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A comprehensive review on basic approaches to improve pharmaceutical solubility

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Abstract

Solubility improvement of pharmaceutical substances can be quite intriguing, especially if they belong to BCS class-II new chemical entities. Solubility and bioavailability are two important concerns of pharmaceutical scientists which hinders the choice of variety of dosage forms of the active substances. Many new chemical entities which are lipophilic in nature and have great therapeutic advantage over contemporary may not be formulated into a dosage form. This review focusses on the basic approaches to improve the solubility around which many advanced techniques can be developed. Traditional approaches of improving solubility are to increase the surface area exposed to body fluids, dispersion or inclusion of lipophilic solutes into hydrophilic carriers. Nanotechnology has emerged as a revolutionary approach in mid-1980's in this area of study. The approaches can be a building-up approach through self-assembly, or precipitation of bits from larger units. Whatever is the approach chosen, ultimate result would be nanosizing of drug particles and there would be an enormous amount of surface energy available. Improper channeling of accessible free surface energy can root the nanosized elements to impulsively cumulate into further thermodynamically steady state.

Keywords: Solubility, Surfactants, Inclusion complexes, Nanosuspensions.

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1. Introduction

Solubility Phenomenon:

Solubility can be defined as the quantitative arrangement of a saturated solution articulated as a part of a particular solute in a selected solvent, as per IUPAC (International union of pure and applied chemistry). Solubility can be read/written in terms of concentration of solute in solvent.

Spontaneous interface of 2 or even more substances resulting in a uniform, consistent molecular dispersion, in simple terms is solubility. It is an inherent natural property of a drug substance that can be altered only by chemical alteration of the molecule (Stegemann, 2007).

A substance is said to be very soluble in a particular solvent, if it takes less than 1 part of solvent to solubilize 1 unit of substance. On a similar note, substance is said to be freely soluble, if it takes 1-10 parts of solvent to solubilize 1 unit of substance. If a substance takes 10-30 parts of solvent to solubilize 1 unit of substance, substance is said to be soluble. Now comes the least soluble substances, which can be termed as sparingly soluble, very slightly soluble and practically insoluble, if 10 mg-< 0.1 mg of solute only goes into solvent. All the data regarding solubility is detailed in British pharmacopoeia (British Pharmacopoeia 2016).

Solubility and bioavailability are the two roadblocks in drug development. It is projected that ~40% of new drug entities discovered are tough to formulate for their dearth of water solubility (Lipper, 1999; Lipinski, 2002). If a drug is aimed at crossing biological membranes for getting absorbed, then the drug has to possess minimum amount of lipophilicity in its structure, and at the same time, possess some grade of aqueous solubility to show activity. The standard approach to tackle this issue is to generate soluble salts of an insoluble or low water-soluble compound without any disturbance to its therapeutic activity. Also, prodrugs or similar compounds with enhanced solubility would be worked on. On successful attempts of producing salts or finding prodrugs, nanoparticle technology can be avoided.

The problem is that, success rates of above mentioned are feeble, particle is forsaken premature in its progress. Solubility is also dependent on presence of other species in the solvent- Common ion effect.

Absorption of drugs with water solubilities less than 0.1 mg/ml is probably restricted at the step of dissolution. Instead, if a drug is excessively hydrophilic, molecule may experience problem in distributing itself into a lipophilic bio membrane. Thumb rule that all of us are aware is: Drugs which do not dissolve in body fluids will not restore the patients. This being the reason, low solubility is a grave factor if the drug has to endure the scrutiny process. Molecules that are extremely valuable with contribution towards health of mankind would not make through the further development process if their systemic availability is restricted by their solubility (Brahmankar and Sunil, 2009).

Biopharmaceutical Classification System:

High throughput scrutiny happening in the R&D and new active substance expansion have opened up to an escalating figure of unsolvable drug constituents, where hinderance of activity is by their insolubility in polar solvents (Amidon et al, 1995). Drugs face limitations due to two key problems, keeping apart the infinite problems that they encounter during the whole development process, Solubility and Permeability. This is the criteria used to categorize drugs into four classes, according to Biopharmaceutical Classification System, conceptualized by Amidon et al.

Class I: Drug candidates with both upright solubility and permeability are put in class I. Great solubility and good permeability will eventually lead drug molecule reaching their target without any rate limiting steps. A quick increase in plasma levels can be observed with class I Drugs. An anecdotal comparison was ascertained in the literature, associating class I drugs to a jet plane, which appear out of blue into the circulation and disappear.

