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SOLUBILITY ENHANCEMENT TECHNIQUES: A REVIEW ON CONVENTIONAL AND NOVEL APPROACHES

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ABSTRACT

Most of the drugs in the developmental pipeline are emerging from the High-Throughput Screening methodology resulting in increased molecular weights and thus consequential bioavailability problems. The bioavailability issue can be due to insufficient solubility of permeability. Most compounds face the solubility problems. Hence, with the advancement of chemical science, the need of development of pharmaceutical technologies is also increasing. Pharmaceutical approaches to correct the bioavailability are definitely being cost-effective in comparison with chemical approaches which are also time-consuming. Hence various methods of solubility enhancement are being developed. Each technique is with several merits and demerits. To tackle the disadvantages of conventional approaches, newer techniques are developed by many researchers. In this review, an attempt of comparing the conventional and novel techniques is done.

INTRODUCTION: As a most discussed but still not completely resolved issue, solubility or dissolution enhancement techniques remain a most vibrant field for the researchers in formulation science. Solubility and dissolution are the core concepts of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any medicine. But as the synthetic approach is growing successfully to deliver many promising lead compounds for most of the pharmacological categories, they are also taking the molecules towards bulkier structures.

As a result, more than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties [1]**.** These properties e.g. rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration and to avoid side effects can exert a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties.

Pharmaceutical companies have been primarily employing two strategies: rational drug design (RDD) and high throughput screening (HTS) for drug discovery. In both, lead compounds are identified according to screening in an environment in relation to biological system. RDD generally lead to compounds with higher molecular weight which ultimately result in to poorer permeability.

On the other hand, HTS has led to compounds with increased lipophilicity and molecular weight; this consequently gives poorer solubility characteristics. Drugs have this property of lipophilicity too little or too much is a bad thing. When this property expressed as Log P gets above about 5, the drug is getting too lipophilic [2].

The idea of permeability and solubility characteristics had been helpful to classify the drug under four classes prescribed by Biopharmaceutics Classification System (BCS). The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids [3].

Therefore, uptake of poorly soluble drug cannot be completed within the time at absorption site due to slow dissolution rate and perhaps leading to possibilities of gastric decomposition of drug due to longer GI residence time. There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100ug/ml and another is dose: solubility ratio. Dose to solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose.

Recently, a quantitative BCS has highlighted the importance of transit flow, in addition to solubility and permeability, on the drug absorption process [4]. The BCS defines three dimensionless numbers- dose number (D_o), dissolution number (D_n), and absorption number (A_n) to characterize drug substances [5]. These numbers are a combination of physicochemical properties of the drug and physiological parameters. The D_o attaches a physiological relevance to dose by considering the volume of fluid required to dissolve the total dose. Drugs with $D_o < 1$ are classified as highly soluble, whereas those with $D_o > 1$ are termed poorly soluble. In a recent attempt to categorize WHO essential drugs based on BCS, 27.7% of drugs were reported to be poorly soluble [6]. The BCS has not only transformed the way scientists today approach drug delivery, but it has also revolutionized the development of new drug molecules.

The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute. Solubility of molecules depends on H-bond donor and acceptor properties of the molecule and of water and crystal lattice of molecule. Effects of these factors can be well explained by equation 1 [7].

S = f (Crystal packing energy + Cavitation energy + Solvation energy) ..... (1)

Where crystal packing energy is energy require for breaking crystal lattice to interact solute molecules with the solvent molecules, cavitation energy is required to form cavity within the solvent and salvation energy is the energy released after favorable interactions between solute and solvent. Cavitation energy can be fulfilled by use of surfactants and crystal packing energy by amorphism or polymorphism of solute.

Therefore together with surface area, the saturation solubility is a key factor in the dissolution rate of drug. It depends on physiochemical properties of drug such as, crystalline form, lipophilicity and pKa.

Dissolution process is composed of two consecutive stages [8]:

1. An artificial reaction results in the liberation of solute molecules from the solid phase
2. Followed by transport of these molecules away from the interface into the bulk of the liquid phase under the influence of diffusion or convection.

