International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.13, No.02, pp 80-93, 2020

Solubility Enhancement of Poorly soluble Drugs by using Novel Techniques : A Comprehensive Review

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Abstract : The primary aim of this review was to improve the solubility and Bioavailability of BCS Class-II drugs because of their low solubility and dissolution rate. Solubility is one of the imp parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Hence the class- II drugs require enhancement in solubility and dissolution rate in there formulation development particularly in solid dosage form such as in tablet and capsule. So because of this there are several methods and newer emerging technologies have been developed for increasing the solubility as well as Bioavailability of class –II drugs. In this article review on literature on newer techniques or methods as well as recent research on formulation development of class- II drugs was done.
Keywords : Bioavailability, Solubility, Lipophilicity, BCS.

Introduction:

The Important Phenomenon and as a most of time discussed but a still or not a completely resolved issue, ‘’Solubility or dissolution enhancement technique remains a most challengeable field for the researchers in the formulation design and developmental process. Solubility and dissolution. These are the core concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine.[1] As a result, recently more than 40% of new chemical compounds are fails before entering into the drug developmental process because of their non-optimal biopharmaceutical properties. These properties such as rate and extent of absorption, rate of distribution etc.[2]

Hence, according to IUPAC, The solubility may be defined as, ‘The analytical Composition of saturated solution expressed in terms of the proportion of a designated solute in a designated solvent is the solubility of that solute. It is expressed as a Concentration, Molality, Mole Fraction, Mole Ratio etc.[3]

DOI= http://dx.doi.org/10.20902/IJPTR.2019.130211

Solubility of a poorly water soluble drug is a frequently encountered challenge in screening studies of New Chemical Entities (NCE) as well as in formulation design and development. There are several methodologies can be developed to improve its bioavailability property. After administration of drugs by orally they are completely absorb but showed fair solubility in gastric medium and good bioavailability. But this bioavailability depends upon the several factors say as drug permeability through lipophilic Membranes. Hence at low concentration solubility is difficult to measure analytically. Therefore to ensure rapid and efficient formulation development a solubility classification for the selection of an appropriate formulation system for highly active compounds with good permeability was introduced.[4,5]

It was in August 2000, the U.S. FDA issued Guidance for Industry covering the Biopharmaceutical Classification System (BCS). The BCS is a scientific framework for the classifying a drug substance on the basis of their equilibrium aqueous solubility as well as intestinal permeability. When combined with the *in vitro* dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, dissolution rate and intestinal permeability. These three factors are govern the rate and extent of oral drug absorption for immediate release solid oral dosage forms. The BCS defines four classes of drug substances on the basis of their solubility and permeability characteristics.[6]

Table 1: The Biopharmaceutical Classification system for drugs.

	High Solubility	**Low Solubility**
High Permeability	Class I	Class II
Low Permeability	Class III	Class IV

Process of Solubilization :

It involves the breaking of intermolecular or interionic bonds in the solute, separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between solvent and the solute molecule or ion.[7] This solubilization process occurs into three steps.