In such cases, an option to retard the release would be to combine it with a polymer, which retards the dissolution and kinetics and makes it a slow release system. Writing much about class I drugs becomes a digression from the main interest

Class II: These chemical entities present a real challenge to the formulators. These are the drug candidate which are characterized by high permeability or their easy penetration through physiological blockades but suffers from insufficient solubility in aqueous body fluids. Active from class II signify the greater number of new chemical entities. However, there are methodologies being advanced to progress solubility of chemical entities, which will be written in detail in later part of introduction.

Class III: Such drug candidates which are soluble in GI fluids but are not absorbed by the body - intestinal wall does not allow all the substances to be penetrated into the portal vein, i.e. Class III actives are characterized by high solubility and low permeability.

There are very few mechanisms that can improve permeation of drug molecules through intestinal wall.

Class IV: these group of entrants is a real horror for formulation scientist. Active substances that do not go into solution or enter the physiological obstructions come under this category. They amalgamate the glitches of class II and class III drugs.

To get out of such situation of dealing with class IV drugs is to revert them to the pill roller and ask for chemical alternatives or to convert them into active molecules under physiological conditions.

Class II drugs embody mainstream new chemical entities (NCE's). Great share of hydrophobic moieties is existing in the molecule and it is obvious that molecules containing hydrogen and carbon will be so nonpolar that they do not get along with water. In Some cases, if the drug molecule is composed of large number of polar units, such molecules do not dissolve either in polar or in non-polar solvents. If it is possible to progress the solubility of these substances, Formulation of these active pharmaceutical ingredients can be successful. This dissertation work throws light on the solubility improvement techniques, out of which formulations were developed using three solubility improvement techniques- Solid Dispersion technology, Inclusion complexation and nanoparticles.

Formulation tactics that upsurge the solubility of BCS II and BCS IV actives without declining their lipid nature will augment absorption through living membranes.

Chi-Yuan Wu and Leslie Z. Benet have contributed towards BDDCS which replaces the permeability factor with metabolism criteria (Chen et al, 2011). If the major route through which drug gets eliminated is through metabolism, then BDDCS suggests that drug is said to exhibiting high permeability and vice versa.

Techniques to Improve solubility:

For the formulation progress, three main approaches to advance solubility:

1. Use of Surfactants
2. Complex Formation
3. Nanotechnology

Surface active agents/Surfactants/Wetter:

Surfactants are amphiphilic natured molecules. Molecules with a hydrophilic head and a non-polar hydrophobic end are put into this category. Polar head can be of ionic type or non-ionic type, leading to differentiation of ionic and non-ionic surfactants(Michael and Shelagh Ferguson-Miller, 2001).

Presence of fairly large hydrophobic share makes these molecules water insoluble. They be as discrete entities only in very low concentrations. They show strange behavior due to company of 2 or more conflicting parts of molecules, when they reach upper limit of solubility. In such cases, they come together and form supra molecular structures of defined size and shape.

Due to the amphiphilic surfactants, hydrophobic parts congregate together, however polar groups do not gather or come together, so, a spherical structure with non-polar groups in the center and polar groups surrounding the core, called as micelles and the concentration at which formation happens, is called critical micellar concentration (CMC). These are usually in the range of 5 nm. Usually, typical CMC for surfactants lies in the range of 10-3 mol/L.

In a micelle, polar heads form exterior part, while nonpolar tails are hidden in the interior. Polar molecules orient themselves to face water. The hydrophobic nonpolar tails face inwards past the liquid. Fatty acids regularly comprise solitary hydrocarbon chain or 2 hydrocarbon tail (Viseshkumar, 2011).

A main aspect regarding surfactants is the existence of hydrophobic province in their middle. The central of a micelle acts as a non-polar solvent for BCS group II candidates. Several extrapolations can be drawn:

1. Drug bits do not get detached from water in fluids, which could be gastrointestinal fluid.
2. Drugs are steady in form of dissolved molecules in the central portion-core.

Surfactants act as dispersants.

Therefore, surfactant molecules are an intriguing cult of particles having momentous influence on pure water's properties (Pallavi et al, 2012). Micelles can be used as a compelling instrument for solubilization of drugs, provided they solubilize in hydrophobic part of micelles. It is a proven fact that surfactants used at right concentrations (CMC) helps in improving the solubility of a low water soluble active. Hence, Self-Emulsifying Drug Delivery System (SEDDS) can attain a formulation that forms emulsion in the GIT.

Surfactants fall into four main classes:

A) Surfactants- Anionic

B) Surfactant- Cationic

C) Ampholytic surfactants- Ampholytic

D) Nonionic surfactants- Nonionic

A)Surfactants- Anionic: Class of surfactants owning negatively charged hydrophilic group is present.

Examples: Potassium laurate, sodium dodecyl sulphate.

B)Cationic surfactants: Class of surfactants with a positive charge on hydrophilic groups.

