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Newer Techniques to Enhance the Bioavailability of Hydrophobic Drugs by Means of Solubility Enhancement: A Review

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ABSTRACT

Enhancement of the solubility, dissolution and bioavailability of the drugs is the challenging task for the research sector. As many of the solubility enhancement techniques are available to achieve the desired goal, but the older techniques don't show the expected results for solubility enhancement and bioavailability as well, and they are unstable also some time. But today the scenario is different because the novel techniques of solubility enhancement are available, such as hydrotropy, supercritical fluid process, sonocrystallisation, inclusion complex system, spray drying, microwave assisted techniques, etc. this novel techniques have the ability to give the reproducible results for solubility enhancement in pharmaceutical product development. present review article deals with the different techniques for the solubility enhancement of the poorly soluble drug candidates.

Keywords: Solubility, hydrophobic drugs, solubility enhancement, solid dispersion, beta cyclodextrin.

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INTRODUCTION

Oral route of administration is one of the most preferred for the drug delivery because of ease of administration and low processing for the drug formulation development. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water.

These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability. 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. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drug.

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. This review is focused on the different novel techniques for the solubility enhancement[1].

Solubility

Solid drugs administered orally for systemic activity must dissolve in GI fluids prior to their absorption. Thus the rate of dissolution can influence rate of absorption. As rate of dissolution of a solid is a function of its solubility in dissolution medium, latter could influence absorption of insoluble drugs. Compounds with an aqueous solubility of greater than 1% w/v do not show dissolution related problems. Mainly BCS class II and Class IV drugs show solubilization problems. Dissolution is the transfer of molecules or ions from a solid state into solution.

The extent to which the dissolution proceeds under a given set of experimental conditions is referred to as the solubility of the solute in the solvent. Thus, solubility is the amount of solute that passes into solution when equilibrium is established between the solution and excess solute [2].

The pharmacopoeia lists solubility in terms of solvent required to dissolve 1g of solute. If exact solubilities are not known, the pharmacopoeia provides general terms to describe a given range as shown in table 1.

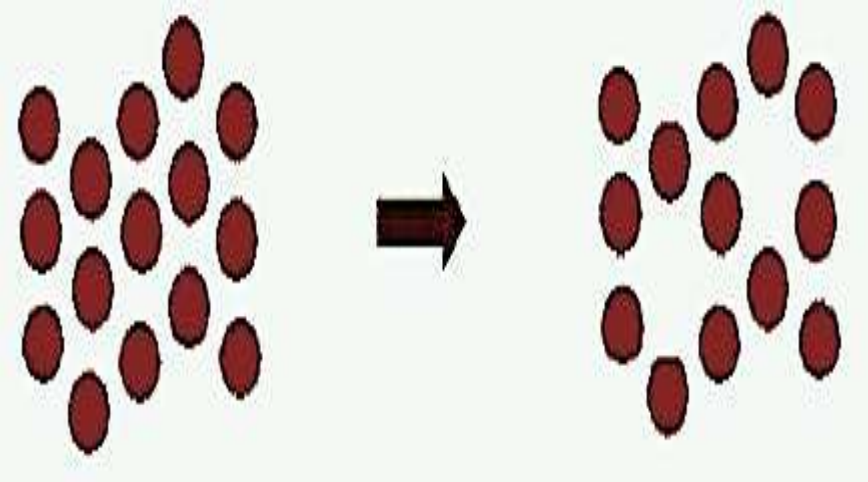
Description of solubility terms: [3]

Table 1: Description of solubility terms

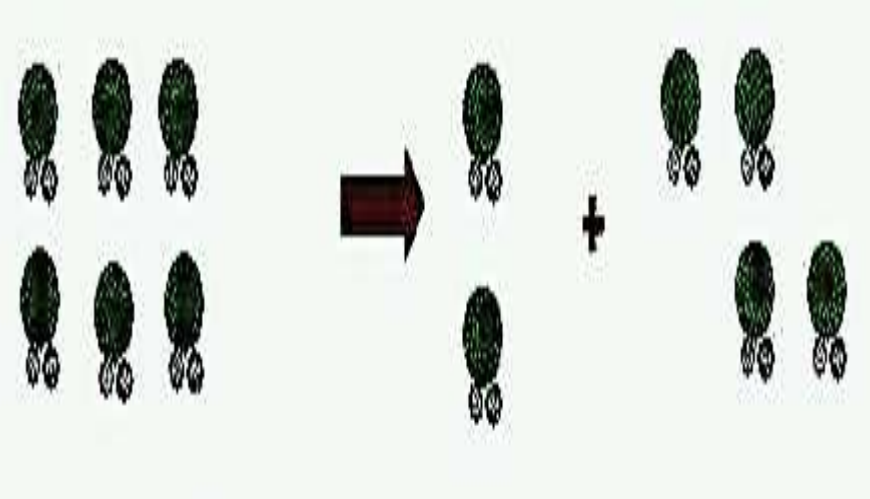
Sr. No.	Descriptive term	Parts of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10,000
7	Practically insoluble, or Insoluble	10,000 or more

