Abstract: As an upshot of modern drug discovery techniques like combinatorial chemistry research and inventive high throughput screening, number of new drug candidates developing, are often lipophilic. For poorly soluble drugs, a good bioavailability is typically needed to evaluate the therapeutic index and aptness of the compound for technical formulation development. This challenges drug delivery institutions to develop carrier systems for optimal oral and parentral administration of these drugs. Comprehensive physicochemical characterization of poorly water soluble compounds can provide the key for outcome of successful formulation development, serving as guide for risk benefit assessment of delivery technology. The higher levels of difficulties are confronted by formulation specialists when these drugs have to be delivered at specific site. The present review addresses the emerging and promising formulation design options for the optimal administration of poorly water soluble drugs.

Keywords: Bioavailability, hydrophobic drugs, lipophilicity, solubility.

INTRODUCTION

The advancements in programmed synthesis led to the production of vast number of potential drug candidates as well as introducing more poorly water soluble drugs in global pharmaceutical world. It is estimated that more than 40% of marketed products are hydrophobic.1

Christopher A. Lipinsky gave a rule of five which predicts that poor absorption or permeation is more likely when a drug compound has more than five H-bond donors, ten H-bond acceptors, the molecular mass is greater than 500 and octanol water partition coefficient (log P) is greater than 5. Additionally, a system that distinguishes drugs on the basis of solubility/permeability was published by Gordon Amidon known as Biopharmaceutics classification system (BCS), which is a scientific framework for classifying a drug substance.2 The BCS takes into account three major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption.3 For the drugs exhibiting low solubility but high membrane permeability (BCS class II Drugs), rate limiting step is dissolution. The bioavailability of these drugs is unacceptable from oral conventional dosage forms, so number of formulation strategies have been designed for improving the delivery of hydrophobic drugs. The key basis of improvement is to enhance dissolution rate of drug or to achieve sustainable solubilization of drug.1,4 Proper formulation is of utmost importance to establish a successful product for administration of hydrophobic drug. To enable a proper selection of compound and corresponding formulation, compounds require special attention regarding physicochemical characterization. It ensures technological match.
between drug and dosage form early on in development. Although, poorly soluble compounds grasp a status of being troublesome development candidates, lipophilicity is necessary for efficient interaction with target. Lipophilicity is a prerequisite to pass the lipidic domain of natural bilayered phospholipid membrane. A holistic consideration is optional to select the appropriate delivery technology by taking into account technical as well as intellectual property considerations. Therefore, first and primary a comprehensive physico-chemical characterization of poorly water-soluble compounds can provide the key for a successful selection and development outcome. In this context, the identified physical form of the compound in the formulation is used as a steer for a risk–benefit appraisal of the selected oral delivery technology which opens new avenues to solubilize poorly water-soluble compounds.

Physical forms of drugs
The physicochemical characterization seems obvious and indeed a common practice in developing a dosage form. The results of characterization serve as basis to decide rationally that whether the drug is suitable for further formulation development and what delivery option could be exploited to maximize the bioavailability. The physical form of drug can be used as transparent guide to understand the pros and cons of various formulation technologies. The drug may be in solubilized form, amorphous form or crystalline form in the formulation.

Solubilized form: The solubilized form is preferred for intravenous administration. This form has the inherent advantage that drugs are already in solution form, therefore eliminating the necessity of dissolution step. But lack of long term chemical stability and risk of drug precipitation on dilution are unfavorable facts associated with this form.

Amorphous form: The amorphous form is considered when drug cannot be solubilized suitably. The use of amorphous form provides with possibility to increase oral absorption but associated with lack of physical and chemical stability.

Crystalline form: The toughest form of drug substance, from perspective of chemical stability, which can be used to develop a dosage form of poorly water soluble drug is the crystalline form. To be orally bioavailable solid crystalline form first has to dissolve.

