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NOVEL APPROCHES FOR ENHANCEMENT OF SOLUBILITY: A REVIEW

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ABSTRACT

One of the most challenging problems occurring in pharmaceutical field with new chemical entity is the solubility in aqueous medium. The therapeutic effectiveness of NCE is depends upon bioavailability and ultimately on solubility. Currently only 8% of new chemical entity (NCE'S) only has good solubility and permeability while more than 40% NCE'S of have a problem of solubility. Most of NCE'S are failing in drug development pipeline because of non-optimal biopharmaceutical properties. Mainly this problem observed in BCS class II drug. Solubility is qualitative as well as quantitative term. It is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the most important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The problem can be solved by different technological approaches during the pharmaceutical product development like solid dispersion, micronisation, micelle formation, novel techniques like lyophilisation, floating granules are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Key Words: Solubility, bioavailability, cyclodextrin, solid dispersion, micro emulsion, cryogenic technique

INTRODUCTION

For orally administered drug shows its therapeutic effectiveness, only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown *[1]*. Currently only 8% of new drug candidates have both high solubility and permeability and more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water *[2, 3]*. As a result, this new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties. These properties e.g. rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration and to avoid side effects can exert a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system[4]. There are numerous approaches available and reported in literatures to enhance the solubility of poorly water soluble drug.

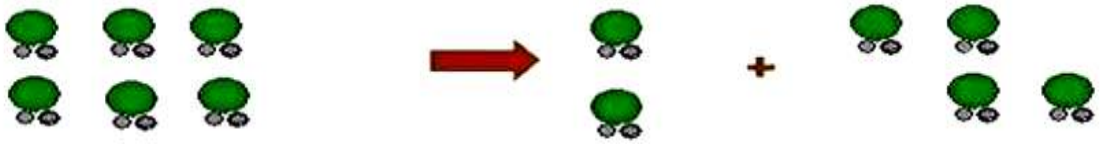
Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. Qualitatively solubility may be defined as the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion. Quantitavely solubility may be defined as the amount of substance that passes into solution in order to establish the equilibrium at constant temperature and pressure produce a saturated solution is known as the solubility of a substance *[5]*.

Process of solubilisation

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. *[6]*

Step 1: Holes opens in the solvent.

Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

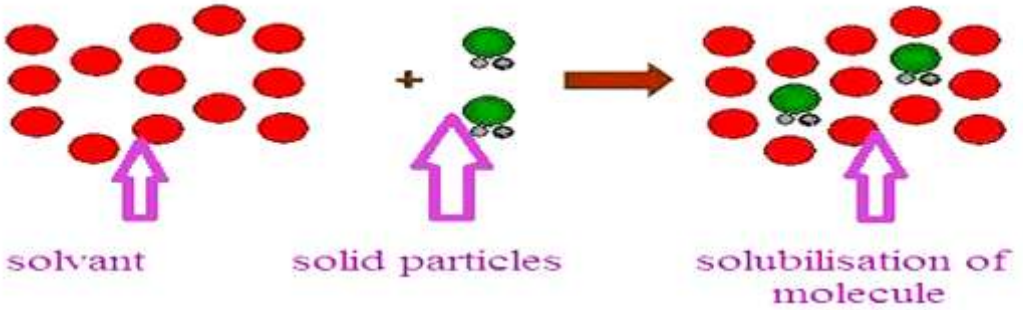


Figure No. 1 Process of Solubilisation

TECHNIQUES OF SOLUBILITY ENHANCEMENT

The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form.

A. Physical methods

1. Particle size reduction

According to the Noyes-Whitney equation, the rate of dissolution (dC/dt) depends on the effective surface area (A) of the drug particles. By reducing particle size, increased surface area improves the dissolution properties. *[5]*

Micronization

Micronisation is another conventional technique for the particle size reduction. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronisation is not

suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Micronisation is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. E.g. Norethindrone and Dienogest, griseofulvin etc. *[7, 8]*

Nanosuspension

Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. There are two methods for preparation of nanosuspension. They are 'Bottom up technology' and 'Top down technology'. For the production of nanoparticles in Bottom up technology the drug is dissolved in a solvent, which is then added to non-solvent that causes precipitation of the fine drug particles10. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. Nanosuspensions are produced by homogenization, wet milling process, Media Milling (Nanocrystals), High Pressure Homogenization in water (Disso cubes), High Pressure Homogenization in nonaqueous media (Nan pure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege).*[9]*