Process of Solubilization [5]

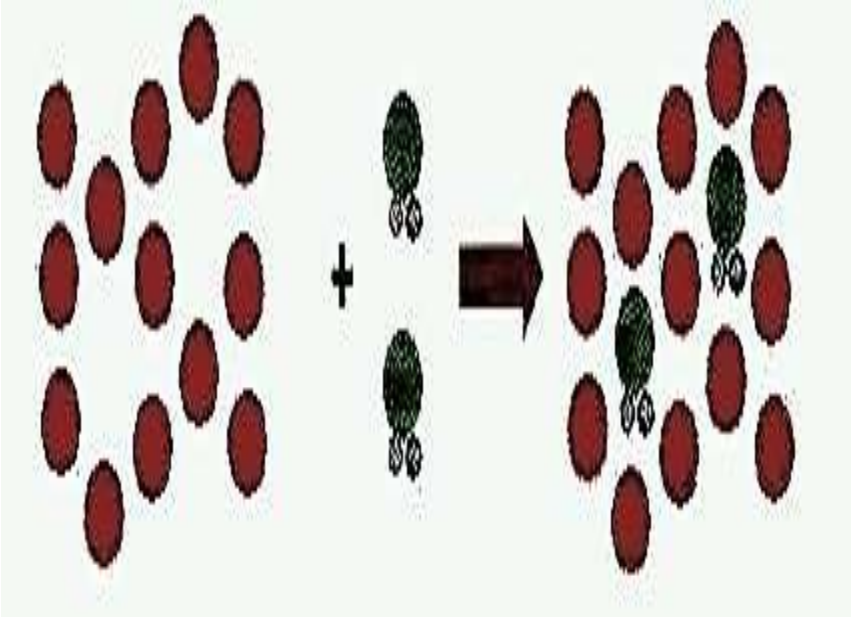
The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.



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

Factors Affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system[6].

- Particle Size
- Temperature
- Pressure
- Nature f the Solute and Solvent
- Molecular Size
- Polarity
- Polymorphs

Particle Size

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

Temperature

If the solution process absorbs energy then the temperature increases which leads to increase in the solubility and vice versa. So the increase in the temperature of the system increases the solubility of the solute to be dissolve.

Pressure

As such there is no effect of the pressure on the solubility of the solids.

Nature of the solute and solvent

Only 1gm of the lead chloride can be dissolved in 100gms of water, but 200gms of the zinc chloride can be dissolved in 100 grams of water, this is due to the nature of the solute changes.

Molecular size

The larger the molecule or the higher its molecular weight compounds are less soluble. As the molecule is larger than it is more difficult to surround with the solvent molecule for solubilization of the molecule.

Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. 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. All molecules also have a type of intermolecular force much weaker than 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 non-polar solvent a chance to solvate the solute molecules[7].

Polymorphs

Polymorph means the same compound available in the different crystal habit. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. When the crystal of a substance can be change in the another form of the crystals, which is reversible the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs.

The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities [3]. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy [8].

Determination of Solubility

A semi- quantitative determination of solubility can be made by adding the solute in small incremental amounts to a fixed volume of solvent, after each addition system shaken vigorously

and examined visually for undissolved particles. Following are the method used to determine the solubility, to determine solubility of solids in liquids following two steps is used.

- Preparation of saturated solution

Solubility indicates the maximum amount of a substance that can be dissolved in a solvent at a given temperature; such a solution is called saturated solution. Solubility is measured either in grams per 100 g of solvent (g/100 g) or number of moles per 1 L of the solution.

- Analysis of saturated solution

Once the saturated solution is prepared its analysis is carried out to check the solubility. It depends upon the nature of the solute and accuracy of the method employed. Methods used for analysis of saturated solution are, evaporation method, volumetric method, gravimetric method, instrumental method.

Need For Solubility Enhancement

- There is variety of new drugs & their derivatives are available. But less than 40% of lipophilic drugs candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmaco-dynamic activities.
- The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action.
- The basic aim of the further formulation & development is to make that drug available at proper site of action within optimum dose [4].

TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques which are available to improve the solubility of the poorly soluble drug candidates. Following are some techniques which are successively used for the solubility enhancement.

PARTICLE SIZE REDUCTION

Particle size reduction can be achieved by various sophisticated techniques. Each technique utilizes different equipments for reduction of the particle size.

Micronization

The solubility of the drug is basically related to the particle size. As the particle size reduces the increased surface area improve the dissolution properties of the drug. Conventional methods of particle size reduction micronization. Micronization is used to increased surface area for dissolution[10]. Micronization increases the surface area which causes the increase in the solubility but do not cause change in the equilibrium solubility[11].

Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.[6-7]

Techniques for the production of nanosuspensions:

- **Homogenization:**

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles.

Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors[8].

- **Wet milling**

Active drug in the presence of surfactant is defragmented by milling.

Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants[9-10].

The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one. Drying of nanosuspensions can be done by Lyophilization or spray drying[11-12].

- **Precipitation Techniques**

In precipitation technique the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles.

The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media[9]. Nanosuspension of Danazol[10] Naproxen[10-11] prepared by precipitation technique to improve their dissolution rate and oral bioavailability[9].

- **Combined precipitation and homogenization (Nanoedege)**

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenisation). They are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step. Table 2 shows the marketed pharmaceutical products utilizing nano crystalline formation.

Table 2: Current marketed pharmaceutical products utilizing nano crystalline formation[13].

Product	Drug Compound	Company	Nanoparticle Technology
RAPAMUNE	Sirolimus	Wyeth	Elan Drug Delivery Nanocrystals
EMEND	Aprepitant	Merck	Elan Drug Delivery Nanocrystals
TriCor	Fenofibrate	Abbott	Elan Drug Delivery Nanocrystals

Supercritical Fluid (SCF) Process

It is another novel particle size reducing and solubilization via supercritical fluid (SCF) processes. 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[14]. 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[14]. 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. Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points[15]. 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[16]. 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) [17].

Sono- crystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents are also used for the particle size reduction. Using the ultrasound the crystallization takes place which causes the particle size reduction, which is called as Sonocrystallisation. In sonocrystallisation the ultrasound of frequency range of 20-100 kHz is utilized. This increases the nucleation rate and causes the size reduction of the active pharmaceutical ingredients. Most application use ultrasound in range 20 kHz-5MHz[18].

SOLID DISPERSIONS

Solid dispersion is the technique in which a poorly soluble hydrophobic drug is dispersed in a highly soluble solid hydrophilic matrix; this causes the enhancement of the solubility. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products[19-20]. A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation vessel was loaded with solution of carbamazepine and PEG4000 in acetone, which was expanded with supercritical CO2 from the bottom of the vessel to obtain solvent-free particles. Eutectic dispersions are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers. In the solid solution form, the drug could be partially or completely soluble in the dispersing matrix. A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris- PEG®) is commercially available. Presence of the drug in microcrystalline state, improved wettability and formation of high free energy amorphous forms of the drug during solid dispersion formation contribute towards enhancement of drug solubilization. Despite the promising aspects of dissolution enhancement and simplicity of concept, the solid dispersion technique has failed to gain popularity due to manufacturing, stability and scale-up issues[21-22]. The concept of solid dispersions was originally 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[23]. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630, Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used. The solubility of celecoxib, halofantrine1, ritonavir can be improved by solid dispersion using suitable hydrophilic carriers. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility.

METHOD OF PREPARATION

- **Hot melt method (fusion method)**

The physical mixture of a drug and a water soluble carrier was heated directly until it 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 can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system[24].

- **Solvent Evaporation Method**

Drug and the carrier is dissolve both the in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophillic R carotene in the highly water soluble carrier polyvinylpyrrolidone. Many investigators studied solid dispersion of meloxicam, naproxen and nimesulide using solvent evaporation technique.

- **Hot melt extrusion**

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

CRYOGENIC TECHNIQUES

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured 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 [25], atmospheric freeze drying [26], vacuum freeze drying and lyophilisation[27].

Spray freezing onto cryogenic fluids

Briggs and maxwell invented the process of spray freezing onto cryogenic fluid. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of aqueous solution [28].

Spray freezing into cryogenic fluids (SFL)

The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability[29]. It incorporates direct liquid – liquid impingement between the atomized feed solution and cyogenic 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. Hua et al produced the rapid dissolving high potency Danazol powders by using Spray Freezing into liquid process[30].