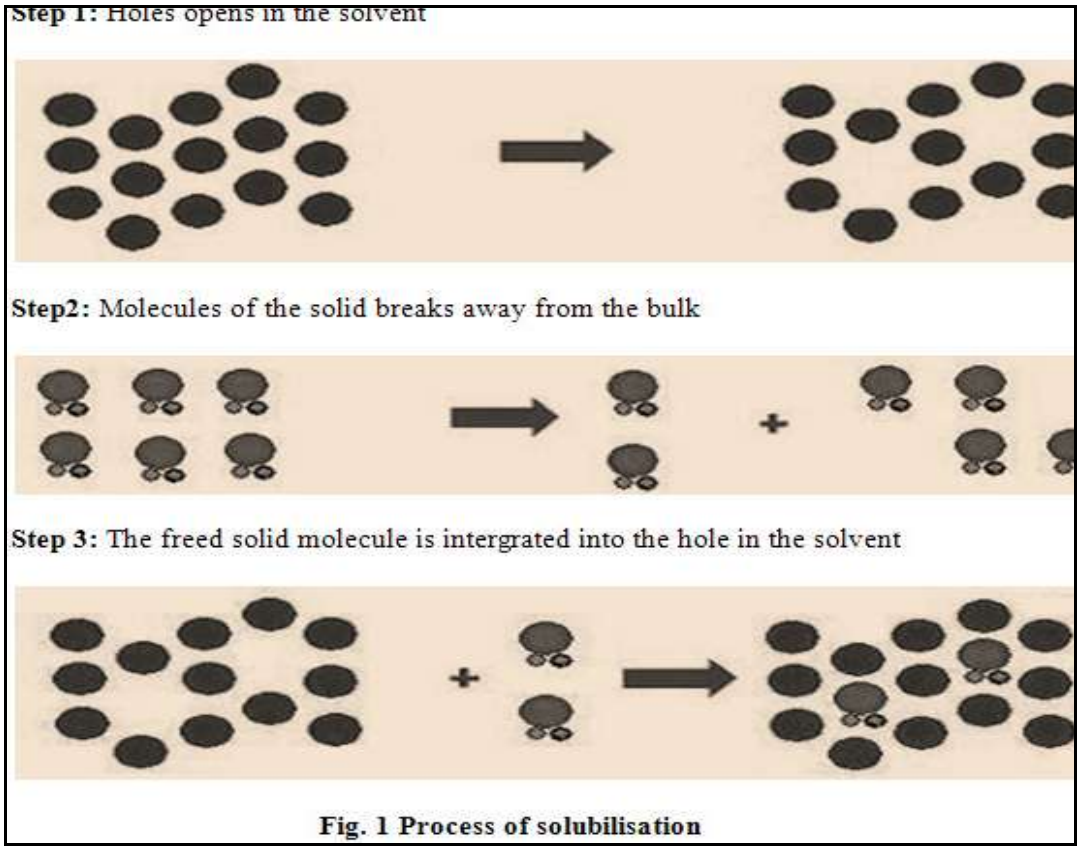

Fig. 1 Process of solubilisation

Factors Affecting Solubilization:

The solubility depends upon the nature and composition of solvent medium the physical form of solid as well as temperature and pressure of system. Let us discuss with a factors with a factors which affect the solubility such as,

1) Particle Size :

The size of the solid particle influences the solubility because as a particle becomes smaller and as that of the surface area to volume ratio increases of the particle. The larger surface area allows a greater interaction with the solvent.

2) Temperature:

As the temperature is increased than the solution process absorbs energy and the solubility will be increased but if the solution process releases energy then the solubility will decrease with increasing temperature. A few solid solutes are less soluble in warm solutions. For examples all gases, solubility decreases as the temperature of the solution increases.

3) Pressure:

For solids and liquid solutes, changes in pressure have practically no effect on solubility but for gaseous solutes, an increase in pressure, increases solubility and a decrease in Pressure, decrease the solubility.

4) Nature of the solute and solvent:

Only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room Temperature while 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures.

5) Molecular size:

The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

6) Polarity:

Polarity of the solute and solvent molecules will affect the solubility. Generally like dissolves like means non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. So The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. The other forces called London dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolar solvent a chance to solvate the solute molecules.

7) Polymorphs:

Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

8) Rate of solution:

The rate of solution is a measure of how fast substances dissolve in solvents. A various factors affecting rate of solution like-

(a) Size of the particles:

Breaking a solute into smaller pieces increases its surface area, when the total surface area of the solute particles is increased; the solute dissolves more rapidly because the action takes place only at the surface of each particle and hence increases its rate of solution.

(b) Temperature:

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. But For the gases reverse is true.

