

REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but poorly solubility of drug is major challenge for formulation scientist. About 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system. To improve solubility and bioavailability of poorly soluble drug we use various methods or techniques. The methods like solid dispersion, complexation, liquisolid, hydrotrophy, sonocrystallization, self emulsifying method, are commonly referred for solubility enhancement. In this review we concentrated on improvement of the solubility of poorly water soluble drugs by applying various methods.

KEY WORDS

Bioavailability, Novel methods, Solubility, Solubility enhancement.

INTRODUCTION

Oral route is most desirable route of administering the dosage form. The major problem faced during the oral administration of active agent is the bioavailability. The solubility is defined as a

maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. [1] As the solubility increase bioavailability increases. Solubility defines as:

Table 1: Definition of Solubility. [2]

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

BCS (Biopharmaceutics classification system) classify the drug in to four classes according to

their solubility and permeability. Solubility challenges are faced in the Class II and Class IV of

the BCS system (where dissolution becomes the rate limiting step for the absorption of drug) which comprises of newer generation of NSAIDs like Zaltoprofen, Aceclofenac, Flurbiprofen, their older congeners like Indomethacin, Ibuprofen,

Ketoprofen and Diclofenac; anti-diabetics Gliclazide, Glipizide ; newer calcium channel blockers (CCBs) like Nimodipine, Felodipine.. The BCS was first devised in 1995 by Amidon et al. [3]

Table 2: BCS Classification of Drug. [4]

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol.
II	High	Low	Neteglinide.
III	Low	High	Cimetidin.
IV	Low	Low	Hydrochlorothiazide.

Poorly soluble drugs are often a challenge in front of pharmaceutical industry. 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. To solve the solubility problem we discuss the various traditional as well as newer method of solubility enhancement. The traditional method includes solid dispersion, complexation and pH adjustment while newer methods include liquisolid, hydrotropy, sonocrystallization, self emulsifying system. 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.

FACTOR AFFECTING THE SOLUBILITY

1 Nature of solute and solvent:

The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved. [5]

2 Particle size:

Particle size affect on solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by, [6]

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

Where,

S is the solubility of infinitely large particles

S_0 is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle.

3 Molecular size:

Solubility affected by molecular size of particle. 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.

4 Temperature:

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature. [7]

5 Pressure:

For solids and liquid solutes, solubility not affected by change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease.

METHODS FOR SOLBILITY ENHANCEMENT

SOLID DISPERSION:

In 1961, Sekiguchi and Obi first introduce the solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. [8,9] In solid dispersion a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug which can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products.[10,11]

CLASSIFICATION OF SOLID DISPERSION

Solid dispersion classified in 3 groups;

1. First generation solid dispersions:

In first generation solid dispersion, formulation of eutectic mixtures or molecular dispersion improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Disadvantage related formulation of crystalline solid does not release drug quickly. Example: Crystalline carriers: Urea, Sugars and Organic acids [12]

2. Second generation solid dispersion:

In second generation we use amorphous state of carrier which improves drug release; likes fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins. [13]

3. Third generation solid dispersion:

In third generation we use carrier which have surface activity and self emulsifying property. The surfactants decrease the recrystallisation of drug and thus improve the solubility of drug.

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14. [14]

Advantages of solid dispersion:

1. Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.
2. Improve wettability of particle: solid dispersion improves wettability of particle.
3. Improve porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate
4. Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages of solid dispersion:

1. Instability due moisture content.
2. Difficulty in incorporating into formulation of dosage forms.

MANUFACTURING METHODS OF SOLID DISPERSION

1. Solvent evaporation method:

In solvent evaporation method we dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. [15] Tachibechi and Nakumara were the first to dissolve both the drug (β -carotene and the carrier PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Commonly use solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some case cosolvent may use because large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. The disadvantages of solvent method such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form. [16]

2. Fusion/melting method:

The physical mixture of a drug and a water-soluble carrier was heated directly until it gets melted.

The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved which improve the solubility and bioavailability of drug. Limitation regarding this method is at high temperature many drug may get degraded. [17]

3. Hot melt extrusion: [HME]

HME can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder. [18]

Advantage of HME [19]

1. Improve the solubility and bioavailability of poorly soluble compounds.
2. Processing in the absence of solvents and water.
3. Economical process with reduced production time, fewer processing steps, and a continuous operation.
4. Uniform dispersion of fine particle occurs.
5. Good stability at varying pH and moisture levels.
6. Safe application in humans due to their non swellable and water insoluble nature.