Spray freezing into vapor over liquid (SFV/L)

Freezing of drugs solution in cryogenic fluid vapors and subsequent removal of frozen solvent produces fine drug particles with high wettability[31]. During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

Ultra-Rapid Freezing (URF)

Ultra rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leading to instantaneous freezing and subsequent Lyophilization for removal of solvent forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug carrier solid dispersions and solid solutions. This technique has been investigated for the solubility enhancement of repaglinide[32].

INCLUSION COMPLEX FORMATION BASED TECHNIQUES:

Now a day cyclodextrins and their derivatives are getting more importance in pharmaceutical field due to their ability to form complexes with variety of drug candidates. The complex which is formed with the cyclodextrins shows the favourable changes in characteristics of guest molecules, such as increase in solubility, enhanced bioavailability, improved stability, reduced side effects etc. Cyclodextrins are cyclic oligosaccharide produced by enzymatic degradation of starch by the enzyme, cyclodextrin glycosyl transferase produced by bacillus macerans.

The most common natural Cyclodextrins are α, β and γ Cyclodextrins which are formed by 6, 7 and 8 glucose respectively. Among all the available cyclodextrin, β cyclodextrin (β-CD) are the cheapest and non-toxic for oral use.

METHOD TO FORM THE CYCLODEXTRIN COMPLEXES

Kneading method

In this technique the β-CD is taken in mortar and wetted with few drops of ethanol/water mixture and then kneaded. The drug to be form complex is added slowly and kneaded with addition of few drops of ethanol water mixture. Finally the wet mass is dried at room temperature and sieved by using sieve no#100. Then the obtained powder is evaluated [33-34].

Microwave irradiation method

This technique involves the microwave irradiation reaction between drug and complexing agent 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 vaccum oven at 40 °C for 48 hrs.

Co-precipitation technique

In this technique the required amount of the drug is weighed and added to the solution of β-CD. The system is kept under the controlled parameters with continuous agitation protected from light. The formed precipitate is the filtered with vacuum filtration and dried at room temperature to avoid the loss of structured water from inclusion complex.

Supercritical Antisolvent 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 drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost [35].

Floating Granules

The floating formulation of the ibuprofen was prepared which is known for the solubility enhancement[36]. Drug having high permeability through stomach because it remains 99.9 % unionize in stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid - 1.2) and 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 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 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 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 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.

HYDROTROPHY

Hydrotrophy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which 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. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts, some are given in the table 3.

Table 3: Classification of hydrotropic agents[37]

Sr. No.	Hydrotrope	Example
1	Urea and its derivatives	Urea, N, N-dimethyl urea
2	Aromatic alcohols	Resorcinol, pyrogallol, catechol, a,b-napthols
3	Organic metal salts and organic acids	Sodium salicylate, sodium benzoate, sodium citrate, sodium acetate, sodium ascorbate, potassium citrate, citric acid, benzoic acid
4	Aromatic hydrotropes	Caffeine, nicotinamide, N,N-diethylnicotinamide, N,N-dimethylbenzamide
5	Surfactants	Sodium dodecyl sulphate, dodecylated oxidibenzene
6	Soluble drugs	Ibuprofen sodium, metformin hydrochloride

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. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute [37].

Advantages of Hydrotropic Solubilization Technique [38]

- Hydrotropy is superior to other solubilization methods such as miscibility, micellar solubilization, co- solvency and salting in as solvent character is not dependent on pH.
- It has simple mixing of the drug with the hydrotrope in water.
- Use of organic solvents is not required so it is eco-friendly.
- No need to prepare emulsion system.
- The hydrotropes are known to self-assemble in solution.

COSOLVENCY

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as co-solvency and the solvent used in combination are known as co solvent[39]. Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly

known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water.

The co-solvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Solubilization by Surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very significant in industrial and natural processes. The addition of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent[1].

The use of surfactants to improve the dissolution performance of poorly soluble drug products is possibly the fundamental, chief, and the oldest method. Surfactants are the agents which reduces surface tension and enhance the dissolution of lipophilic drugs in aqueous medium.

The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants more than their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs [39].

Neutralization

Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β- Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried [40].

CONCLUSION

In this review we have discussed newer techniques of solubility enhancement. Comparative to older techniques of solubility enhancement newer techniques have many advantages which make more preferable. As newer techniques gives the reproducible results and more stable products. Now a days in the pharmaceutical product development solubility enhancement plays an important role for hydrophobic drugs.

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