Example: quaternary ammonium compounds.

C)Ampholytic surfactants: Zwitter ionic surfactant molecules, with negative and a positive charge like sulfobetaines.

D)Surfactants – Non Ionic: There is no charge present on a hydrophilic molecule but are water soluble because of highly polar groups. Examples: Sorbitan esters (Spans), poly - sorbates (Tweens) (Satish et al, 2011).

Complex formation

The second approach which can overcome the aforesaid problems with surfactants and can be applicable to a comprehensive range of drugs, including the BCS class IV drugs, to the maximum extent with few exceptions is complexation with polymeric solubilisers. Polymeric solubilisers are water soluble polymers which can be in a complex state with other molecules in system. This principle has been in use since sometime, as this form the base line principle in detergents to avoid unwanted transfer of color to white ones.

Complexation: Complexation happens with aid of moderately feeble forces such as hydrogen bonding, hydrophobic interactions and other weak forces amongst 2 or even more particles to form a non-bonded unit. Chelates such as Ethylene diamine tetra acetic acid, EGTA, molecular complexes- polymers, and cyclodextrins can be quoted as examples.

Complexes are of two categories:

1. Association of apolar region of drug and chelating agent fallouts in stacking complexes, resulting in exclusion of hydrophobic regions of molecule in interaction with water.

2. Inclusion complexes are shaped by reason of the aptitude of a compound to include in another complex. They are also called as no bond complexes, since no covalent bond is formed during the process (Uekama et al, 1998).

Inclusion complexation scheme has been most hired to progress the solubility, drug dissolution pace, availability in blood of few actives. A guest molecule's nonpolar region is inserted into structure of another molecule, host molecule, which enables formation of inclusion complex. Commonly employed pharmaceutically applied host molecules are cyclodextrin. Macrocyclic ring consisting carbohydrates, have glucose monomers and set in the form of ring/doughnut, with a water penchant exterior and water phobic outer surface are formed by break down of starch in the presence of enzymes such as cyclodextrin glycosyl transferase (CGT). α- cyclodextrin, β- cyclodextrin, and γ-cyclodextrin are the available cyclodextrins, consisting of 6,7 and 8 dextrose units, attached by α-1, 4 linkages respectively(Rao and Stella, 2003).

How is complexation able to improve physicochemical characteristics of a compound?

Cyclodextrins improve drug solubility by captivating an oleophilic/hydrophobic component of drug into its central crater. During this process, no covalent bonds are made. Physicochemical properties like solubility, chemical reactivity, absorbance, fluorescence, NMR chemical shifts, pKa values, chemical stability and permeability through membranes of free substances are unlike complexed molecules (Loftsson et al, 2002). Methods to study complexation can be applied since complexation produces changes in the physicochemical properties. Nevertheless, structural data on drug/cyclodextrin complexes can be obtained

only by a few methods (Patil et al, 2010).

Various methodologies to complex low soluble drugs are as follows:

Kneading Method

Cyclodextrins are converted into a slurry or paste with required water or blend of water and alcoholic solutions. Drug is then slowly added into the cyclodextrin slurry. The stirred mixture is dried out and classified according to its size. Mortar and pestle, kneaders and extruders can be used for the process. This method is economic, most common and convenient method of production available for complexation.

Lyophilization/Freeze-Drying Technique

Porous, amorphous free flowing powder with good amount of complexation between drug and complexing agent can be produced by lyophilization/ freeze drying technique. Sublimation principle is followed. First solvent present in solution is converted into solid form by freezing and successive drying out solution of drug and chelating agent at lower pressures. This technique comes handy in case of complexation of thermolabile drugs. Specialized equipment need and time are restricting the uses.

Microwave Irradiation Method

Microwave irradiation of drug and complexing agent is initiated by dissolving drug and cyclodextrin in water-organic solvent mixture in a round bottom flask. Reaction is carried out and continued for 1-2 minutes in the microwave oven, set at 60°C. Later, unreacted drug and complexing agent is removed. Precipitate obtained from chemical reaction is filtered and dried at 40°C. Owing to its shorter reaction period and high produce of the product, Microwave irradiation method is considered advantageous (Friedrich et al, 2005).

Amalgamation method

Blend of active and cyclodextrins can be prepared in a simple mortar by trituration and classified through desired sieve to get a fine sized product. Rapid mass granulator helps in thorough amalgamation of the drug with cyclodextrins in a large scale industry. These pulverized mixes are then warehoused at controlled conditions.

Co-precipitation technique

Active substance is added to cyclodextrins, under magnetic agitation. Obtained precipitate from the above step is dried and stored. This technique yields complexed drug in saturated conditions. This method is not well-liked in industrial scale due to tediousness of the process, usage of organic solvents, and low yield value (Broadhead et al, 1992).