FORMULATION TECHNIQUES
Underestimating the significance of formulation for poorly water soluble drugs may result in selecting incorrect lead candidates, extended development period and finally leading to significance shoot in development cost. Several emerging formulation designs for the delivery of poorly water soluble drugs which are more in focus and critically reviewed are discussed below

PHYSICAL APPROACHES
Particle Size Reduction
This is the most extensive and conventional approach used to advance the solubility. Micronization implies transfer of coarse drug powder to ultrafine powder with mean particle size typically in range of 2-5 mm, generally in range of 0.1-25mm. Reduction in particle size leads to increase in surface area, thereby resulting in improvement of dissolution properties of drug. Micronization can be done through variety of micronization technologies such as spray drying, freeze drying, crystallization but these techniques are associated with several drawbacks like production of coarse drug powder with broad size distribution, degradation of product due to thermal or mechanical stress and contamination of particles in toxic solvents. Also, micronization is not suitable for drugs having high dose because it does not alter saturation solubility of drug. In order to overcome these drawbacks various other technologies have been developed, these patented engineering process are discussed below in table I which describes the novel techniques of particle reduction

Crystal Engineering
The approach of crystal engineering offers potentially fruitful method for improvement in solubility, dissolution rate and finally bioavailability of poorly water soluble drugs. Crystal engineering techniques are developed for controlled crystallization of drugs to produce high purity powders with well defined properties as particle size, shape etc leading to stable and robust pharmaceutical products. Various methodologies of alteration of crystal habit are:

A) Polymorphs: Most of the drugs reveal a phenomenon known as Polymorphism, defined as ability of drug moiety to exist in more than one crystalline form. Polymorphs are different crystalline forms of drug that may have different physicochemical properties and biological activities such as shelf life, melting point, vapor pressure,
solubility, morphology, density, bioavailability and efficacy.

Metastable forms are associated with higher energy and increased surface area and later solubility, bioavailability and efficacy. Development of thermodynamically stable polymorph of drug is assured to lead reproducible bioavailability of the product over its shelf life under real world storage conditions. For example, tablets produced from the form A polymorph of oxytetracycline dissolved significantly more slowly than the tablets with form B polymorph of same drug. 12 In another study it was shown that stable α polymorph of chloramphenicol palmitate produced low serum levels whereas metastable β polymorph yielded much higher serum levels when same dose was administered. 13 The order of dissolution of different solid forms of drug is amorphous > metastable > stable.

B) Hydrates and Solvates: The stoichiometric type of molecular adducts in which solvent molecules are incorporated in the crystal lattice of solid are called as solvates. The solvates can exist in different crystalline forms and called as pseudopolymorphs and this phenomenon is called as pseudopolymorphism. When solvent in association with drug is water, the solvate is known as hydrate. As hydrates are already in interaction with water and thus have less energy for crystal breakup when compared to anhydrous forms. For example, the antidiabetic drug glibenclamide has been isolated as pentane and toluene solvates which exhibited higher solubility and dissolution rate than the non solvated polymorphs. 14

Solid Dispersions

Solid dispersions refers to dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting method, the addition of solvent method, or melt solvent method with an aspire to increase oral bioavailability of hydrophobic drugs. Due to the greatly enhanced surface area obtained this way, the dissolution rate and the bioavailability of poorly water-soluble drugs are expected to be high. 15 When solid dispersion is exposed to aqueous media, drug is released as very fine colloidal particles and surface area is increased, therefore dissolution and bioavailability of drug is enhanced. A solid dispersion can be produced at a lower temperature than the melting point of the drug and the softening temperature of the polymer (carrier), preventing their decomposition. This technique has been used to prepare a solid dispersion of 17 β - estradiol hemihydrate in 50% PVP/Gelucire 44/14, 16 itraconazole in hydroxypropylmethylcellulose to improve the solubility and dissolution properties of these poorly soluble drugs. 17,18

Nitrendipine solid dispersions prepared by melt mixing method using silica particles as carriers, showed improved dissolution properties in comparison to original nitrendipine crystals. 19 The solid dispersions of water insoluble drug aceclofenac prepared by solvent evaporation technique using hydrophilic carriers showed remarkable enhancement in dissolution rate as compared with pure aceclofenac. 20

The melt method requires relatively high temperatures (> 100°C) which may result in thermal degradation of drugs and problems associated with solvent method embrace health concerns because of possible residual organic solvents, time consuming and sturdy process. A method eliminating problems associated with both abovementioned methods is melt extrusion method as solid dispersion can be produced at temperature lower than the melting point of drug and there is no requirement of using organic solvents.

Eutectic Mixtures

A simple eutectic mixture consist of two compounds which are completely miscible in liquid state but to a limited extent in solid state, when the mixture is cooled both crystallize out spontaneously. Solid eutectic mixtures are usually prepared by cooling of co-melt of two compounds in order to obtain fine mixture of both compounds.

