NOVEL STRATEGIES FOR POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Solubility of drug plays critical role in achieving the optimum therapeutic levels of the drug in blood and thus bioavailability. There are many drugs of various therapeutic categories fall in BCS class II and IV as they lack solubility. For all these drugs dissolution is the big hurdle for the absorption process. Present review's focus is mainly on novel techniques of improving the solubility apart from the description of the few popular and traditional techniques.

Keywords: Poor water solubility, solubilization techniques, and solubility problems.

INTRODUCTION

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug[1]. In case of poor water soluble drug dissolution is rate limiting step in the process of drug absorption. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class III and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250mL water over a range of pH from 1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 per cent absorption of the administered dose. In contrast, compounds with solubilities below 0.1mg/mL face significant solubilisation obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilisation during formulation. Aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic molecules, especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability[2].

The increasing frequency of poorly soluble new chemical entities exhibiting therapeutic activity is of major concern to the pharmaceutical industry such drugs are difficult to process or administer to patients due to poor dissolution. This is the major hurdle that prevents the commercialization of poorly water soluble drugs[3].

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are.

1. Physical approaches

1.1. Particle size reduction

This is a conventional and widely used approach to improve the solubility. Particle size reduction can be achieved by micronisation. 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. Micronization of drugs can be done by milling techniques using jet mill, rotor stator colloid mills etc[4]. Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

1.2. Modification of crystal habit

Polymorphism is the phenomenon exhibited by most of the drugs. It is the ability of drug moiety to exist in more than one crystalline form. These different polymorphs of drug are chemically identical, but they exhibit different properties like melting point, density, texture, stability and even in solubility which plays very important role in absorption and execution of therapeutic effect. Among the existing polymorphs, metastable forms of crystal are associated with higher energy and thus the higher solubility. In the same manner the amorphous form are always preferred than the crystalline form because of their higher energy, improved surface area and thus the higher solubility. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is Amorphous >Metastable polymorph >Stable polymorph**.** Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug[5].

1.3. Drug dispersion in carriers

1.3.1. Solid dispersion

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state. The solid dispersion approach to reduce particle size and thus increasing the dissolution rate and absorption of drugs was first recognized in 1961. They are

frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium lauryl sulfate are used. The solubility of various drugs was improved by preparing the solid dispersions using suitable hydrophilic carriers. Few examples of those drugs are etoposide[6], glyburide[7], itraconazole[8], ampelopsin[9], halofantrine[10], Etoricoxib[11].

Table 1: Various carriers used for solid dispersions[12].

Chemical class	Examples
Acids	Citric acid, Tartaric acid, Succinic acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, Hydroxypropyl methyl cellulose, Dextrin, Cyclodextrins, Galactomannan
Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

1.3.2. Eutectic mixture

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. When a mixture of I and II with an appropriate composition is cooled, I and II crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of two compounds in order to obtain a physical mixture of very fine crystals of the two components. Sekiguchi and co-workers[13,14] have proposed that when the eutectic mixture is exposed to the gastrointestinal fluids, the soluble carrier dissolves rapidly, of subdivision. The large surface area of the resulting suspension should result in an enhanced dissolution rate and, consequently, improved bioavailability. Eutectic mixtures preparation with a hydrophillic agent also increases the solubility of drugs eutectic combination of chloramphenicol/urea[15] and sulphathiazole urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

1.4. Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

1.4.1. Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. Some compounds that are known to form staching complexes are as follows: Nicotinamide[16], Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc.

1.4.2. Inclusion complexation

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. The most commonly used host molecules are cyclodextrins Cyclodextrins (CDs) are cyclic oligosaccharides containing six (a-CD), seven (b-CD), and eight (g-CD) or more a- (1, 4)-linked glucose units. The most important structural feature of these compounds is their toroidal or doughnut shape with a cavity that exhibits a hydrophobic character, whereas the outside of the molecule is hydrophilic. With the aim of extending the physicochemical properties and inclusion capacity of natural CDs, various kinds of CD derivatives such as hydrophilic, hydrophobic, and ionic derivatives have been synthesized. Hydrophilic CDs can be used to improve the bioavailability of poorly water-soluble drugs in immediate release formulations. On the contrary, hydrophobic CDs can act as sustained-release carriers for water-soluble drugs[17].

1.5. Use of surfactants

Surfactants are molecules with distinct polar and nonpolar regions. The polar group can be anionic, cationic, zwitterionic (amphoteric) or nonionic[18]. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent[19]. Here are few approaches by which surfactants increase the solubility of poor water soluble drugs.

