- Less intra and inter individual variability in drug pharmacokinetics.[5]

- **Self microemulsifying drug delivery system**

SMEDDS or SEDDS is an important method to enhance the solubility and bioavailability of the poorly water soluble drugs. SMEDDS can be defined as the isotropic mixture of solid or liquid surfactant, natural or synthetic oils, or alternative, one or more hydrophilic solvent and surfactant/co-solvent. SMEDDS form a transparent microemulsion which have a droplet size of less than 50 nm while SEDDS typically produce an emulsion with a droplet size between 100-300 nm. On a little stirring followed by the dilution in aqueous media like GI fluids, these systems may form fine oil-in-water emulsions or microemulsion. Self-emulsifying formulations spread easily in the GI tract and the intestine; and the digestive motility of the stomach provide the agitation necessary for the self-emulsification. SEDDS are physically stable and easy to manufacture. The composition of SEDDS is combination of drugs, oils, surfactants and co-surfactants or the co-solvent. The self-emulsifying process depends on:-

- The concentration of surfactant
- The nature of oil and surfactant
- The temperature at which self-emulsification occurs.[8]

C. Other methods:- other methods of solubility enhancement include:-

1. Co-crystallisation

It is a novel approach available for increasing the drug solubility through the application of co-crystals, also referred as molecular complexes. A co-crystal can be defined as a crystalline material which consists of two or more molecular species which are electrically neutral and are held together by non-covalent forces. The co-crystallizing agents are generally recognised and classified as safe (GRAS) which includes nicotinamide, saccharin and acetic acid limiting the pharmaceutical applications.[1, 2, 5]

2. Co-solvency

Another technique for enhancing the solubility of poorly soluble drug is solubilisation of drugs in co-solvents. It is generally known that addition of an organic co-solvent to water can greatly change the solubility of drugs. Nonpolar molecules and weak electrolytes are having poor water solubility and thus their solubility can be enhanced by altering the polarity of the solvent. This alteration in polarity of solvent can be achieved by the addition of another solvent. This process is known as co-solvency. The solvent which is used to increase the solubility is known as co-solvent.[20, 29] It is commonly referred to as solvent blending. Most of the co-solvents are having hydrogen bond donor and acceptor groups and small hydrocarbon regions. The hydrophilic hydrogen bonding groups of these co-solvents ensure the water miscibility, while the hydrophobic hydrocarbon regions interfere with the waters hydrogen bonding network which reduces the overall intermolecular attraction of water. By disturbing waters self-association, the co-solvents reduces waters ability to squeeze out hydrophobic, nonpolar compounds, thus increasing the solubility.[5]

3. Hydrotropy

Hydrotropy increases the solubility in water because of the presence of a large amount of additives. The mechanism by which it increases the solubility is by the complexation involving weak interaction between hydrophilic agents (urea, sodium alginate, sodium benzoate) and solute. The example is, sublimation of theophylline with sodium alginate and sodium acetate.[28, 29, 30]

4. Solubilising agent

By the use of various solubilising materials, the solubility of poorly water soluble drugs can be improved. For example PEG 400 is used for improving the solubility of hydrochlorthiazide.[1, 2]

5. Solvent adsorption on insoluble carrier

A highly active adsorbent like inorganic clays example Bentonite can increase the dissolution rate of the poorly water soluble drug such as indomethacin, griseofulvin and prednisone by maintaining the concentration gradient at its maximum. There are two reasons which are suggested for the rapid release of drugs from surface of clays:-

- hydration and swelling of clay in the aqueous media
- weak physical bonding between the adsorbate and adsorbent

6. Solvent deposition

In solvent deposition, a poorly water soluble drug example Nifedipine is dissolved in an organic solvent such as alcohol and deposited on an inert solid, hydrophilic matrix such as microcrystalline cellulose or starch and then evaporation of solvent is done.[1]

7. Functional polymer technology

Functional polymer increases the dissolution rate of poorly water soluble drugs by avoiding lattice energy of drug crystal, which is main barrier to the rapid dissolution in aqueous media. The dissolution rate of poorly water soluble and ionisable drug like anionic, cationic and amphoteric actives can be enhanced by the use of this technology. This method can be applied to oils and sensitive materials.[2]

8. Use of soluble prodrugs

The most common prodrug method involves the incorporation of ionisable or polar moiety into parent compound to improve the water or aqueous solubility. Example: the water solubility of corticosteroids benzodiazepine has been successfully improved by the use of prodrug approach.

9. Microparticle technology

The poorly soluble drug is embedded in a microparticle which have a water soluble, porous, sponge like matrix and dissolves by wetting the drug and leaves a suspension of rapidly dissolving drug particles. These drug particles provide a large surface area for the increased dissolution rate.[5]

10. Precipitation

In this method, a poorly water soluble drug like cyclosporine is dissolved in a suitable organic solvent by rapid mixing with a non-solvent to precipitate the drug in nano size particles.[10]

11. Nanotechnology approaches

Nanotechnology approaches can be used to enhance the solubility of poorly water soluble drugs. Nanotechnology broadly refers to the study and use of the materials and structures at nanoscale level of approx. 100 nm. For many of the new chemical entities with very low aqueous solubility, the oral bioavailability enhancement by the use of micronisation is not

sufficient because the micronized product is having very low effective surface area for the dissolution and the next step taken is nanonisation.[2]

FUTURE PROSPECTS AND CONCLUSION

Dissolution of drugs is the rate determining step for oral absorption of the poorly water soluble drugs, which can affect the in vivo absorption of drugs. Currently only 8-10% of the new drug candidates have both high solubility and permeability. Because of the solubility problem of many drugs their bioavailability gets affected and therefore solubility enhancement becomes necessary. To overcome the various solubility problems, various solubility enhancement techniques have been developed which is industrially applicable. By the use of these techniques which are discussed above, it is possible to improve the solubility of poorly water soluble drugs.

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