Solvent evaporation method

A mutual solvent for active substance and cyclodextrins is used to dissolve both the substances to obtain molecular level dispersion. Cyclodextrin solution is added to alcoholic drug solution. Vacuum evaporation is used to evaporate the solvent present and to obtain solid inclusion complex. This simple and economical process is used both in small scale as well as large scale production. (Tirucherai and Mitra et al, 2003).

Neutralization precipitation method

Drug in alkaline solution is mixed with aqueous cyclodextrin and the resultant basic solution is counteracted via hydrochloric acid solution. At the point of neutralization, a white precipitate is formed. Precipitate of inclusion complex is filtered, dried and stored. Drugs which are prone to acid and alkaline degradation cannot be complexed using this technique.

Milling/Co-grinding technique

Milling of the drug and cyclodextrins by use of mechanical devices result in inclusion complexes. Intimate mixture of drug and cyclodextrin is introduced into an oscillatory mill/ball mill and grinded. Unlike other methods of complexation, this method does not need any organic solvents (Van Hees et al, 1999).

Atomization/Spray drying method

Dry product from a liquid phase can be obtained using the abovesaid method and spray drying can improve storage stability (Charoenchaitrakool et al, 2002). Competent interaction of active substance and cyclodextrins to obtain a flawless composite is the edge that atomization possesses over other complexation techniques. Contact to high temperatures and low practical produce are the major drawbacks of this technique.

Supercritical antisolvent technique

Carbon dioxide will be miscible in organic solvent but used as anti-solvent for the solute. Supercritical carbon dioxide has advantages of having low critical temperature and pressure, being nontoxic, nonflammable and inexpensive and hence used for thermo labile drugs most frequently)(Al-MarzouqiAHet al, 2007). Most innovative and effective methods of complexation is supercrtitical antisolvent technique (Vamsi and Gowrisankar, 2007). This method has the advantages of being nontoxic, fast, and a low maintenance process with hopeful results and requiring high investment as disadvantages (Horn D and Rieger J,2001), (Suzuki, H et al., 2007).

Nanotechnology

Solubilisation of any drug relies on ultimate concentration reaching GIT. Solubilization increases the bioavailable quantity of drug in GI tract. Crystalline, coarse will not be able to penetrate the GI wall. This relationship between concentration and permeation through wall of GI tract was well explained by Fick's rule of diffusion.

Adolf Fick theorized Fick's laws back in the 19th age:

1.The flux (a vector) from diffusion is proportional to diffusivity and inversely proportional to concentration gradient.

2. The rate of concentration shift (increase or decrease) changes with time and is proportional to concentration gradient curvature.

Fick's First Rule of Diffusion

Mathematical expression is as follows:

$$N_i = -D_i \nabla C_i \quad \text{------(1)}$$

Where, for i, Ni - flux stated in mol m-2 s-1, Di - diffusion coefficient stated in m2 s-1, Ci – concentration in mol.

Fick's second rule:

$$\frac{\partial C_i}{\partial t} = D^i \nabla^2 . C_i \quad \text{---(2)}$$

Di is a constant.

This law is accurate in the cases of solids, dilute solutions, water and CO2 in air.

Fick's Second Rule of Diffusion

Unique diffusion of each entity makes mathematical simulation easy. Crystallization may happen once the concentration reaches supersaturation level under physiological conditions.

Two prominent impressions on solubility of an active ingredient can be sensed if drug is existing in nanoparticular dimensions: solubility is a function of particle dimensions according to kelvin equation if material is existing in size less than 100 nm

$$S(r) = S_\infty . exp \frac{2_\gamma . V_m}{r . RT} \quad \text{-------(3)}$$

Where, S(r) - solubility, S∞ - solubility of a bigger particle, γ - stiffness at interface, Vm - molar volume of substance, R - universal gas constant, T - absolute temperature in kelvin. This equation evidently demonstrates that solubility upsurges extremely when dimensions decline. This effect becomes more pronounced when the particle size is under approx. 100 nm.

As size declines, there would be high surface area accessible for dissolution and hence contributing to enhancement of solubility and bioavailability of nanoparticular formulations. This effect can be articulated by noyes- whitney equation:

$$\frac{dc}{dt} = \frac{D.A}{h}(C_r - C) \quad \text{------(4)}$$

Where, D is the diffusion co-efficient (m.sec-1), A is the surface expanse of a particle (m2), h is the thickness of layer, Cr is the section of high drug concentration close to the particle surface(Kg or moles/L), C is the concentration of drug in bulk medium (Kg or moles/L) and dc/dt is the concentration gradient of drug in given medium as a function of time (kg.sec-1). The intrinsic dissolution rate (kg.m-2.sec) is the dissolution rate of a pure solute, regularized to the solute surface area, and actually declines with time.