Disadvantages:

1. Not applicable to heat sensitive material.

2. Limited number of available polymer.
3. This method requires high energy input.

HME are complex mixture of active drug and excipient. The commonly use polymer in HME is Polyethylene glycol, Polyethylene oxide, Hydroxypropyl cellulose, Hydroxypropylmethyl cellulose, Poly(dimethylamino ethyl methacrylate-co- methacrylate ester), Ammonio-comethacrylate copolymer.

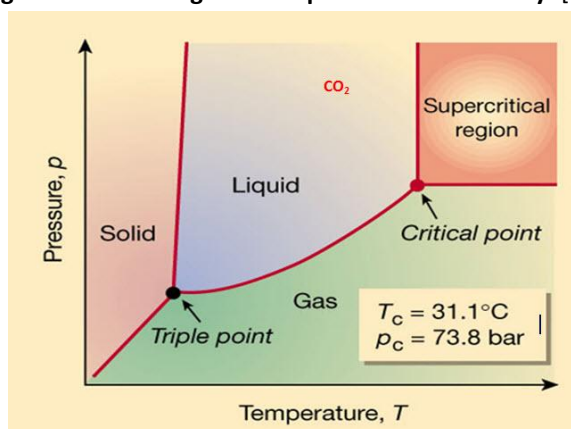
Application of HME: [20]

- 1) Masking the bitter taste of an active drug.
- 2) Formation of polymer-drug solutions/dispersions which increased drug solubility and increased drug dissolution rate.
- 3) Formulation of controlled release dosage forms (including implants).
- 4) Formulation of targeted release dosage forms.

4. Super Critical Fluid Method: (SCF)

Super critical fluid is fluid which exists as single fluid above its critical temperature and pressure. SCF shows the properties of both a liquid and a gas above its critical condition. 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. [23] Once the drug particles are solubilised within SCF, they may be re-crystallized at greatly reduced particle sizes.

Figure 1: Phase diagram of super critical fluid study. [21]



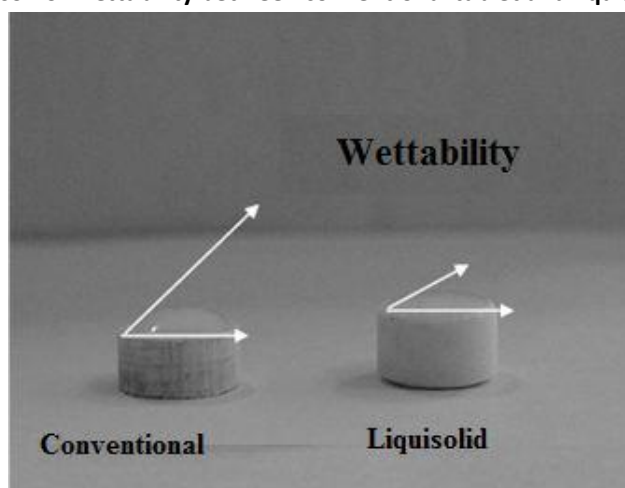
Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable. Other supercritical solvents include nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. [22, 23]

LIQUISOLID METHOD:

In liquisolid technique liquid may be transfer into free flowing, readily compressible and apparently dry powder by simple blending with selected carrier and coating material. [24] The liquid portion which can be liquid drug, drug suspension or drug solution in a suitable non volatile liquid vehicle can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The acceptable flowing and compressible powder form of liquid medication is liquisolid compact. The liquisolid is

newer and promising approach because of simple manufacturing process, low production cost, and applicable for industry due to good flow and compact property of liquisolid formulation. When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics. [25]

Figure 2: Comparison of wettability between conventional tablet and liquisolid compacts. [26]



The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. **Fig.2** Shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability. [27]

Classification of liquisolid system:

Classification based on type of liquid medication contain there in;

1. Powdered drug solutions.
2. Powdered drug suspensions.
3. Powdered liquid drugs.

Classification based on technique use for formulation;

1. Liquisolid compacts.
2. Liquisolid Microsystems

Table 3: Components of Liquisolid System. [28]

Component	Examples
Non Volatile Liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guar gum
Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidone, Pregelatinized Starch.
Glidant	Talc.
Lubricant	Magnesium Stearate.
Release retardant material	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

Advantages of liquisolid method: [29]

1. Method improves the solubility and bioavailability of orally administered water insoluble or poorly soluble drugs.
2. Method is applicable in industry.
3. Useful for the formulation of oily drugs/liquid drugs.
4. By using different carrier and additives drug release can be modified like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit etc.
5. A number of poorly soluble drugs can be formulated in to the system.
6. Production cost is low compared to that of preparation of soft gelatin capsules
7. This system is specifically for the powdered liquid medications.