The overall rate of mass transport that occurs during dissolution will be determined by the rate of slowest stage. In the absence of chemical reaction between solute and solvent then the slowest stage is usually the diffusion of dissolved solute across the static boundary of layer of liquid that exist at a solid-liquid interface. The dissolution rate of a solid in a liquid may be described quantitatively by the Noyes-Whitney equation:

$dm/dt = ka (Cs - C)$ .....(2)

where, m is the mass of solute that has passed into solution in time t, dm/dt represent the rate of dissolution, A is the surface area of undissolved solid in contact with the solvent, Cs is the concentration of solute required to saturate the solvent at the experimental temperature, C is the solute concentration at time t and ka is the intrinsic dissolution rate or simply the dissolution rate constant.

Methods of Solubility Enhancement: Classical and highly employed approaches to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs especially, BCS Class II drugs involve the solubilization by application of principles like pH adjustment, cosolvency, microemulsification, self-emulsification, micelles, liposomes and emulsions [9]. Each method is dealing with some merits and demerits. Hence the decision of the method is a crucial step in the formulation process.

1. **Surfactants:** Conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization [10].

2. **pH adjustments:** Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug. The change in the ionic milieu can also result to *in situ* salt formation. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract [11].

3. **Salt formation:** Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Of approximately 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form [12]. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts [13]. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion.

   Several reviews have outlined general strategies and considerations for salt selection. For the salt formation drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows:

   - There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
   - Counter ion should decrease crystal lattice forces.
   - It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.

   This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.

4. **Colsolvents:** Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. For example, Procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d-α- tocopherol (vitamin E) and oleic acid.

Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil [14].

5. **Polymeric Alteration:** Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability [15, 16]. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy [16, 17]. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

6. **Particle Size Reduction:** Micronization or nanonization is one of the most potential approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level [18]. Particle size is a critical parameter which should be strictly controlled during the preformulation studies of any formulation. Although the reduction in the particle size is a successful way to enhance the solubility, if uncontrolled and un-optimized, it can lead to re-crystallization and re-aggregation of drug on storage. Hence a thorough study on particle size and physical stability should be done.

   Size reduction to submicron range is not possible by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling high-pressure homogenization, solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS) [19].

   a. **Co-grinding/Co-micronization:** Cogrinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (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 [20]. 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.

      Co-micronization 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 microcrystalline cellulose-Drug mixture [21].

   b. **Pearl Milling:** Based on pearl milling the drug microparticles are ground to nanoparticles (< 400 nm) in between the moving milling pearls. The milling efficiency is dependent on the properties of the drug, the medium and the stabilizer. Rapamune, an immune suppressant agent, is the first FDA approved nanoparticle drug using Nano-Crystals technology developed by Elan Drug Delivery. Emend is another product containing 80 or 125 mg Aprepitant formulated by this technique. In general the limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations and the risk of microbiological problems after milling in an aqueous environment [22].

c. **High- Pressure Homogenization:** DissoCubes manufacture involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently nanosuspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from microparticles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. The possible interesting features of nanosuspensions are [23]:

   i. Increase in saturation solubility and dissolution rate of drug

   ii. Increase in adhesive nature, thus resulting in enhanced bioavailability

   iii. Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility

   iv. Possibility of surface modification of nano-suspensions for site-specific delivery

   v. Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market.

However, only brittle drug candidates might be broken up into nanoparticles by this technique. A few points has to be considered, such as chemical instability of fragile drugs under the harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants, redispersibility of the dried powder, batch-to-batch variation in crystallinity level and finally the difficulty of quality control and the stability of the partially amorphous nanosuspensions.

d. **Solution Enhanced Dispersion by the Supercritical Fluids (SEDS):** The SEDS process was developed and patented by the University of Bradford. The use of a coaxial nozzle provides a means whereby the drug in the organic solvent solution mixes with the compressed fluid CO2 (antisolvent) in the mixing chamber of the nozzle prior to dispersion, and flows into a particle-formation vessel via a restricted orifice. Such nozzle achieves solution breakup through the impaction of the solution by a higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials has been prepared as carriers of microparticles and nanoparticles using the SEDS process [24]. A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to form bigger droplets. In another study, a significant decrease in the particle size is achieved by using the ultrasonic nozzle-based supercritical antisolvent process [25, 26].

e. **Rapid expansion from Supercritical to Aqueous Solution (RESAS):** This process induces rapid nucleation of the supercritical fluid dissolved drugs and surfactants resulting in particle formation with a desirable size distribution in a very short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug + surfactant + CO_2) into an aqueous solution containing a second surface modifier [27, 28]. The low solubility of poorly water soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in pharmaceutical industry.