1.5.1. Microemulsion

The term microemulsion was first used by Jack H. Shulman in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the co-surfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the

internal or dispersed phase is < 0.1 µ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions[20]. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production. Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, and increased bioavailability.

1.5.2. Micelles

Micelles are spherical nanoparticles of a colloidal size, into which many amphiphilic molecules self-assemble. In water, hydrophilic parts of such molecules form the micelle corona, while hydrophobic fragments form the core of a micelle that may serve as a cargo space for poorly soluble pharmaceuticals. Because of their small size (approx. 5-50 nm), micelles are able to spontaneously accumulate in pathological areas with the damaged ("leaky") vasculature, such as infarcts and tumors, via the enhanced permeability and retention (EPR) effect[21]. Micellar systems can solubilize poorly soluble drugs and thus increase their bioavailability, and also they stay in the body (blood) long enough to provide gradual accumulation in the required area, and their sizes permit them to accumulate in areas with leaky vasculature. Another advantage is that the micelles can be obtained in an easy and reproducible manner on large scale[22].

1.5.3. Self-Emulsifying Drug Delivery Systems

Self-Emulsifying Drug Delivery Systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants[23]. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsions. Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. An additional advantage of SEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic poor water soluble drugs with dissolution-limited oral absorption, these systems may offer an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles. Self assembling formulations are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/ excipients precipitation may also be problematic[24]. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation.

1.6. Liquisolid Systems

A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, nonadherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials[25]. Various grades of cellulose, starch, lactose, *etc*., may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material. The emulsification process increases the surface area for release of drug from the vehicle. The surfactants can also mimic formation of bile salt micelles, and thereby increase the solubility characteristics of a poorly water-soluble drug. If dissolution and solubilization characteristics of a hydrophobic drug change, then the rate and extent of absorption can be affected[26].

1.6.1. Liquisolid Tablets

A newly developed technique by Spireas et al, [27] liquisolid systems, has proved to be important technique for the dissolution rate improvement of water insoluble drugs. The liquisolid systems show acceptable flow properties and compressibility. Liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free flowing, non adherent, dry looking, and readily compressible powders with use of carrier and coating materials. As the drug is in the form of liquid medication, it is in either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablets of water insoluble drugs show improved dissolution properties and in turn increase in bioavailability[28]. Also the low cost incurred during the manufacture of liquisolid systems prove them useful with respect to industrial production using this technique.

1.6.2 Glassy solid solutions

Glassy solid solutions are a specific kind of solid dispersions, wherein a drug is dissolved in an amorphous carrier at the molecular level. In order to distinguish between solid suspensions and solid solutions in the case of isomalt as carrier, hot stage microscopy (HSM), dissolution testing and differential scanning calorimetry (DSC) is used. The carrier isomalt (1-O-α-D-glucopyranosyl-D-mannit dihydrate/6-O-α-D-glucopyranosyl-Dsorbit) is registered as sugar substitute and is mainly used for the production of sugar free hard candies. Isomalt can be heated above its melting point without decomposition. By cooling the melt to room temperature, it solidifies amorphously with a glass

transition at 60°C. Other sugar polyols exhibit lower glass transition temperature (Tg) values, e.g. mannitol and sorbitol have reported values of 10.7°C and 0°C. Thus, glassy systems of isomalt should be more stable than glassy systems of other polyols[29].

1.7. Spray freezing into liquid (SFL) particle engineering technology

Compositions containing poorly water soluble drugs prepared by cryogenic and nucleation processes have been reported. These processes are used to reduce the primary particle size of poorly water soluble drugs and form stable formulations that are readily wetted and have high dissolution rates, and in some cases high levels of super saturation. Cryogenic processing techniques, such as spray freezing into liquid (SFL), have shown promise in the areas of oral delivery, pulmonary delivery, and nanoparticle encapsulation Cryogenic processes can offer significant improvement over other conventional processing methods such as milling, solvent evaporation, and spray-drying. Ball milling and colloid milling introduce frictional forces into the system during processing, allowing for the potential of drug degradation. Solvent evaporation and spray drying techniques require the use of scrubbers to prevent release of organic solvent into the atmosphere. High temperatures needed for the evaporation of aqueous solvents during the spray-drying process can also lead to degradation of thermally labile drugs[30].

In SFL an aqueous or aqueous-organic co solvent drug containing solution is atomized into a cryogenic liquid, providing for ultra-rapid freezing of the drug solution. Liquid nitrogen has been employed as the cryogenic liquid due to nearly instantaneous freezing rates of the drug solutions resulting from the low boiling point of the liquid (−196°C). The low temperatures inhibit the degradation of thermally labile drugs. The drug containing feed solution is atomized below the surface of the liquid, creating high turbulent forces and producing micro particles composed of nano structured aggregates with high surface areas. The suspended frozen droplets can then be separated from the cryogen by allowing it to evaporate. Lyophilization of the aqueous or aqueous-organic solvents from the resulting frozen slurry produces a fine powder.