(c) Amount of solute already dissolved

When there is little solute already is in solution, dissolution takes place relatively very rapid. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

(d) Stirring:

With liquid and solid solutes particles, stirring brings fresh portions of the solvent in contact with the solute and which results in increasing the rate of solution.[8]

Techniques of Solubility And Bioavailability Enhancement:

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the recent approaches as well as newer techniques to improve the solubility are ;

1) By using Surfactant:

A Conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting salvation interaction. A Wide variety of surfactants like Tweens, spans, polyoxyetylene glycerides, polyoxyetylene stearates and synthetic block copolymers etc. are very successful as excipient and carrier for dissolution enhancement.[9]

2) pH Adjustment :

Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase the water solubility behavior. Therfore as per the pH partition hypothesis and Handerson- Hesselbatch equation , ionization of a compound is dependent on the pH of media and pKa of drug. Also the change in the ionic compound can result to in –situ salt formation. Therefore this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in GIT.[10,11]

3) Manipulation of solid state:

From the stability and bioavailability aspects, the crystalline form of a drug is of pharmaceutical importance. Polymorphism (existence of a drug substance in multiple crystalline forms) can cause variations in melting point, density, stability and drug solubility as these properties depend on the escaping tendency of the molecules from a particular crystalline structure. As a rule, for a drug that have the highest order of crystallinity is the most stable form, exists in multiple polymorphic forms, i.e. with the least amount of free energy, and, consequently, possesses the highest melting point and the least solubility. By controlling the crystallization process, amorphous or meta stable forms of drugs possessing high free energy can be forcibly created. They offer the advantage of higher solubility but suffer from stability issues unless stabilizers intended to inhibit crystal growth are incorporated in the formulation.A typical example for this is a high profile case involving polymorphism was withdrawal of ritonavir (Norvir®) capsules from the marke in 1998 because a less soluble (and consequently less bioavailable) polymorph was identified two years after the product was approved and marketed, causing a decrease in bioavailability of the drug. This incident sensitized the pharmaceutical industry

to the critical importance of polymorphism and encouraged the inclusion of polymorph screening as a routine component of preformulation studies.[12]

4) Self- Emulsifying Drug Delivery System:

A self-emulsifying or self-micro emulsifying system is the concept of in situ formation of emulsion in the gastrointestinal tract. It is defined as the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophillic drug dissolution and absorption. So The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. .

The large quantity of surfactant in self-emulsifying formulations (30- 60%) irritates GIT. Most self-emulsifying systems are limited to administration in lipid filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell .A Neoral® is an classical example of self microemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine A administered as Neoral® could be 174- 239% of the bioavailability of cyclosporine A from Sandimmune®, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long-term use due to the potential of causing diarrhea.[13,14]

Advantages:

1) In relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation.

2) They are thermodynamically stable.

Disadvantages:

1) It includes chemical instabilities of drugs and high surfactant concentrations.

5) Micro emulsion:

A Micro emulsion is an optically clear, isotropic, thermo dynamically stable translucent system which contains a mixture of oil, Hydrophilic surfactant and hydrophilic solvent in which the poorly water soluble drug dissolves. When comes in contact with water the formulation is spontaneously disperse or self emulsified to form a very clear emulsion of exceedingly small as well as uniform oil droplets containing the solubilized poorly soluble drug.

These systems have been employed to increase the solubility of many temperature which are practically insoluble in water along with incorporation of proteins for oral, parentral as well as percutaneous or transdermal use.[15,16] These homogeneous systems can be prepared by using a wide range of surfactant concentration and oil to water ratio are of fluids of low viscosity. So for improving the solubility of drugs formulated as a micro emulsion various parameter play an important role such as Surfactants, Surfactant Mixtures and co – surfactants.

The surfactants like polyoxy ethylene surfactants for ex. Brij 35or sugar esters like sorbitan monooleate (Span 80) , cationic or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate or zwitter ionic such as phospholipids like lecithin because of it exhibits excellent bio-compatability.[17,18,19.]

6) Particle Size Reduction:

Micronization or nanoization is one of the most potential approaches to improve the bioavaliblity of lipophilic drugs by an means of reduction of the particle size to its submicron level. During the Preformulation

studies of any formulation particle size is an critical parameter which should be strictly controlled. [20]To enhance the solubility the reduction in the particle size as a successful way but if it is in uncontrolled or un-optimized it can forms the recrystallization as well as re-aggregation of drug upon storage. Because of this a thorough study on the particle size and physical stability should be done. By using the conventional techniques size reduction to submicron range is not possible[21].