f. **Spray freezing into liquid (SFL):** The SFL technology was developed and patented by the University of Texas at Austin in 2003 and commercialized by the Dow Chemical Company. This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO_2, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon, or hydro-fluoro ethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders [24]. Using of acetonitrile as the solvent increased the drug loading and decreased the drying time for lyophilization. The dissolution rate was remarkably enhanced from the SFL powder contained amorphous nano-structured aggregates with high surface area and excellent wettability [29].

g. **Evaporative precipitation into aqueous solution (EPAS):** The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented towards the aqueous continuous phase. The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles and therefore facilitates dissolution rates [30].

h. **Ultra-Rapid Freezing:** Ultra-rapid freezing is a novel, cryogenic technology that creates nano-structured drug particles with greatly enhanced surface area. The technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions. This process involves freezing a dissolved drug in a aqueous of anhydrous polymer water 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, resulting in highly porous, agglomerated particles.

The polymer acts as a stabilizer acting as a crystal growth inhibitor. Because of rapid conductive heat transfer, resulting in high super-saturation 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 [31]**.** As with controlled precipitation, this process uses pharmaceutically acceptable solvents, excipients and conventional process equipment making it fast and scalable. Recrystallization of the drug is avoided by the inclusion of high glass-transition temperature (Tg) polymers such as PVP or HPMC. This technique is widely applicable to enhance in vivo absorption for the BCS class-II compounds [32].

7. **Co-evaporate System / Co-precipitation:** Weak basic drugs like prochlorperazine maleate contain good solubility in acidic pH but in alkaline pH solubility is significantly reduced and when a conventional formulation containing weak base is given orally precipitation of poorly soluble free base occurs within formulation in intestinal fluid. Precipitated drug is no longer capable of release from formulation leading to decrease in bioavailability of drug. This problem can be solved by use of co-evaporate system which incorporates a carrier with solubilizing effect in alkaline intestinal fluid which may operate in the microenvironment, immediately surrounding the drug particle and polymers for controlling the dissolution rate to formulate dosage forms ensuring maximum bioavailability with controlled release of weak base [33].

8. **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 ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wetability of the particles brought about by the carrier [34].

9. **Inclusion Complexes:** Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups orientated outwards. Consequently, cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic

drugs for oral or parenteral delivery [35]. The lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained through cyclodextrin complexation. Pharmaceutical applications of cyclodextins in drug solubilization and stabilization [36], *in vivo* drug delivery [37], toxicological issues and safety evaluation and mechanisms of Cyclodextrins modifying drug release from polymeric drug delivery systems have been previously reviewed.

This cavity enables cyclodextrins to complex guest drug molecules and hence alters the properties of the drugs such as solubility, stability, bioavailability and toxicity profiles [38].

The forces driving complexation were attributed to-

(i) the exclusion of high energy water from the cavity,

(ii) the release of ring strain particularly in the case of -CD,

(iii) Van der Wal's interactions,

(iv) Hydrogen and hydrophobic bindings [39]

ß-CD, the most widely used native cyclodextrins, is limited in its pharmaceutical application by its low aqueous solubility (1.85 g/100 ml, 25°C), toxicity profile and low aqueous solubility of the formed complexes. Accordingly, derivatives such as hydroxypropyl-ß-CD (HP-ß- CD) and sulphobutylether-ß-CD (SE-ß-CD) have been developed to produce more water- soluble and less toxic entities. This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs by using cyclodextrins. 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 [40].

b. **Co-precipitation:** 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 [41].

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 [42].

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 [43].

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 [44].

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 [45].

10. **Solid solutions/dispersions:** Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. It was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. It was defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by melting (fusion), solvent or melting-solvent method. More than 500 papers have been published on the subject and various materials are employed as drug carriers.

Despite an active research interest, the number of marketed products arising from this approach is disappointing mainly caused by the physical and chemical instability and scale-up problems [46]. Solid dispersion can be prepared by the melting (fusion), solvent, or melting solvent method [47]**.** 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 [48].