Disadvantages of liquid solid method:

- 1) High solubility of drug in the non-volatile liquid drugs for the improvement of dissolution rate and bioavailability.
- 2) It requires recipients of high adsorption properties and high specific surface area.

3) It is not applicable to high dose insoluble drugs (>100 mg).

4) During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness.

HYDROTROPY METHOD:

The term Hydrotropy was coined by *Carl Neuberg* in 1916 but the practical implications were introduced as late as 1976 by *Thoma and coworkers*. [30] In this method by adding large amount of secondary solute increase the aqueous solubility of water insoluble drug.

Mechanism of action of Hydrotropes:

Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. The hydrophilicity increase by anionic group and the ring system interacts with the solute to be dissolved. [31] The mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium alginate, sodium benzoate etc. [32]

Table 4: Classification of hydrotropes. [33]

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate.
Aromatic cationics	Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

Advantages of hydrotropy method:

1. In the hydrotropy method solvent character is independent of pH, has high selectivity and does not require emulsification.
2. In this method simply mix the drug with the hydrotropes in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Mixed Hydrotropy:

In mixed hydrotropy method the blends of hydrotropes is use. in blends of hydrotrops the combination of hydrotropes gives synergistic effect on solubility of poorly water soluble drug . By reducing the concentration of individual hydrotropic agent we reduce the side effect of hydrotropes. It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents. As example in case of ketoprofen by using 1.25M sodium citrate increase the solubility of 180 fold as compair to solubility in distilled water. *Maheshwari and co-workers* increased solubility of Paracetamol using Urea and of aceclofenac

using mixed hydrotropic phenomenon using Urea and Sodium acetate. [34]

Advantages of Mixed Hydrotropy method: [35]

1. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
2. The use of hydrotropic solubilizers as permeation enhancers.
3. Application of mixed- hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
4. Application of hydrotropic solubilisation in nanotechnology (by controlled precipitation).
5. Application of hydrotropic solubilisation in extraction of active constituents from crude drugs (in pharmacognosy field).

Application of hydrotropy in pharmacy:

1. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
2. Quantitative estimations of poorly water soluble drugs by UV-Visible spectrophotometric analysis precluding the use of organic solvents.
3. Quantitative estimations of poorly water soluble drugs by titrimetric analysis. Such as ibuprofen, flurbiprofen.

Table 5: Solubility enhancement of poorly water soluble drug by using Hydrotropes.

Drug name	Hydrotropes use
Glipizide [36]	Sodium Benzoate, Sodium acetate, Sodium salicylate
Pacilitaxel [37]	N N Diethyl Nicotinamide, N N Dimethyl Benzamide
Amlodipine besylate [38]	Urea
Chartreusin[39]	Sodium Benzoate, Sodium trihydroxy Benzoate

SONOCRYSTALLIZATION:

Melt sonocrystallization is newer particle engineering technique. In this method by applying ultrasound energy in range of 20 to 100 kHz crystallization process achieve. [40] In pharmacy industry ultra sound energy was introduced traditionally to increase the solubility of sparingly soluble drug. Ultrasound system use to influence the initial nucleation stage of crystallisation. The ultrasonication causes disaggregation or deagglomeration of particle. cavitation is an

important phenomenon of ultrasonication.[41] In sonocrystallization the energy of ultrasound cause repeated compression and expansion. After several cycle the bubble forms, grows and collapses. Due to bubble collapses the energy produced .This energy was responsible for breaking of particles. This results in high repeatable and predictable crystallization.

Applying Ultrasound to crystallization results in:

- a. Nucleation at the lowest level of supersaturation where the crystallization

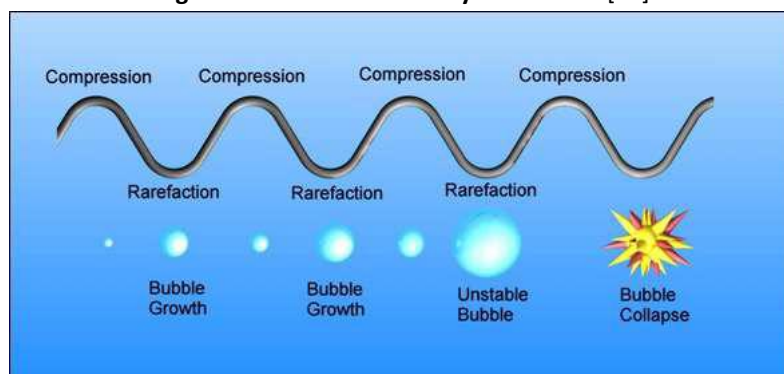
overcomes the tendency of the compound to re-dissolve in the solution.

