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REVIEW ARTICLE

Solubility Enhancement Technologies and Research Emerged

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ABSTRACT

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Some drugs pose challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates. Poorly water soluble drugs often require high doses and enhancement in solubility and dissolution rate in their formulation development especially solid dosage forms such as tablets and capsules. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Several conventional methods and new emerging technologies have been developed for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, nanosuspension, Superdisantigrant, liquisolid technique, complexation, co-solvency, micellar solubilization, hydrotropic, salt formation etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability.

Keywords: Solubility, solubility enhancement, co-solvent, pH, emulsions, Bioavailability.

INTRODUCTION

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it can be a defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Practically the solubility of a solute in a solvent at a particular temperature is the number of grams of the solute necessary to saturate 100 gm of the solvent at that temperature. Understanding solubility properties will provide a basis for understanding the golden rule of solubility- "Like dissolves like" [1]. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility and dissolution rate of drug molecules. Solubility and dissolution rate are the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The solubility of a drug can be expressed quantitatively in number of ways like in terms of molarity, morality, percentage, mole fraction and parts per million etc.

Table 1: Expressions for approximate solubility

Terms	Parts of Solvent Required for One Part of Solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly Soluble	30 to 100 parts
Slightly Soluble	100 to 1,000 parts
Very Slightly Soluble	1,000 to 10,000 parts
Practically Insoluble or Insoluble	More than 10,000 parts

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. As Solubility & permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by

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enhancement techniques like[2,3]Biopharmaceutical Classification System Biopharmaceutical Classification System1 (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability. Class I: High Permeability and High Solubility Propranolol, Metoprolol, Diltiazem, Verapamil Class II: High Permeability and Low Solubility Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam Class III: Low permeability and High solubility Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate Class IV: Low permeability and Low solubility Chlorthiazide, Furosemide, Tobramycin, Cefuroxime [4]. This review thus begins with discussion regarding the traditional approaches to drug solubilisation include pH adjustment, cosolvency and particle size reduction. While microemulsion and self-emulsifying systems are novel approaches. The different approaches of solubility enhancement are discussed below.

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. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. 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. Ionizable 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. Solubilized 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 [5]. The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. 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. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

Advantages:

- Simple to formulate and analyse.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

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) is an example of a pH adjusted formulation containing co-solvents.

HYDROTROPHY

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. 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. 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. 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 hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs [6, 7].

Advantages:

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

The hydrotropes are known to self-assemble in solution98.The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, a- and b-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene [8]. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive piorbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, etc. Other techniques that enhance the solubility of poorly water soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble prodrug, Application of ultrasonic waves, spherical crystallization[24].

CO-SOLVENCY

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents [9]. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Cosolvents or solvent blends are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water soluble substances or to enhance the chemical stability of drug. The need to employ cosolvents in the formulation of new drugs as solutions for oral, parenteral and topical use remains high, especially with the increasing structural complexity of new therapeutic agents. Cosolvency can increase the solubility of a non polar drug upto several orders of magnitude above the aqueous solubility by one or two mechanisms. Cosolvents work by reducing the hydrogen bond density of water and consequently its ability to"squeeze out" nonpolar solutes from the aqueous mixture. In other words, they increase the solubility of nonpolar drugs by reducing the polarity of the aqueous mixture [10]. The primary advantages of Cosolvency include not only the large potential increases in drug solubility but also its relative simplicity. Other advantages include increase in the stability of the drug. Suppose the drug undergoes a hydrolytic degradation in water, cosolvents may reduce the degradation of the drug by reducing the concentration of water in the formulation [19]. Alternatively, a cosolvent may enhance the stability of a drug by providing a less

suitable environment for the transition state of the reactants, provided the transition state is more polar than the reactants themselves. Cosolvency is often considered at early stages due to its huge solubilization potential. Because of their safety, cosolvents are employed in approximately 10% of FDA approved parenteral products [11].