7) Supercritical Fluid Process (SCF) :

Another novel nano-sizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. Super critical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power[22]. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids).At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power Once the drug particles are solubilized within SCF, they may be re-crystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. The flexibility and precision offered by SCF processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. Current SCF processes have demonstrated the ability to create nano-particulate suspensions of particles 5- 2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement[23] . Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed anti-solvents process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical anti-solvents processes (SAS) and aerosol supercritical extraction system (ASES).[24]

8) Complexation:

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzyamatic degradation of starch. The three major cyclodextrins are α,β, and ʎ-CD are composed of 6,7and 8 D-(+) glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups oriented outwords. Importantaly cyclodextrins have a hydrophilic exterior and hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parentral delivery. When the aqueous solubility of the pure drug is low then there is a greater relative solubility enhancement which is obtained through cyclodextrin complexation[25]. There are certain forces which plays an imp role for the formation of complexation were attributed to-

1. The exclusion of high energy water from the cavity,
2. The release of ring strain particularly in the case of -CD,
3. Hydrogen and hydrophobic bindings
4. Van der Wal's interactions,[26]

The most widely used native cyclodextrin is β- CD but its application in the pharmaceutical application because of its low aqueous solubility (1.85 gm/100 ml, 25^0C), toxicity profile and low aqueous solubility of the formed complexes. Accordingly derivatives such as hydroxypropyl β-CD , and sulphobutylether- β-CD have been developed forto produce more water soluble as well as less toxic entities. This is the most widely method

to enhance the water solubility and increase the stability of hydrophobic drugs by using cyclodextrins. By using following methods solid dispersion complexes can be prepared.

8.1) Kneading Method:

In this technique cyclodextrin (CD) is impregnated with water and forms a paste. after that drug is added and kneaded for specific period of time. The kneaded mixture is then added and dried and passed through sieve if required.[27]

8.2) Lyophillization / Freeze drying technique:

In this technique the solvent system from the solution is removed through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermo labile substances can be successfully made into complex form by this method.[28]

8.3) Supercritical Anti solvent Technique:

In this technique supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of the drug with CD in the solid state.[29]

Advantages:

1. It is a non-toxic Method.
2. Fast process, maintenance cost is very low with promising results.

Disadvantages:

1) It requires high initial cost.

8.4) Microwave Irradiation Method:

This technique uses the microwave irradiation reaction between the Complexing agent and Drug by using a microwave oven.T he drug and CD in definite molar ratio are dissolved in a mixture of water as well as organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time nearly about one to two minutes at 60^{0} C. in the microwave oven. After the reaction is completed adequate amount of solvent mixture is added into the above solution or reaction mixture to remove the residual uncomplexed free drug and CD. Then the remained precipitated is separated by using a whatman filter paper, and dried in vaccum oven at 40^{0} C for 48hrs.[30]

9) Hydrotrophy :

It is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. It designate the increase in the solubility in water because of the presence of large amount of additives. In the point of Mechanism,it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[31] Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increases the solubility in given solvent are said to be “salt in” the solute and those salts which decrease the solubility known as “salt out” of the solute. There are Several salts with large anions or cations which are very soluble in water resulted in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Whereas Hydrotropic solutions does not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Specific examples may include Ethanol, aromatic alcohols like resorsinol, pyrogallol, catechol and b-napthols as well as salicylates, various alkaloids like caffeine and nicotine, ionic surfactants like diacides, SDS and dodecylated oxydibenzene.[32]

10) Solid Dispersion:

The concept of solid dispersion was firstly proposed by Sekiguchi and obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water soluble carrier in the early 1960.[33] In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which increases the dissolution of the drug. Solid dispersion technique can yield eutectic (Non-Molecular Lebel mixing) or solid solution.(Molecular –lebel Mixing) products.[34,35] eutectic Dispersions are homogeneous dispersion of crystalline or amorphous drug in crystalline or amorphous carrier. Despite the promising aspect of dissolution enhancement and simplicity of concept , the solid dispersion technique has failed to take popularity because of Manufacturing, Scale Up- as well as Stability Problems. Solid dispersion is a useful pharmaceutical technique for increasing the dissolution of drug in dosage form. Some of the hydrophilic carriers which are used in yhe pharmaceutical industry are polyvinyl pyrolidone, PEG, Plasdone, Tween 80 , sls etc. There are various technique used to enhance the aqueous solubility of hydrophobic drug such as Holt Melt method (Fusion Method),Solvent Evaporation Method, Hot Melt Extrusion.