- b. Narrowing of the metastable zone width.
- c. Narrow particle size distribution.
- d. Decrease in the level of cooling necessary to achieve crystallization.

- e. Highly repeatable and predictable crystallization
- f. Polymorph control.

In 2012 *Vikram Deshmukh and co-workers* study the melt Sonocrystallization tech for carbamazepine. [42] *Chaudhari and co-workers, 2009*, studied the process on Valdecoxib. [43]

Figure 3: Process of Sonocrystallization. [44]



SELF EMULSIFYING SYSTEM:

SEDDS or SMEDDS are the important method to improve the solubility and bioavailability of poorly water soluble drug. SEDDS are define as isotropic mixture natural or synthetic oils, solid or liquid surfactant, or alternative, one or more hydrophilic solvent and co-solvent/surfactant. [46] SEDDS typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro-emulsions with a droplet size of less than 50 nm. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or micro-emulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture.

Composition of SEDDS: [45]

The composition of self emulsifying system is simple combination of drug, oils, surfactant and co surfactant or co-solvent.

The self-emulsifying process depends on:

The nature of the oil and surfactant

The concentration of surfactant

The temperature at which self-emulsification occurs

1. Oils:

Oils can solubilise the lipophilic drug in a specific amount. Oil can facilitate self-emulsifying and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, increasing absorption from GIT. Example; olive oil, oleic oil, sesame oil.

2. Surfactant:

Non-ionic surfactant with high hydrophilic-lipophilic balances (HLB) value is used in the formulation of SEDDS. High HLB and hydrophilicity of surfactant assists the immediate formulation of o/w droplets and rapid spreading of formulation in the aqueous media. Example; Tween, Labrasol, Labrafac CH 10, cremophore etc.

3. Co-surfactant/ co-solvent:

Dissolve large amount of hydrophilic surfactant or hydrophobic drugs in lipid phase. It increases fluidity of the interfacial film. Example: ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate tetrahydrofurfuryl alcohol, Glycofurol etc.

Mechanism of self emulsification:

Self-emulsification takes place when the entropy change favouring dispersion is greater than the

energy required to increase the surface area of the dispersion. Free energy in the micro-emulsion formation is directly proportional to the energy

$$\Delta G = \sum_i N_i \pi r_i^2 \sigma$$

Where;

G is the free energy associated with the process (ignoring the free energy of mixing)

N is the number of droplets of radius **r**,

S represents the interfacial energy.

The type of self emulsifying dosage form includes Self emulsifying tablet, capsule, pellets, solid dispersion, powder etc. Method use for preparation of self emulsifying system is melt granulation, spray drying, capsule filling, and melt extrusion etc.

Advantages of Self Emulsifying system:

- Improvement in oral bioavailability enabling reduction in dose.
- Ease of manufacturing and scale up.
- High drug loading efficiency.
- Protection of drugs from the gut environment
- More consistent and reproducible profile of drug absorption and blood time profile.

Disadvantages of Self Emulsifying system:

- High surfactant concentration irritates the GIT.
- Chemical instability of drug and surfactant in formulation.

COMPLEXATION:

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

Two type of complex available:

1. Stacking complexes:

It is driven by association of non polar area of drug and complexes agent this results in exclusion of the non polar area from contact with water, thereby reducing total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.

require to create new surface between the two phases, and is given by the equation; [46]

2. Inclusion complexes: [47]

It is formed by the inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes. Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α , β , and γ -CD are composed of six, seven, and eight D-(+) -glucopyranose units. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrine and their derivatives commonly use in Complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug.[48] Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation.

The forces driving complexation were attributed to-

- The exclusion of high energy water from the cavity,
- The release of ring strain particularly in the case of -CD,
- Van Der Waal's interactions,
- Hydrogen and hydrophobic bindings.

Solid inclusion complexes can be prepared by using following methods: [49]

1 .Kneading method:

This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a

specified time. The kneaded mixture is then dried and passed through sieve.

2. Co-precipitation:

In this method, in the solution of CDs the required amount of drug is added. The complex kept under magnetic agitation with controlled process parameters. The complex is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. This method is applicable to industry.

3. Physical blending method:

It is simple trituration method. In this method the CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product.