2. Modification of crystal habit

Polymorphs

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. The polymorphs differ from each other with repeat to their physical properties as solubility, melting point, density, hardness and compression characteristics. Certain classes of drug are particularly susceptible to polymorphism; for example, about 65% of the commercial sulfonamides and 70% of the barbiturates used medicinally are known to exist in several polymorphic forms. The particular polymorph formed by a drug depends on the conditions of crystallisation; the solvent used the rate of crystallisation and temperature. Under a given set of conditions the polymorphic form with the lowest free energy will be the most stable, and other polymorphs will tend to transform into it. E.g. Chloramphenicol palmitate A, B, C where B form-best bioavailability, A and C form-inactive biologically, Riboflavin III form is 20 times more water soluble than form.*[5]*

When some compounds crystallise they may entrap solvent in the crystal. Crystals that contain solvent of crystallisation are called crystal *solvates*, or crystal *hydrates* when water is the solvent of crystallisation. Crystals that contain no water of crystallisation are termed anhydrates. The particular solvate formed by a drug depends on the conditions of crystallisation, particularly the solvent

used. The solvated forms of a drug have different physicochemical properties to the anhydrous form. The rates of dissolution of various solvated forms of a drug differ but are generally higher than that of the anhydrous form. There may be measurable differences in bioavailabilities of the solvates of a particular drug; for example, the monoethanol solvate of prednisolone tertiary butyl acetate has an absorption rate in vivo which is nearly five times greater than that of the anhydrous form of this drug. *[4, 10]*
Aq. Solubility order - Amorphous > Detestable polymorph > Stable polymorph.

3. Drug dispersion in carriers

Solid dispersion

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Sekiguchi and Obi in 1961 first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures and once the carriers dissolved, the drug precipitated in a finely divided state in water. *[11]* Later, Goldberg et al. demonstrated that a certain fraction of the drug might also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug might be embedded in the matrix as amorphous materials. *[12]*

Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies. Such a crystalline solid dispersion may differ from that solid dispersion described under Drug and Polymer exhibiting immiscibility in fluid State, where even the drug–polymer fluid mixture is not miscible.

Eutectic Mixtures

Eutectic mixtures are formed when the drug and polymer are miscible in their molten state but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug and a carrier are co-melted at their eutectic composition, the melting point of the mixture is lower than the melting point of either drug or carrier alone. While some researchers claim eutectics to be an intimate but inert physical mixture of the two components, others claim that the reduction in the melting point of eutectic mixtures is a direct evidence of molecular interaction between the drug and the carrier. At the eutectic composition, both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug. *[13]*

Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. Most pharmaceutical solid solutions are amorphous in nature. A crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Amorphous solid solutions have shown to enhance the dissolution rate of poorly soluble drugs. As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility. *[14-16]*

4. Complexation

Use of cyclodextrin complexes

Cyclodextrin are able to form dynamic molecular inclusion complexes with many drugs by incorporating the drug molecule, or more commonly a lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the drug/cyclodextrin complex formation. The driving forces leading to the inclusion complex formation include release of enthalpy rich water molecules from the cavity, electrostatic interaction, vanderwaals interaction, hydrophobic interaction, hydrogen bonding, release of conformational strain, and charge-transfer interaction. All these forces are relatively weak, allowing free drug molecules in solution to be in rapid equilibrium with drug molecules bound within the cyclodextrin cavity. Most drug molecules (D) form 1:1 complexes with cyclodextrin molecules (CD) and the value of the stability constant (K1:1) is most often between 50 and 2000 mol–1 with a mean value of 129, 490 and 355 mol–1 for α-, β-, and γ-cyclodextrin, respectively.

$$D + CD \xrightarrow{K1:1} D/CD\ Complex$$

This is a somewhat oversimplified description of a much more complex mechanism but is sufficient to explain the role of cyclodextrins in oral drug delivery. In a given aqueous Complexation medium, saturated with the drug, the concentration of free drug [D] is constant and equal to the apparent intrinsic solubility of the drug in the aqueous medium (i.e. drug solubility in absence of cyclodextrin).*[17,18]* Cyclodextrin encapsulation of a drug will change the drug's physicochemical properties, such as its aqueous solubility and chemical stability. The cyclodextrin molecule forms a hydrophilic shield around applicable lipophilic moiety of the drug molecule. This will, in general, increase the apparent aqueous solubility of the drug. The cyclodextrin can also protect chemically labile drug molecules from potentially corrosive environments and in this way reduce or even prevent drug hydrolysis, oxidation, racemisation and enzymatic decomposition. The recent research shows the increase in solubility of drugs like

diclofenac, meloxicam, simvastatin, glimipride, fenofibrate etc. *[19, 20]*

Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. Chemically they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. Cyclodextrins, with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes. *[21]*

5. Solubilisation by surfactant

Surfactants (surface-active-agents) are substance which at low concentration, adsorb onto the surface or interface of a system &alter the surface or interfacial free energy &alter the surface or interfacial tension, thus facilitate the solubilisation. Surfactants have a characteristic structure, possessing both polar (hydrophilic), & non-polar (hydrophobic) regions in the same molecule.