10.1) Hot Melt Method (Fusion Method):

In this method the physical mixture of a drug and water soluble carrier was heated directly upto it melted. Then thee melted mixture was cooled and solidified rapidly in an ice bath under the vigorous stirring. After that the final solid mass was crushed, pulverized and sieved, which can be compressed into tablets with the help of tablet excipient.[36]

10.2) Solvent Evaporation Method:

In this technique the drug and carrier was dissolved both in a common solvent and then evaporate the solvent under vaccum until to produce a solid solution. Many Investigators studied solid dispersion of Meloxicam 15, Nimuselide and Naproxen using a this technique

10.3) Hot Melt Extrusion:

This is a essentially same as that of fusion method except that intense mixing of the components which is induced by the extruder. Just like as that of traditional fusion process, miscibility of drug and matrix can be a problem. Also for heat sensitive materials high shear forces high local temperature in the extruder**.**

11) Co-Solvency :

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents. These are the mixtures of water and one or more water miscible solvents which is used to create a solution with enhanced solubility for the poorly water soluble compounds. Historically, this is one of the most widely used techniques because its simple to produce and evaluation purpose. Co-solvency has been utilized in different formulations including solids and liquids. Examples of solvents used in co-solvent mixtures such as PEG 300, propylene glycol or ethanol. Various concentrations (5-40%) of the solid binary systems with polyethylene glycol 6000 were employed to increase solubility and dissolution of meloxicam. Co-solvency techniques have also found use in spray freezing of liquid like in danazol with polyvinyl alcohol, poloxamer 407, and poly vinyl pyrrolidone K-15 in a micronized powder formulation. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophillic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co- Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Seedher and Bhatia (2003) investigated that the aqueous solubility of celecoxib, rofecoxib and nimusulide could be enhanced significantly by using ethanol as the second solvent and PEG-400-ethanol had highest solubilization potentiality among the mixed solvent systems. However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. Advantages: Simple and rapid to formulate and produce. Disadvantages: As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.[37-40]

12) Floating Granules:

Firstly, Patel Rajanikant et al[41]. utilized a novel approach for the dissolution enhancement of ibuprofen (a weekly acidic, non-steroidal anti inflammatory drug) by preparing the floating formulation. The Drug having high permeability through stomach because it remains 99.9 %unionize in the stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid -1.2) and mostly permeable through stomach but due to its solubility limitation property it can't enter in to the systemic circulation and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilized but can't permeate through its membrane. It was logically decided to design such formulations which retain in stomach for more than 2 hrs because of the drug was not completely soluble within 2 hrs hence to dissolve completely in stomach region, this can be achieved by making floating dosage form. Floating ibuprofen granules were prepared by using the fusion method. Ibuprofen (200 mg divided in to 50 mg and 150 mg), gelucire 44/14 (350 mg melted) and ibuprofen (50 mg) added, disperse with glass road for uniform distribution of drug in to molted carrier, remaining 150 mg ibuprofen added in to molted Gelucire 44/14, this whole dispersion added in to the molted gelucire 43/01. In optimized formulation, Granules remain floated for 3 hrs., gave 100%drug release in 150 minute in stomach region where it remain in 99.9% unionize form and absorbed to systemic circulation.[42,43]

13) Nano- Suspension:

A pharmaceutical Nano-suspension is a biphasic systems which consist of nano sized drug particles which is stabilized by using the surfactants for either oral or topical use or parenteral and for pulmonary administration. This technology has been developed as a promising candidate for the efficient delivery of hydrophobic drugs.[44] this technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. There are various methods which are used for preparation of Nano-suspension such as Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege).[45] Out of these Some techniques are discussed here,

13.1) Precipitation Technique:

In this technique the drug is dissolved in a solvent, which is then added in to non-solvent for precipitate of the crystals. The drugs such as Danazol, Naproxen etc are prepared by using this technique to improve their dissolution rate and oral bioavailability.