The amorphous structure, high surface area, and enhanced wettability of the SFL nano structured particles were the predominant characteristics of the poorly water soluble APIs that enhance the dissolution.[31, 32].

1.8 Microcrystal Technology

Micronization is the common method to increase specific surface area. Various types of mechanical mills are used to reduce the large crystals into smaller. There are certain disadvantages for the micronization caused by mills. Few of them include extreme inefficiency in reducing size disruption in crystal lattice which may lead thermodynamic imbalance and thus recrystalize when it absorbs atmospheric moisture[33]. One more disadvantage is that, due to high specific surface, micronized particles are often agglomerated and result in poor flow [34].

Microcrystals can be produced using milling by high pressure homogenizer. The drug crystals with a starting size as small as possible are suspended in an aqueous stabilized surfactant solution. This dispersion is homogenized at high pressure causing the changes in the crystal structure and the amorphous fraction in the particle increases ideally complete amorphous state is obtained. The stabilizing agents used are poloxamer and modified gelatins[35, 36, 37].

1.9 Adsorption onto high surface area carriers

Reduction of the particle size/increase in the surface area of the drug is a widely used and relatively simple method for increasing dissolution rates. However, micronized drugs have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. Other methods to reduce the tendency of drug agglomeration and to increase the dissolution rate include the incorporation of the drug into hydrophilic carriers (solid solutions/dispersions) or drug solution deposition onto adsorbents. The surface area of the drug available for contact with the dissolution medium is increased by the use of particulate adsorbent carriers, whereby the drug is bound to the carrier and thus cannot agglomerate. This is accomplished by dissolving the drug in an organic solvent and adsorbing this solution onto the carrier. The evaporation of the organic solvent results in a rapid precipitation of the drug either on the surface or within pores of the adsorbent material. This is a simple and time-saving procedure and has been described for silica many years ago. Other authors used microcrystalline cellulose, modified corn starch, magnesium trisilicate, aluminium glycinate and magnesium stearate. Organic solvents, such as acetone, chloroform or methylene chloride were mostly used to dissolve the drug followed by soaking the carrier with this drug solution. However, organic solvents are not desirable because of their potential toxicity, processing hazards and environmental and solvent residual concerns[38].

2. Chemical modifications

2.1. Salt formation

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant of the solvent by the use of co-solvents rather than the pH of the solvent. The use

of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs[39]. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

2.2. Prodrug approach

A prodrug is a drug molecule covalently bound to a pharmacologically inactive moiety (promoiety) with the aim to overcome various physicochemical, biopharmaceutical and/or pharmacokinetic limitations of the parent drug so that the therapeutic effect of the drug would be realized. A prodrug must undergo a chemical or biochemical transformation to the parent drug within the body at a reasonable rate, prior to exerting a pharmacological effect. When the prodrug approach is applied to a poorly soluble drug for IV delivery, solubility enhancement becomes the key objective. Ideally, a prodrug for IV administration should possess adequate solubility to be formulated into a solution, acceptable solution stability to provide an appropriate product shelf life, and the ability to rapidly convert to the pharmacologically active parent drug. In addition, the promoieties must also prove to be nontoxic. Water-soluble prodrugs of steroids such as sodium hemisuccinate esters and sodium phosphate esters represent the successful examples for the use of prodrugs of poorly soluble drugs for intravenous (IV) administration. Some recent developments in prodrug design strategies are reviewed below.

2.2.1. Phosphate prodrugs

The synthesis of phosphate esters is the most commonly used approach in enhancing the aqueous solubility of poorly soluble drugs. Phosphate esters are highly ionizable and exhibit significantly higher aqueous solubility than the parent drug. Their stability in both solid state and in aqueous solution allows development of stable injectable dosage forms.

2.2.2. Phosphomonoxymethyl prodrugs

The development of phsophonooxymethyl (PMO) prodrugs involves the attachment of the phosphate group to the parent drug through a methoxy spacer. Fosphenytoin, a disodium phosphate ester of 3-(hydroxymethyl)phenyotin is a good example for the use of a PMO prodrug as a water soluble injectable form of phenyotin, commercially marketed as Cerebyx[40].