Drug elements dissolve when:

Solubility of drug is greater than the solvent concentration; this can be attained by reducing the particle dimensions as desired.

The drug particles have an enlarged surface area, which in turn can also be accomplished by reducing the particle size.

Coming back to the core topic, certainly, nanoparticles have excessive specific surface area. Smaller particle sizes will upsurge solubility and dissolution, which in turn has great effect on oral bioavailability.

All in all, nanotechnology has been proven to upsurge solubility and oral bioavailability.

Nanoparticle formulations:

Nanoparticle as a drug delivery approach was familiarized by Poste et al., 1976; Poste and Kirsh, 1983; Davis et al., 1987; Douglas et al., 1987; Papahadjopoulos, 1988. In pharmaceutical context, can be described as discrete particles with particle size less than 1 micron .

There are copious ways in which nanosuspensions of poor soluble molecules in water are made (Torchilin, 2005). The approaches can be a building-up approach through self-assembly (Bansal et al, 2002), or precipitation of bits from grander units.

Whatever is the approach chosen, ultimate result would be nanosizing of drug particles and there would be an enormous amount of surface energy available. Improper channeling of accessible free surface energy can root the nanosized elements to impulsively cumulate into further thermodynamically steady state. Important to the production of physically stable nanosuspensions is the use of stabilizers that channel the surface energy of the nanosuspensions by way of steric and/or ionic stabilization. An adequate stabilizer should not only own properties that wet the exterior of low water soluble compounds but is also projected to be inert. Process of stabilization transpires by the superficial adsorption of the stabilizer to the outward of the ill soluble entity.

Also attention has to be catered to regulate Ostwald ripening. Ostwald ripening outcomes from unrestrained precipitation or crystallization. Ostwald ripening can be controlled by monitoring strictures such as unit dimensions or size, arithmetic distribution, concentration of solids, option of stabilizer, and a fluid phase with negligible possibility to solubilize the ill soluble part.

Nanoparticle-Based Approaches for Solubility Enhancement

There are two broad categories under which all the methods of nanoparticle production fall under: the

first class is disintegration scheme which encompasses size reduction of coarse larger sized elements to desired size subdivisions (top-down procedures) and the another is nucleation of particles from the atomic or molecular level (bottom-up methods). Top-down method of production is based on size reduction of the particles whereas bottom-up methods rely on the principle of molecular level build-up. High-pressure homogenization (Junghans and Muller, 2008) or high-energy wet milling fall under the category of top-down processes (Radtke, 2001). Hydrosol way or spray freezing into liquid, or supercritical fluid technology or self-assemblage or precipitation of active drug particles can be quoted as references for bottom-up methodology (Tong and Cheng, 2007). As a delivery vehicle, nanoparticles have verified rewards (Keck and Muller, 2006).

Nanosuspensions

Processes of production of Nanosuspensions:

Nanosuspensions can either be prepared by dispersion based or precipitation-based processes. Proper selection of a preparation method should take into consideration of following:

1. Simplicity, reproducibility and efficiency.
2. Large scale-up capability
3. Following regulations
4. Capability to incorporate diverse amounts of drug.

The formulation methodologies of nanosuspensions could be considered into two techniques which are top-down and bottom-up techniques.

Media Milling:

Media mill contains a milling chamber, where the actual Media mill contains a milling chamber, where the actual milling takes place, a shaft and a recirculation chamber, where particles get recirculated until desired particle size is obtained. The media milling system industrialized by Liversidge et. al. uses pearl or media mills to yield nanoparticles (Figure 6). A suspension of active ingredient, stabilizer and milling media(pearls) are introduced into the milling chamber and operated at high shear rates. Attrition and collisions produce nanosized particles. Scale-up from pilot plant to large scale and invariability from lot to lot are the advantages of media milling. Erosion of pearls surface may contaminate the product during the process (Barrett, 2004). Examples of marketed nanoparticles are quoted in the below Table 1.

Homogenization at high pressure

Passing a suspension of active substance and stabilizers forcibly, through a regulator with a small slit under high pressure is the dogma of this process. Wong et al, 2003) It is habitually separated into two broad categories:

a) Dissocubes,

b)Nanopure

Dissocubes

This methodology forces a suspension of drug and stabilizer through a small slit at high pressure. This passage of suspension through a small vent causes a surge in pressure which in turn causes water to boil. When suspension exits orifice, reaches regular air pressure, the bubbles from scorching of water implode and active ingredient particles rush to the middle and in the progression, collide against each other triggering a drop in the size. Most of the times, process requires multiple passes (Dearns, 2000). Premilling can be done prior to homogenization to obtain nanosuspensions of higher solid content.