Micro emulsions

Micro emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use. A micro emulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilised poorly soluble drug. Micro emulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and to water ratio, are all fluids of low viscosity. *[22]*

Self Micro emulsifying Drug Delivery System

SMEDDS is an anhydrous system of micro emulsions. It has also been referred to as micro emulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w micro emulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility. The surfactant can be non-ionic like polyoxyethylene surfactants e.g. Brijor sugar esters like sorbitanmonooleate (Span 80), cationic, or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate, or zwitterionic such as phospholipids like lecithin (phosphatidylcholine) commercially available from soybean and eggs. Lecithin is very popular because it exhibits excellent biocompatibility. Combinations of ionic and

non-ionic surfactants are also found to be effective.

Solubilisation using microemulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactants mixtures. 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. 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 diarrhoea. Drug for which work is done are fenofibratr, simvastatin, β artamesium and sulpiride etc.*[23-25]*

Micellar solublisation

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They can also be used to stabilise drug suspensions.

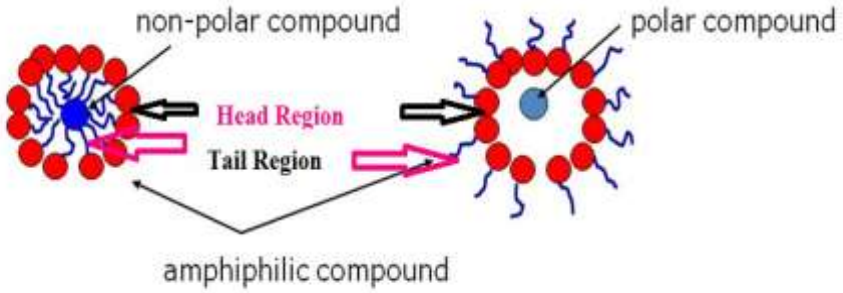


Figure No.2 Solubilisation of molecule by micelles

When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles. This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroylmacroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. E.g. of poorly soluble compounds that use Micellarsolubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride,

glipizide, repaglinide, pioglitazone, rosiglitazone, simvastatin. *[22, 23]*

B. Chemical Modification

1. pH Adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5 so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines.

Ionisable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds. Solubilised excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. Commercial products using pH adjustment: Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule). *[23, 27]*

2. Derivatisation

It is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure called derivative. Following approaches are

Formation of prodrug

Prodrug is a compound that must undergo bioconversion before existing its pharmacological effect. The term prodrug refers to a drug with a covalently bound to the inactive moiety (promoiety) that provides the desired pharmaceutical properties, where the promoiety must be removed upon administration to regenerate the parent drug. E.g.Clindamycin2 phosphate, chloramphenicol palmitate.

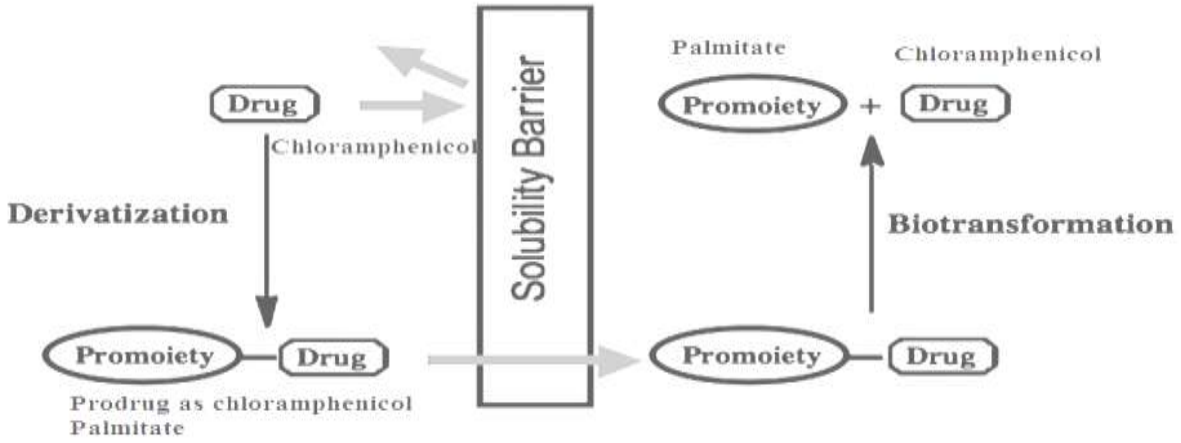


Figure No. 3 An illustration of the prodrug concept.