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. Solid dispersion technique improves the solubility, dissolution rate, and as a result the bioavailability of poorly water-soluble drugs [49]. The higher dissolution rates of solid dispersions can be ascribed to a number of factors which includes:

i) The formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present [50]

ii) The reduction of particle size to nearly a molecular level [51]

As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption [47].

iii) Formation of amorphous forms of drug and carriers [52]

iv) The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution[53].

v) Cosolvent effect on the drug by the water soluble carriers [52]

vi) Intermolecular hydrogen bonds between drug and carrier [54]

vii) Local solubilization effect of carrier at the diffusion layer [48]

Various factors affecting dissolution of drug from solid dispersion includes the method of preparation of the solid dispersion, amount and properties of the polymer carriers, drug polymer contact and drug-polymer interactions [55].

Many water-soluble excipients were employed as carriers of solid solutions/dispersions. Among them, polyethylene glycols (PEG, Mw 1500-20000) were the most commonly used due to their good solubility in water and in many organic solvents, low melting points (under 65°C), ability to solubilize some compounds and improvement of compound wettability. The marketed Gris-PEG is the solid dispersion of griseofulvin in PEG 8000. The others carriers include polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinyl pyrrolidone polyvinylacetate copolymer (PVP-PVA), hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose (HPC), urea, Poloxamer 407, sugars, emulsifiers (SDS, Tween 80) and organic acids (succinic acid and citric acid). Because of the rapid dissolution of the water-soluble carriers than the drugs, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions.

Therefore, surface-active or self-emulsifying agents including bile salts, lecithin, lipid mixtures, Gelucire 44/14 [33] and Vitamin E TPGS NF [34] were used as additional additives, acting as dispersing or emulsifying carriers for the liberated drug to prevent the formation of any water-insoluble surface layer. In addition, the release behaviors of many drugs are also improved by using water insoluble polymers such as crospovidone [35, 36] and enteric polymers such as hydroxyl propyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), Eudragit L100 and S100 and Eudragit E3 [56].

11. **Lipid-Based Delivery Systems:** 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 [57]:

i) Particle size reduction to molecular size yielding a solid-state solution within the carrier

ii) Enhanced wetting of hydrophobic solids resulting in enhanced dissolution

iii) Increased rate of dissolution into aqueous environment from oil droplets of high surface area

iv) Promotion of absorption via intrinsic lipid pathways

v) Enhanced thermodynamic activity via super-saturation of the aqueous environment of the gastrointestinal tract

a. **Microemulsion:** Microemulsion is a thermodynamically stable isotropical dispersion composed of a polar solvent, oil, a surfactant and a co-surfactant. The formation of microemulsions is spontaneous and does not involve the input of external energy. One theory considers negative interfacial tension while another considers swollen micelles. The surfactant and the cosurfactant alternate each other forming a mixed film at the interface contributing to the stability of the microemulsion.

Microemulsions are potential drug delivery systems for poorly water-soluble drugs due to their ability to solubilize the drugs in the oil phase, thus increasing their dissolution rate. Even if the microemulsions are diluted after oral administration below the critical micelles concentration (CMC), the resultant drug precipitates have a fine particle size allowing enhanced absorption [58].

b. **Self Emulsification:** In the absence of external phase (water), the mixture of oil, surfactant, cosurfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). This forms fine O/W emulsions or microemulsions spontaneously upon dilution in the aqueous phase and is used for improving lipophilic drug dissolution and absorption [59, 60]. The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet.

A few parameters have been proposed to characterize the self-emulsifying performance including the rate of emulsification, the emulsion size distribution and the charge of resulting droplets. Among them, emulsion droplet size is considered to be a decisive factor in self emulsification/ dispersion performance, since it determines the rate and extent of drug release and absorption[61]. In addition, positively charged emulsion droplets could be obtained by incorporation of a small amount of cationic lipid (oleyl amine) into such system. The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation [62].

One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the

precipitation of the lipophilic drugs. As an example of self-emulsification, Neoral® is composed of ethanol, corn oil- mono-, di-, triglycerides, Cremophor RH 40 and propylene glycol. It exhibits less variability and better drug uptake compared to Sandimmune®. There is a long list of water soluble, insoluble and surfactants, which can use as solubilizing excipients [63].

12. **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 [64]. Prerequisite for fast dissolution from an ordered mixture includes that the carrier particle should dissolve rapidly, delivering a fine particulate suspension of drug particles[65]. Higher concentration of drug shows reduced dissolution rates particularly at loadings above monolayer coverage.