13.2) Nano –Crystals or Nano systems (Media Milling) :

In this technique by using the high shear media mills nano-suspensions are prepared. Firstly The milling chamber charged with the milling media, water, drug and stabilizer which is rotated at a very high shear rate under controlled temperature for several days of time(at least 2-7 days).In that the milling Medium is composed of glass, Zirconium Oxide or Highly Cross- linked polystyrene resin.

14) Nano-Crystallization:

The nanocrystallization is the process in which decreasing of drug particles into the sizerange of 1-1000 nanometers. There are two distinct methods which are used for producing nanocrystals say as 'bottom-up' and 'top-down' development. In the top-down methods (i.e.

Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

14.1) Milling:

Nanoscale particles can be produced by using wet milling process. In ball mills,by using the Impact and attrition forces the particle is reduced. The most common models are a tumbling ball mill and a stirred media mill. The degradation of mill surfaces and subsequent suspension contamination are problems of this method.

14.2) High pressure homogenization:

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenization can be performed in water or alternatively in nonaqueous media or water-reduced media. The particles are disintegrated by cavitations and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature .The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

14.3) Precipitation

In the precipitation method, a dilute solution is first produced by dissolving the substance in a solvent. The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air.

Newer Techniques for Solubility and Bioavailability Enhancement:

In concern with the New Chemical Entity (NCE) for exhibiting there therapeutic activity to increase the frequency of poorly soluble drug is of major tool in the pharmaceutical industry now days. Such drugs are very difficult to process as well as administered into the patient because of their poor dissolution property. This is an Imp. Task for the scientist to increase the solubility of poorly water soluble drug. There are various methods or techniques available for improvement of solubility of poorly water soluble drug some of the approaches are discussed here with as follows,

A) Liquisolid Technique:

This system is refers to the Formulations which is formed because of the liquid drugs, drug solution or drug suspension in a nonvolatile solvent into a Dry, Free flowing, Non adherent and a Compressible powder as well as stable Mixture by blending the suspension or solution, using the suitable carriers and coating materials. There are various grades of starch, Lactose and cellulose available and that can be used as a Carrier. Also Silica powder may be used as an good coating material by using a very fine grade.

The process of emulsification which increases surface area of particles and that can leads to increase in the drug release profile from the suitable vehicle. In this the surfactant play an Imp. Role which can mimic the formation of micelles in a bile salts and because of this solubility characteristics of poorly water soluble drug is increases. The Rate and Extent of absorption of drug is affected if the dissolution as well as solubilization characteristics of hydrophobic drug are changed.[46]

A.1) Liquisolid Tablets:

It is a newly technique developed by Spireas et al.[47] Liquisolid technique showed as a Imp.techniqe for the improvement of dissolution rate of the water insoluble drugs. This system showed that a acceptable flow property as well as good Compressibility. Liquid lipophic drugs or water insoluble drugs are dissolved in a non volatile solvent and this liquid form which can be converted into a dry, non adherent, free flowing as well easily compressible powder blendwith the use of suitable carrier as well as coating material. As we know the drug in the form of liquid medication it is in either solubilized or into a molecular dispersed form so because of this it increases the surface area and wetting time for the dissolution of liquid solid tablet of water insoluble drugs shows better or improved dissolution characteristics and which is turn into a good bioavailabilty.The advantage of this system is as its low manufacturing cost hence now a day's most of the pharmaceutical company applied this technique during the production.[48]

A.2) Glassy Solid Solution:

It is a specific kind of solid dispersions Technique, where in a drug is dissolved in an amorphous carrier at the molecular level. In order to distinguish between solid suspensions and solid solutions in the case of isomalt as carrier, hot stage microscopy (HSM), dissolution testing and differential scanning calorimetry (DSC)

is used. The carrier isomalt (1-O-α-Dglucopyranosyl- D-mannit dihydrate/6-O-α-Dglucopyranosyl- Dsorbit) is registered as sugar substitute and is mainly used for the production of sugar free hard candies. Isomalt can be heated above its melting point without decomposition. By cooling the melt to room temperature, it solidifies amorphously with a glass transition at 60°C. Other sugar polyols exhibit lower glass transition temperature (Tg) values, e.g. mannitol and sorbitol have reported values of 10.7°C and 0°C. Thus, glassy systems of isomalt should be more stable than glassy systems of other polyols.[49]