Ideal Properties of Cosolvents [12]

1. It should be non-toxic, non-irritating, and nonsensitizing.
2. It should be easily available and sufficiently pure.
3. It also must exert no pharmacologic activity of its own.
4. It should not adversely affect the action of the medicament.
5. Ideal solvent should not be affected by acids or alkalies.
6. It should be stable under normal conditions of pharmaceutical use.
7. The viscosity of solvent should be as such so as to allow ease of administration.
8. It should remain fluid over a wide temperature range.
9. The solvent should have sufficiently high boiling point so as to allow heat sterilization.
10. Additionally, it should be miscible with water and body fluids.

Table2: List of commonly used cosolvents in formulation

Ethanol	Propylene Glycol	N-Methyl-2-Pyrrolidone
Polyethylene Glycol	Glycerin	γ-Butyrolactone
N,N-Dimethyl Acetamide	Dioxolanes	N,N-Dimethyl Formamide
Triglyme	Triacetin	N-(β-hydroxyethyl)-lactamide
Dimethyl Isosorbide	Diacetin	Benzyl Alcohol
1,2-Butylene Glycol	Glycerol Formal	Ethyl Lactate
Transcutol	Labrasol	Acetyl Triethyl Citrate

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Classification of Residual Solvents by Risk Assessment

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have permitted daily exposures of 50 mg or more per day.

Co-solvent products: Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

MICELLAR SOLUBLIZATION

The surface active agents enhance the solubility primarily by promoting wetting and penetration of solvent medium into the drug molecule. They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the solvent medium. Nonionic surfactants like polysorbates (Tween) are widely used. It is commonly encountered in parenteral products but generally at very low levels (<0.05%) and most commonly to prevent aggregation in formulations of macromolecules. The use of surface active agents in drug formulations may result in toxicity problems, especially when given by parenteral route [13].

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. 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, lauroyl macroglycerides 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. Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs [14-17].

Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone.

PRODRUG FORMATION

Hydrophilic or water soluble drugs are desired where solubility is the rate limiting step in the dissolution and absorption of poorly aqueous soluble agents or when parenteral or ophthalmic formulation of such agents are desired. Drugs with hydroxyl function can be converted into their hydrophilic forms by use of half-esters such as hemisuccinates, hemiglutarates or hemiphthalates; the other half of these acidic carriers can form sodium, potassium or amine salts and render the moiety water soluble. Although prodrug formation method can result in high increase in solubility, they require synthesis of essentially new drug entities as well as additional animal studies to confirm their efficacy and safety.

Example : Acetyl Salicylic Acid is a prodrug form of Salicylic Acid.

SALT FORMATION

Most of the drugs are either weak acid or weak base. Salt formation is a mode of changing the pharmacokinetic properties of a drug by modifying its physical and chemical properties. Salts have improved solubility and dissolution characteristics in comparison to the original drug. Although salt formation method can result in high increase in solubility, they require synthesis of essentially new drug entities as well as additional animal studies to confirm their efficacy and safety.

Example: Rosiglitazone maleate, Pioglitazone HCl, Atropine sulphate [18].

MICROEMULSIONS

Microemulsions 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 microemulsion 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 (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug. Microemulsions 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 oil to water ratio, are all fluids of low viscosity. A self microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions. It has also been referred to as microemulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion 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. Brij or sugar esters like sorbitan monooleate (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. The major disadvantage of microemulsions is their high concentration of surfactant/cosurfactant, making them unsuitable for IV administration. Dilution of microemulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug; however, the fine particle size of the resulting precipitate would still enhance absorption. Compared to macroemulsion pre-concentrates, microemulsion preconcentrates remain optically clear after dilution and usually contain a higher amount of water soluble surfactant and a higher content of a hydrophilic solvent. These formulations are only administered orally due to the nature of the excipients. Solubilization 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 diarrhea [18-20].

Advantages:

- The pre-concentrates are relatively easy to manufacture.
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state).

Disadvantages:

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
- Formulations containing several components become more challenging to validate.