13. **Controlled Precipitation:** Controlled precipitation is a particle engineering technology that creates crystalline nano-structured drug particles with rapid dissolution rates. With this technology, the drug is dissolved in a suitable solvent then precipitated into an aqueous solution in the presence of crystal growth inhibitors to form drug nanoparticles. Particles prepared by controlled precipitation have the advantage of a narrower particle size distribution as compared to particle size reduction technologies, such as wet milling.

    The process is fast, continuous, and scalable with conventional process equipment. Levels of residual solvents are low, and the excipients used are pharmaceutically acceptable. The danazol powder prepared by controlled precipitation shows substantially improved bioavailability compared to the drug as-received (micronized danazol). Tablets prepared on a Carver press from precipitated danazol (equivalent to 200 mg danazol) formulated with microcrystalline cellulose and carboxy methyl cellulose (47.5:47.5:5) show further enhancement in bioavailability. The increased bioavailability observed with the control is due to an excipient effect that enhances wettability of the powder [66].

14. **Hydrotropic Solubilization:** The peculiar solvent property of micelle forming surfactants is closely related to the peculiar nature of the self-association responsible for the formation of the micelles themselves. In the case of the flexible chain surfactants, if the rate of change of the solubility of a hydrophobic solubilizate with surfactant concentration is plotted against the concentration, the cooperative self-association that is responsible for the existence of the critical micellization concentration in such systems [6- 9] is clearly reflected in the plot. Formation of micelles is a prerequisite for micellar solubilization in simple systems. Such diagrams clearly demonstrate the difference between the solubilizing patterns of flexible chain surfactants from the patterns exhibited by other surfactants such as the bile salt sodium cholate which shows a lower degree of co-operativity of self-association, good cosolvents such as ethanol, and hydrotropic agents [67].

15. **Cavitation & Melt Sono-Crystallization:** Cavitation can be in general defined as the generation, subsequent growth and collapse of cavities resulting in very high energy densities of the order of 1 to 1018kW/m^3. Cavitation can occur at millions of locations in a reactor simultaneously and generate conditions of very high temperatures and pressures (few thousand atmospheres pressure and few thousand Kelvin temperature) locally, with the overall environment being that of ambient conditions [68].

    Thus, chemical reactions requiring stringent conditions can be effectively carried out using cavitation at ambient conditions. Moreover, free radicals are generated in the process due to the dissociation of vapors trapped in the cavitating bubbles, which results in either intensification of the chemical reactions or in the propagation of certain unexpected reactions. Cavitation also results in the generation of local turbulence and liquid micro-circulation (acoustic streaming) in the reactor, enhancing the rates of transport processes.

Melt Sono-Crystallization (MSC): Sonocrystallization can be used to impart a variety of desirable characteristics to high-value products. Dow Chemical, USA is already using sonocrystallization for adipic acid crystallization, but it is a closely guarded secret. Impurities have been reduced from 800 to less than 50 ppm. Ultrasound can be used beneficially in several key areas of crystallization such as:

a. Initiation of primary nucleation, narrowing the metastable zone width.

b. Secondary nucleation.

c. Crystal habit and perfection.

d. Reduced agglomeration.

e. A non-invasive alternative to the addition of seed crystal (seeding) in sterile environment.

f. Manipulation of crystal distribution by controlled nucleation.

The formation of primary nuclei is a function of ultrasonic parameters such as frequency of oscillations, intensity of irradiation and physical properties of the liquid such as degree of super-saturation and operating parameters such as temperature [69].

16. **Steam-Aided Granulation:** Steam instead of water can be used in wet granulation because it provides a higher diffusion rate into the powder and a more favorable thermal balance during the drying step. After condensation of the steam, water forms a hot thin film, requiring only a small amount of extra energy for its elimination and evaporates more easily. The use of steam instead of liquid water in a wet granulation method can considerably decrease the amount of water used and as a result the whole operational time [70].

17. **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. 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 ascribed 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 PEG [71, 72].

18. **Direct Compaction:** In this process, polymers like HPMC and drug is dry-blended, compressed into slugs and then milled into a granular powder. The process results in enhanced dissolution rate of poor water soluble 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 [73].

19. **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 nonvolatile 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 [74, 75].

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