2.2.3. Amino acid prodrugs

Numerous examples can be found in the literature on the use of amino acids and amine-containing derivatives as water-soluble prodrugs for IV delivery. Using this approach, the synthesis of water-soluble prodrugs of camptothecin and its derivative has been reported.

2.2.4. Polymer prodrugs

Water-soluble polymers have been investigated for their use in preparing prodrugs (conjugates) of poorly soluble anticancer drugs. Polymer bound prodrugs are not only water-soluble but also capable of tumor targeting via the enhanced permeability and retention (EPR) effect. N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer has been extensively explored for the formation of polymer drug conjugates[41].

3. Nanotechnology Approaches

3.1. Nano Particles

In pharmaceutics, nanoparticles are typically defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 micron in an external phase[42]. There are various ways in which nanoparticles of poorly water-soluble molecules are generated[43] or precipitated. Alternatively, nanoparticles can be successfully generated using drug- fragmentation process such as homogenization, microfluidation, or milling.

3.2. Nano Crystals

Drug nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. A nanosuspension consists of drug nanocrystals, stabilizing agents such as surfactants and/or polymeric stabilizers, and a liquid dispersion medium. The dispersion media can be water, aqueous solutions, or nonaqueous media. The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Nanocrystallization is thought to be a universal method that can be applied to any drug[50]. There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development[51]. The top-down methods (i.e. Milling[46] and High pressure homogenization[47] start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation[48] and Cryo-vacuum method[49]), nanoscale materials are chemically composed from atomic and molecular components.

3.3 NanoMorph

The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a

polymer induces precipitation of the drug substance. The polymer keeps the drug particles in their nanoparticulate state and prevents them from aggregation or growth. Water redispersable dry powders can be obtained from the nanosized dispersion by conventional methods, e.g. spray-drying. Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles[50].

3.4. Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The advantages offered by nanosuspension is increased dissolution rate which 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[51].

4. Other Techniques

4.1. Co-Crystallization

A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces[52]. This is the new approach available for the enhancement of drug solubility is through the application of the co-crystals; it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex). Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognized as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystallization between two active pharmaceutical ingredients has also been reported. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

4.2. Co-Solvency

The solubilisation of drugs in co-solvents is another technique for improving the solubility of poorly soluble drugs. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending. Most co-solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with water hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water self-association, co-solvents reduce water ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. By co-solvency the solubility enhancement can be as high as 500-fold with 20% 2-pyrrolidone[53].

4.3. Hydrotrophy

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 (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute[54]. The classes of compounds that normally increase the aqueous solubility of sparingly-soluble solutes are called hydrotropes. Besides solubilization, hydrotropes have uses in vesicle preparation and selective separation, as stabilizer of o/w microemulsion, viscosity modifiers and as clearing agents in cloudy detergent formulation. Alkylbenzene sulphonates based on toluene, xylene and cumene, polyhydroxy benzene, sodium salts of lower alkanols and derivatives of aromatic acids are generally considered to be effective hydrotropes. The hydrotropes are known to self-assemble in solution 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. The enhancement of both dissolution and permeation properties of drugs has been observed in the presence of hydrotropes. Hydrotrope–solute complex formation and 'salting-in' mechanism gain support from drug– hydrotrope interaction. The solubilization of a drug has been found to increase linearly with increasing hydrotrope.

4.4. Osmotic Drug Delivery

The historical developments of osmotic systems include seminal contributions such as the Rose-Nelson pump[55], the Higuchi-Leeper pumps[56], the Alzet osmotic pump[57], the elementary osmotic pump (EOP) [58] and the push-pull osmotic pump[59]. The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports[60]. To obviate the need for complicated laser drilling,

tablets coated with a membrane of controlled porosity have been developed. These membranes consist of a leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. However, due to the relatively low permeability of the dense coatings, osmotic delivery of drugs with moderate to low solubility is limited. It offers the advantages like pH and gastric motility independent drug delivery.

4.5. Combination with other drugs

Although a number of solubilizing agents are available, each of these has a number of significant disadvantages. The idea of combining two or more drugs with the drugs having complementary mode of action can give the additive therapeutic effect along with the improvement in the solubility.

In a research when clarithromycin and prednisolone were combined with paracetamol, caffeine and ibuprofen, for both the solubility was significantly increased up to a certain optimum concentration of the paracetamol. The magnitude of solubility enhancement was relatively smaller in case of prednisolone than clarethromycin[61, 62].

CONCLUSION

Not only the therapeutic activity of the active drug is important for the execution of the activity, also its physical properties including solubility play an important role. The use of above mentioned techniques either alone or in combination will help the drug molecules to overcome the hurdle of dissolution and in achieving good bioavailability.

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