Microemulsion products: Examples of poorly soluble compounds that use micro-emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus® capsules, Boehringer Ingelheim GmBH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral® capsules, Novartis AG).

PARTICLE SIZE REDUCTION:

The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction, it is done by milling techniques using jet mill rotor stator colloid mills etc. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Particle size reduction can be achieved by micronisation and nanosuspension.

MICRONIZATION:

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution2. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. 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. Techniques for the production of nanosuspensions include Homogenization and 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. 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 one4. Drying of nanosuspensions can be done by lyophilisation or spray drying [21].

SONOCRYSTALLISATION:

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size

reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz [22]

SOLID DISPERSION:

Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method. In melting method carrier is melted and drug is added with stirring and melted until homogenous melt is obtained which is then cooled to room temperature while in solvent method drug and carrier is dissolved in minimum amount of solvent and solvent is removed by evaporation under reduced pressure. Solid dispersions are also prepared by dissolving drug and carrier in a common solvent followed by evaporation of the solvent. Melting-solvent method involves use of heating and solvent action to dissolve the drug and carrier in solvent followed by evaporation of the solvent. A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available. Solid dispersion technique improves the solubility, dissolution rate, and as a result the bioavailability of poorly water-soluble drugs. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Traditional methods suffer from the use of mechanical forces and excess organic solvents. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products. 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. 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 [23].

COMPLEXATION:

This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs. Complexing agents are molecules that have the ability to form soluble complexes with poorly water soluble drugs. The best example is cyclodextrin which have been widely used in solubilization and stabilization. They have the ability to increase the aqueous solubility of some poorly soluble drug molecules by forming inclusion complexes. Complexing agents, mainly α- and β- cyclodextrins are not considered suitable for parenteral use because they can cause severe nephrotoxicity, in addition, identification of a suitable substance that will form a soluble complex with the drug may not be possible, unless the drug conforms to certain structural requirements. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability.

Solid inclusion complexes can be prepared by using following methods:

a) Kneading Technique: In this technique, cyclodextrin (CD) is impregnated with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.
b) Coprecipitation: The required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and 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.
c) 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.

d) Co-grinding: Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time.
e) Spray-Drying Method:Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer .
f) Microwave Irradiation Method: Drug and cyclodextrins mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.

CO-GRINDING / CO-MICRONIZATION:

Co grinding of a poorly water-soluble drug with water soluble polymers like hydroxypropyl methylcellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small amount of water is extremely effective to improve its apparent solubility with maintenance of drug crystallinity to some extent. Small particles produced by milling or micronization have increased surface area and expected to have enhanced dissolution rate. However, energy added to reduce particle size results in increased van der Waal's interactions and electrostatic attraction between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate. Comicronization of drugs by using excipients like microcrystalline cellulose can be used as an alternative to reduce or eliminate cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a reduction in particle-particle agglomeration or by reducing van der Waal's interactions. Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of the microcrystalline cellulose-drug mixture [24].

LIPID-BASED FORMULATIONS:

Lipid-based delivery systems like emulsions, microemulsions, liposomes, microspheres, solid-lipid nanoparticles, etc have ability to avoid resistant chemical and physical barriers to oral absorption and are most successful in enhancing the bioavailability of molecules that are poorly water-soluble but highly permeable drug molecules (BCS class II). Some proposed mechanisms of action of lipid-based systems to enhance oral bioavailability of compounds include:

a) Particle size reduction to molecular size yielding a solid-state solution within the carrier.
b) Enhanced wetting of hydrophobic solids resulting in enhanced dissolution.
c) Increased rate of dissolution into aqueous environment from oil droplets of high surface area.
d) Promotion of absorption via intrinsic lipid pathways.
e) Enhanced thermodynamic activity via supersaturation of the aqueous environment of the gastrointestinal tract.[16]

MELT-GRANULATION:

In this technique powdered drugs are efficiently agglomerated by the use of a meltable binder which can be a molten liquid, a solid or a solid that melts during the process usually in high shear mixers, where the product temperature is raised higher than the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades[8]. In this technique no water or organic solvents are needed and there is no drying step therefore the process is environmentally safe, less time consuming and uses less energy than conventional wet granulation. Polyethylene glycol is widely used as a molten binder due to its complimentary solution properties, low melting point, rapid solidification rate, low toxicity and little cost. The increase in dissolution rate can be described to the hydrophilic character of the system due to the presence of water-soluble carriers and the fact that the drug forms monotectic mixtures with PEG24.