Nanopure or Piston- Gap homogenization in a water reduced mixture:

Unlike Dissocubes, Nanopure is homogenization in water-free media35. Cavitation or imploding of gas bubbles from boiling of oils and oily fatty acids is deficient in producing collisions since oils have high boiling point due to their very low vapor pressure. Cut in static pressure will be inadequate.

Nanoedge

Combined principles of precipitation and homogenization used in nanoedge technology results in reduced size and better stability in a briefer time. This skill can resolute chief drawbacks of precipitation procedure alike crystal progress and instability. Precipitated suspension is homogenized. Precipitation is carried out in aquatic environment using water mixable solvents. An evaporation step has to be included in the production to remove solvents completely.

Nanojet technology

This method uses a high-pressure chamber where particles in suspension are separated into portions, bombarding with one another at high pressure. Inflated shear energy formed in the hyperbaric chamber leads to diminution. Equipment based on the above working principle include M110L and M110S microfluidizer. The chief restrictions in using this practice is the sum of times that the particle has to pass through microfluidizer to obtain desired size.

Nanoprecipitation method

In this method, drug nanosized particles are precipitated out by adding drug solution into organic solvent containing stabilizers. Nanoprecipitation can be carried out by top down and bottom up approaches. Stabilizers help in prevention of particle aggregation and ostwald ripening.

Emulsification–solvent evaporation technique

Drug is emulsified in an anti-solvent for active ingredient. Disappearance of solvent results in precipitation of the drug. High shear forces created

using fast moving mixer blades can keep a check on crystal growth and particle aggregation.

Hydrosol method

This method bears a resemblance to above method. The solitary variance among the two procedures is that the drug solvent is mixable with the Anti-solvent. Inflated shear energies created using high speed mixer blades can be used in this method also to keep a check on crystal growth and particle aggregation.

Supercritical fluid method

RESS, SAS and PCA have been reported to produce nanosuspensions. This method involves rapid extension of the drug solution in supercritical fluid leading to salting out of the active substance as fine subdivisions. Precipitation with compressed anti solvent method atomizes drug solution into a compartment comprising compressed CO2, causing supersaturation, which ultimately leads to precipitation(Pasquali et al, 2006).

Various other techniques also have been reported and used since decades in an effort to recover solubility and rates of dissolution of low water solubility drugs:

1. Solid Dispersion
2. Size Decrease
3. Nanonization
4. Co solvency
5. Hydrotropy
6. pH Tuning
7. Ultrasound energy restrained crystallization
8. Supercritical Fluid (SCF) Process
9. Inclusion Complexation
10. Self-Emulsifying or Self-Micro Emulsifying Systems
11. Liquisolid Approaches

Solubility improvement practices can be categorized into physical alteration techniques, chemical amendments and miscellaneous methods (Ketan Savjani et al, 2012).