B) Spherical Agglomeration:

It is a process in which combined unit process of crystallization, Agglomeration and Spheronization. The resultant crystals can be designated as spherical agglomerates. Due to the their spherical shape, the particle characterization properties such as flowability as well as compressibility of the obtained crystals are more, which makes it more viable for direct tableting or coating without any further made by simply fusing with Gelucire 44/14 which showed a 3 hrs. residence time with 100% drug release. Furosemide granules with Hydroxylpropyl β- cyclodextrin were prepared by three methods such as kneading method, physical mixture and solvent evaporation method which dissolved completely in 30 mins.[50,51]

C) Sono Crystallization :

It is the process in which the application of ultrasound energy to modify the nucleation of crystallization. The energy of ultrasound leads to compression as well as expansion. After completion of some cycles it forms a bubbles and grows then it collapse. This collapse of formed bubbles gives the energy to enhance the nucleation process which leads to a highly repeatable as well as predictable crystallization process.

Significance of applying Ultrasound to crystallization is as follows,

1. It narrows the metastable zone width,
2. Narrows the distribution of particle size,
3. Minimizes the level of cooling process for achieving the crystallization,
4. The process is highly repeatable as well as predictable.
5. Controls the polymorphs.

For the development of Inhalational drug delivery there are two methods used in an industrial level say as Ultrasound Mediated Amorphous to Crystalline Transition (UMAX) and Dispersive Crystallization with Ultrasound (DISCUS).[52]

D) By using Prodrug:

A prodrug is a drug molecule which is a covalently bound to a pharmacologically inactive moiety also known as promoiety with the aim to overcome on the various physicochemical and biopharmaceutical limitations of the parent drug so because of that the therapeutic effect of the drug would be realized. For getting a accurate pharmacological result or effect a prodrug have must undergo a chemical or biochemical transformation to the parent drug within the body at a reasonable rate and extent. It is an key objective when applying into a class II or IV poorly soluble drug with respect to solubility enhancement. Perticullarly, a prodrug should possess an adequate solubility to be formulated into a solution for IV administration. also acceptable solution stability to provide an appropriate product shelf life and the ability to rapidly convert to the pharmacologically active parent drug. In addition, the promoieties must also prove to be nontoxic. Water soluble prodrugs of steroids such as sodium hemisuccinate esters and sodium phosphate esters represent the successful examples for the use of prodrugs of poorly soluble drugs for intravenous (IV) administration. [53-54]

E) Combination With Other Drug:

There are a number of solubilizing agents are available, each of these has a number of significant disadvantages. The idea of combining two or more drugs with the drugs having complementary mode of action can give the additive therapeutic effect along with the improvement in the solubility. In a research when clarithromycin and prednisolone were combined with paracetamol, caffeine and ibuprofen, for both the

solubility was significantly increased up to a certain optimum concentration of the paracetamol. The magnitude of solubility enhancement was relatively smaller in case of prednisolone than clarethromycin.[55-56]

Conclusion:

The Most Critical Factor in the formulation development is an solubility of drug molecule. Because it is the key factor which controls the formulation of the drug as well as its therapeutic efficacy. For oral absorption the dissolution of the drug is an rate determining step therefore solubility is an Imp requirement for formulation as well as manufacturing of different dosage form of different drugs.

Here, various techniques have described either in alone or with combination for the improvement or enhancing the solubility. on the basis of their Effectiveness as well as its safety with respect to biocompatibility of the excipients the choice of the method is differ. In concern with the orally administered drugs, the solubility is an one of the tare limiting parameter for achieving the desired concentration in the systemic circulation to get a Pharmacological response. Solubility enhancement is an very imp. and also necessary because many drugs that have bioavailability gets affected when used.

So, now it is possible to increase the solubility of poorly water soluble drug with help of various techniques which are discussed above**.**

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