DIRECT COMPATION:

In this process polymer like hydroxypropyl methylcellulose and drug is dry-blended, compressed intoslugs and then milled into a

granular powder. The process results in enhanced dissolution rate of poorly watersoluble drugs without the use of solvent or heat addition to overcome the disadvantages of solid dispersion by these methods. This process is also cost effective and quicker. The compaction processes are believed to be particularly effective at enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the polymer particles during drug dissolution, in contrast with a physical mixture where the drug and polymer particles may rapidly disperse and be separated in the dissolution medium.

SOLVENT EVAPORATION BY ULTRA-RAPID FREEZING (URF):

This process involves freezing a drug contained in a polymer solution onto the surface of a cryogenic substrate with a thermal conductivity (k) between 10 and 20 W/(m K), collecting the frozen particles and removing the solvent. Because of rapid conductive heat transfer, resulting in high supersaturation and nucleation rates, the URF technology has the potential to create powders with superior physicochemical properties, similar to those produced by other rapid freezing technologies. As in other freezing technologies, the rapid freezing of the drug/polymer composition is decisive in preventing phase separation during freezing, allowing for the active to be molecularly dispersed with the polymer. Recrystallization of the drug is avoided by the inclusion of high glass-transition temperature (Tg) polymers such as PVP or hypromellose (HPMC). This technique is widely applicable to enhance in-vivo absorption for some drugs.

ORDERED/INTERACTIVE MIXING:

Ordered mixing is described as method to prepare ordered units in the mix such that the ordered unit will be the smallest possible sample of the mix and will be of near identical composition to all the other ordered units in the mix. Ordered mixing yields nearly the perfect mix and may be obtained in a number of ways like mechanical means, adhesion, coating and other methods. Prerequisite for fast dissolution from an ordered mixture includes that the carrier particle should dissolve rapidly, delivering a fine particulate suspension of drug particles. Higher concentration of drug shows reduced dissolution rates particularly at loadings above monolayer coverage because high concentration of drug forms agglomerates rather than discrete particles with. Resulting decreased surface area and thicker diffusion layers causing reduction in dissolution rates. In an ordered powder mix fine drug particles are distributed fairly evenly on coarse carrier particles. The drug powder is therefore deagglomerated in the dry state. This may be used to increase the dissolution rate of drug powders because a larger contact surface area is exposed to the dissolution medium [9]. Adsorption of Drugs onto High Surface Area Carriers: In this technique drug is absorbed onto carriers having large surface area (like cross linked polyvinylpyrrolidone, Kollidone) from solutions of the drug in appropriate solvents like methanol, polyethylene glycol, and 2pyrrolidone. The dissolution rate of drug increases due to increase in surface area and drug particles have good wettability due to the surrounding solubilising materials.

LIQUISOLID COMPACTS:

Liquid Compacts are compressible powdered forms of liquid medications. The term "liquisolid medication" implies oily liquid drugs and solutions or suspensions of water insoluble drugs carried in suitable non volatile solvent systems. Using this technique, a liquid medication may be converted into a dry, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients such as the carrier and coating material. Surfactants like tweens are used to improve aqueous solubility of poorly soluble drugs.

SOLVENT DEPOSITION /EVAPORATION:

In this technique drug is dissolved in a solvent like methylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The Increase in the dissolution rate is described to the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier.

Carriers for Dissolution Enhancement:

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in

pharmaceutical formulations to enhance dissolution of drugs.

CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and selfemulsifying systems have been successfully developed for formulation development of poorly water soluble drugs.

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