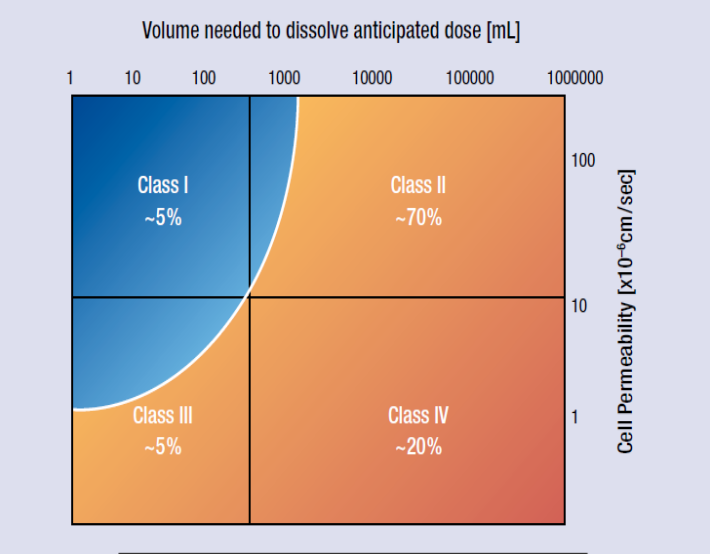

Figure 1: Biopharmaceutical classification system

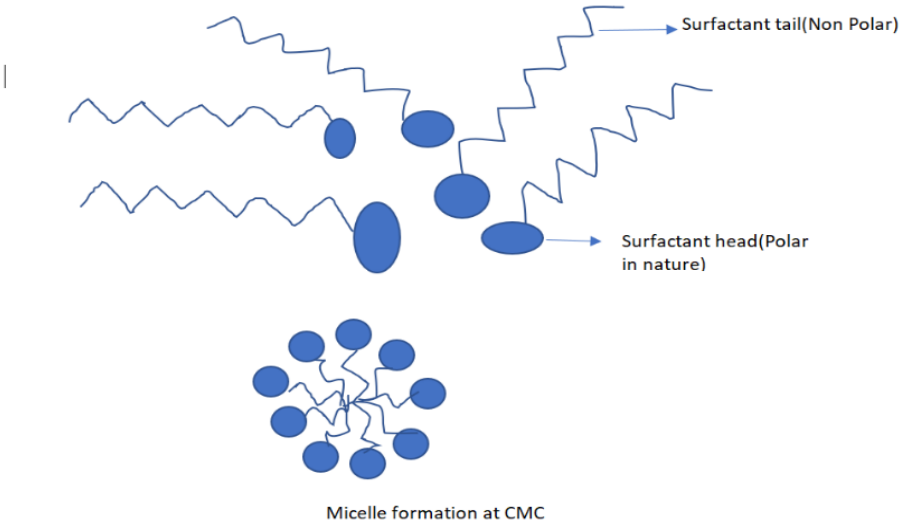

Figure 2: Surfactant monomers and micelle formation

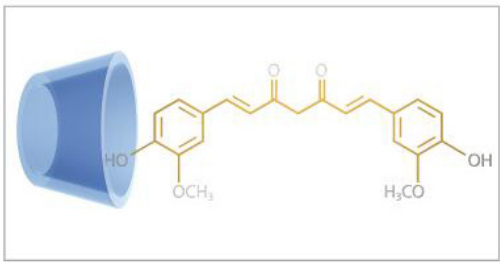

Figure 3: Inclusion complexation using a model drug

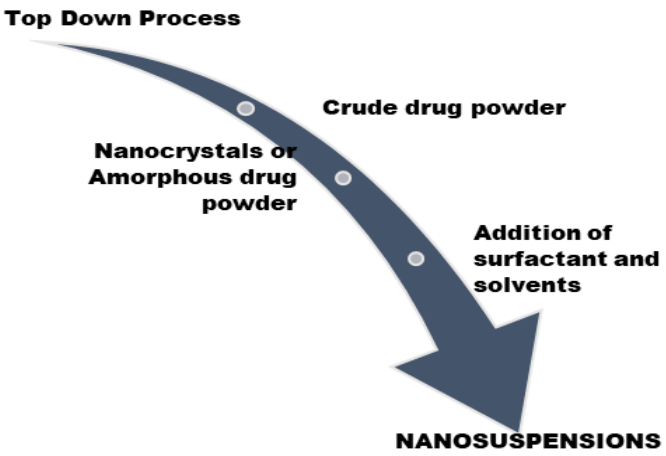

Figure 4: Preparation of Nanosuspensions- Top down process

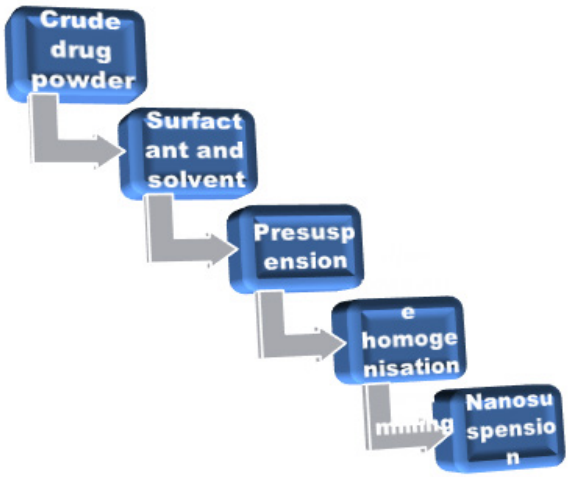

Figure 5- Preparation of nanosuspension- Bottom up process

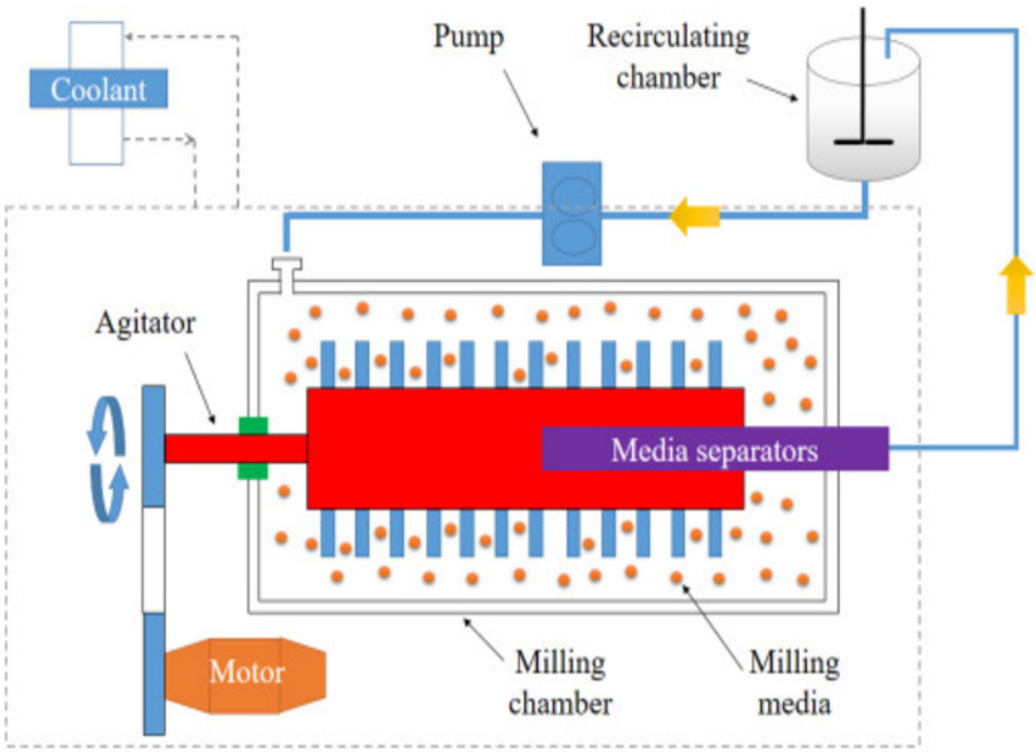

Figure 6: Milling chamber using pearls or media

Table 1: Few examples of marketed nanoparticles using media milling technique

Brand/Autonym	Active ingredient	Suggested in	Dosage Form
Tricor	Fenofibrate	Hypercholesterolemia	Oral tablet
MegaceES	Megestrol	Anti-anorexia	48-145 mg

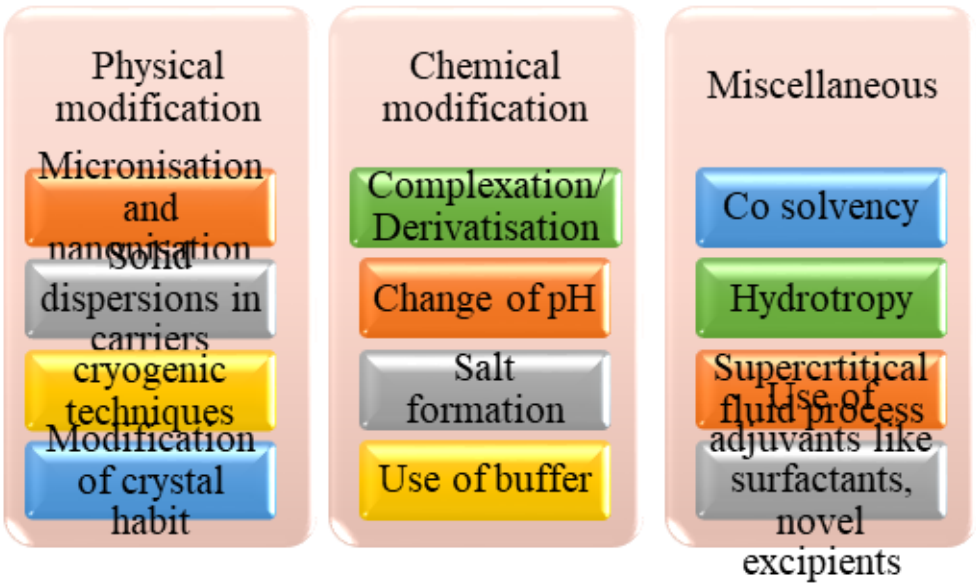

Figure 7: Other methods to improve solubility and bioavailability

CONCLUSION:

Solubility and bioavailability are two important factors Solubility and bioavailability are two important factors which greatly influence rate of dissolution and ultimately, quality of therapeutic activity. There are many methods available to improve solubility, all of them cut down to the roots of basic approaches that can be modified, maneuvered to higher level engineering and science of solubility enhancement. Above-described approaches can be treated as basic building blocks of solubility enhancement. These methods can be used in combination or alone to improve solubility of chemical entities with low solubility. The above manuscript focusses on use of surfactants or hydrophilic carriers to disperse solid substances, use of complexing or chelating agents to complex molecules with low solubility and also improvement in surface area exposed to solvent atmosphere- nanonization, all of which help in solubility enhancement of BCS class II drugs.

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