4. Neutralization method:

In this method precipitation of inclusion compounds by neutralization technique take place. In this dissolve the drug in alkaline solutions like sodium/ammonium hydroxide and mix with an aqueous solution of CDs. The clear solution is obtained. This solution is neutralising under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment. This precipitate is filtered and dried.

5. Milling/Co-grinding technique:

By using this method a solid binary inclusion compounds of drug and CD is prepared. In this method Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Ball mill is also use for preparation of binary complex.

6. Lyophilisation/ Freeze drying technique:

Lyophilisation/ freeze drying technique is considered as a suitable technique to get a porous, amorphous powder with high degree of interaction between drug & CD. This technique is suitable for thermo labile substances. 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 is form.

7. Microwave irradiation method:

In this technique the microwave irradiation reaction between drug and complexing agent takes place using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40°C for 48 hrs. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.

8. Supercritical antisolvent technique:

In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. This method is important for improving bioavailability of pharmaceutically active compounds. Supercritical carbon dioxide due to its properties of improved mass transfer and increased solvating power it proved as a new complexation medium.[50] In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.

CO-SOLVANCY METHOD:

By the adding water miscible solvent in which the drug has good solubility the solubility of a poorly

water soluble drug can be increased frequently known as co solvents also known as solvent blending. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. It is also commonly referred to as solvent blending. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with water's hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water's self-association, co solvents reduce water's ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility.

Advantages:

1. Compared to other solubilisation approaches very high drug concentrations of poorly soluble compounds can be dissolved.
2. Co- Solvents can enhance the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent.
3. It is simple and rapid method to formulate and produce.

FLOATING GRANULATION:

Floating granulation is a newer technique developed in 2010 by Patel Rajanikant and co-workers to improve the solubility and bioavailability of drug by increasing mean gastric residence time. Floating ibuprofen granules were prepared by fusion method. Ibuprofen is poorly soluble but highly permeable in stomach. After gastric residence time it goes into small intestine but in intestine where it is solubilised but can't permeate through its membrane. To overcome this problem 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. By using polymer Gelucire 44/14 (immediate release polymer for loading dose) and Gelucire 43/01 (sustain release

granule) they prepare floating granule which give result as Granules remain floated for 3 hrs., gave 100% drug release in 150 minute in stomach region where it remains in 99.9% unionized form and absorbed to systemic circulation. [51]

SPHERICAL AGGLOMERATION:

It is a particle engineering technique. It combines the process of crystallization, agglomeration and spheronization, which convert fine crystals into spherical shape particles. This method is important for improving the flow property, wettability and dissolution rate of poorly soluble drugs. Amount and mode of addition of spherical liquid, temperature and agitation speed this parameter must be optimized in this technique for production of spherical crystals. [52]

Advantages:

1. Micromeritics properties of drug molecules increase.
2. This method helps to improve the wettability and flow property of drug.
3. This method is also useful for taste masking of some drugs.

Disadvantages:

1. Solvent selection is tedious for this method.
2. Difficult to maintain process parameters.

NANO SUSPENSION:

Nanosuspension technology is an important tool for solubility enhancement of poorly soluble drugs. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is between 200 and 600 nm. In nanosuspension the particle size of drug reduces which increases the surface area and therefore the dissolution rate and solubility increases which enhance bioavailability. Basically nanosuspension is submicron colloidal dispersion of pure particles of drug which is stabilized by surfactants. Compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses for that nanosuspension is a favourable method. Nanosuspension technology can also be applicable for drugs which are insoluble in both water and organic solvents.

Advantages of nanosuspension: [53]

1. This method improves the solubility and bioavailability of drug which gives rapid onset of action.
2. To increase the bioavailability of drugs with high log P value can be formulated as nanosuspensions.
3. Dose reduction is possible.

Methods for preparation of nanosuspension: [54]

There are two important methods for preparation of nanosuspension is

1. Bottom up technology
2. Top down technology

In bottom up technology the drug is dissolved in a solvent, which is then added to nonsolvent that causes precipitation of the fine drug particles. Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non aqueous media.

In case of top down techniques various methods include:

- A. High pressure homogenization (dissocubes/nanopure)
 - a. Combined precipitation and homogenization (Nanoedge)
 - b. Nanojet technology.
- B. Milling techniques
 - a. Media milling (Nanocrystals)
 - b. Dry co-grinding.
- C. Emulsion solvent diffusion method.
- D. Super critical fluid method.

CONCLUSION

Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. The basic approaches followed by all the currently available technologies engaged in the solubility and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy. To overcome the solubility problem various solubility enhancement methods are developed today which is

industrial applicable. By using newer techniques which are discussed above it is possible to improve solubility of poorly water soluble drugs.

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