Many prodrugs designed to increase water solubility involve the addition of an ionizable promoiety to the parent molecule. Because charged molecules have greater difficulty crossing biological membranes, one must balance increased water solubility with the potential for decreased permeability. For example, one might argue that a phosphate ester of a drug with alcohol functionality in its structure would produce a poorly, membrane permeable prodrug. However, phosphate esters have been shown to be very effective at improving the delivery of poorly water-soluble parent drug molecules after oral delivery *[5, 27]*

C. OTHER TECHNIQUES

1. Cosolvancy

The process of enhancing solubility of weak electrolytes and non polar molecules by the addition of water miscible solvents in which drug has good solubility. The solvents used to increase the solubility of solute are known co-solvents. Mechanism: Co-solvents reduce the interfacial tension between the predominantly aqueous solution and hydrophobic solutes and reduce the contact angle between solid and liquid. Cosolvents reduce the difference between the polarity of drug and water system thereby increases the solubility. The solution solubility enhanced exponentially as a function of the cosolvent added. Examples for Co-solvents are dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), ethanol, Propylene glycol 300 and 400, and N- methyl-2-pyrrolidone (NMP). *[4, 28]*

2. Hydrotrophy

Hydrotrophy designates the increase in solubility in water due to the presence of large amount of additives. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute

and those salts that decrease solubility "salt out" the solute. The mechanism of hydrotrophy related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute. Actually these are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. E.g. Solubilisation of Theophylline with sodium acetate and sodium alginate. *[10, 22, 26]*

D. NOVEL TECHNIQUES

1. Cryogenic Techniques

This technique has been developing to enhance the dissolution rate of drugs by creating nanostructure amorphous drug particles with high degree of porosity at very low temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilisation *[29]*.

2. Lyophilisation/ Freeze drying technique

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilisation/ freeze drying technique is considered as a suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilisation/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent. *[29]*

3. Spray freezing into cryogenic fluids (SFL)

The SFL technology has been used to produce amorphous nanostructure aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid – liquid impingement between the atomized feed solution and cryogenic liquid to provide more intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. *[29-31]*

4. Floating Granules

A novel approach for dissolution enhancement of ibuprofen by preparing floating formulation. Ibuprofen, a weekly acidic and it remain 99.9 % unionize in stomach (pKa of Ibuprofen - 4.43, pH of

gastric fluid - 1.2). Ibuprofen mostly permeable through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilised but can't permeate through its membrane (Ibuprofen having pH depended solubility and permeability). It was logically decided to design such formulations which retain in stomach for more than 2 hrs because drug was not completely soluble within 2 hrs hence to dissolve completely in stomach region, this can be achieved by making floating dosage form. *[32]*

5. Supercritical Antisolvent technique

This method has been introduced in the late 1980s. Since the first experiences of Hannoy et al in 1879, a number of techniques have been developed & patented in the field of supercritical fluid-assisted particle design. In order to improve the dissolution properties of poorly water-soluble drugs, some drugs were subjected to micronization or prepared as composite particles using supercritical fluid (SCF) technology with carbon dioxide (CO2). Solubility in CO2 is the key when using this method. Solubility affects the supersaturation of the materials in the solvent as well as the mass transfer of that solvent, which are both critical to the micronization of the materials and the formation of the composite particles. Some useful techniques that can be used to avoid the problems posed by the characteristics of the drug itself are combining SC-CO2 with other technologies, such as the formation of coacervates or emulsions, and other equipment types, such as milling or ultrasound fields. SC-CO2 can improve the solubility of poorly water-soluble drug substances using few or no organic solvents and with little or no heating. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid. *[33, 34]*

CONCLUSION

Solubility of the orally administered drugs is one of the rates limiting parameter in order to achieve their desired concentration in systemic circulation for desired therapeutic response. Problem of solubility is a major challenging step for formulation scientists in new chemical entity development. Various techniques, described in this review alone or in combination can be successfully used to enhance the solubility of hydrophobic drugs or BCS class II drugs for improving their

dissolution rate and ultimately improves bioavailability, but successful improvement is mainly depends on selection of method. The techniques of solubility are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. Among all the solubility enhancement techniques super critical fluid, cryogenic and inclusion complex formation are most attractive techniques to resolve the solubility problems of hydrophobic drugs such as simvastatin, fenofibrate, atorvastatin, clopidogrel, glipazide, rosuvastatin, acyclovir, meloxicam etc In future these novel methods become a most acceptable way to enhance the bioavailabiity.

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