When eutectic mixtures are exposed to gastrointestinal fluids, the soluble carrier dissolves rapidly. The large surface area should result in enhanced dissolution rate thereby improved bioavailability. Eutectic mixture prepared with hydrophilic agent also increase solubility of drugs. Eutectic combination of chloramphenicol/urea and sulfathiazole urea increased the solubility. 21

Emulsion Systems

Emulsified formulations have shown their ability to increase absorption of poor water soluble drugs. The corn oil emulsion of greisofulvin has been evaluated in humans and showed two-fold increase in bioavailability when compared with either aqueous suspension or commercial tablet. 22 However major problem troubled with emulsion is their thermodynamic instability. To overcome this problem attractive approach is conversion of emulsions into dry powdered emulsions by spray drying, referred as solid state emulsions. 23 This dry powdered emulsion can be compressed into tablets as would be advantageous from dosing and handling point of view.
Presently microemulsions are of immense concern in pharmaceutical world due to their considerable potential to act as vehicle for delivery of vast range of drug molecule. 24 Microemulsions are defined as liquid system of water, oil and surfactant which is single, optically isotropic and thermodynamically stable usually in range of 20-200 nm. It differs from emulsions by being thermodynamically stable, clear and translucent in appearance. Low surface tension in conjugation with enormous increase in interfacial area due to nanosized droplets of microemulsion influences the drug penetration across the skin. 25 An o/w formulation prepared by using medium chain fatty acid triglyceride diglyceril monooleate, polyoxyethylene hydrogenated castor oil40, ethanol and phosphate buffer saline( pH 6.8) as an oil phase utilizing nine drugs as ibuprofen, ketoprofen, tamoxifen etc and increase in solubility was 60-20,000 times. 26 Another microemulsion formulation was formulated of poor water soluble drug simvastatin amd characterized. It showed higher dissolution rate profile which further resulted in superior performance of drug when characterized in vivo in rats. 27

Self microemulsifying drug delivery systems (SMEDDS) are defined as mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as gastrointestinal fluids (GI) fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for Self-Emulsification. The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOIF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20% as compared to 40-80% in SEDDS. 28, 29, 30 when compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules.

Often co-surfactants and co-solvents are added to improve the formulation. They are closely related to microemulsions, includes a mixture of oil, surfactant and drug (preconcentrate) which emulsify spontaneously when introduced in gastrointestinal tract, and produce fine droplets of drug solution, leading to enhanced absorption. Compared with microemulsions they have improved stability profile in long term storage. SMEDDS formulation of poor water soluble drug candesartan cilexetil was formulated showed enhancement in dissolution rate and bioavailability. 31 Microemulsion base gel of ibuprofen was formulated and increase in topical delivery recorded is 5.72- 30.0 times when compared with control. 32

Cyclodextrin Inclusion Complexes

Cyclodextrins (CD) are bucket shaped cyclic oligosaccharides composed of 6-8 dextrose units (α, β, γ CD ) respectively joined through C-C double bonds. The interior of these molecules is lipophilic and exterior of these molecules is hydrophobic. Lipophilic molecules can be incorporated into interior cavity of CD leading to better stability, high water solubility, and increased bioavailability or decreased undesirable side effects. 33 The presence of hydroxyl groups on the external surface of the CD molecule increases the possibility of hydrogen bonding with the drug molecules resulting in the formation of non-inclusion complexes as well. 34 At present most widely used CD are 2-hydroxy propyl-β cyclodextrin, methyl β cyclodextrin etc due to high water solubility and low toxicity. The complex of praziquantel with β CD showed significantly improved dissolution profile compared with that of pure drug whereas hydrophobic CD can act as sustained release carriers for water soluble drugs. 35 Hydrophilic CD can be used to improve bioavailability of poorly soluble drugs. The drug – CD complexes are prepared by freeze drying, spray drying, and co- precipitation of CD drug solution. 36 The inclusion complexes of aceclofenac with hydroxypropyl-β-cyclodextrin provided increased dissolution rates as well as improved therapeutic effect. 37

CHEMICAL MODIFICATION

By modification in chemical structure of the drug molecule, solubility can be enhanced. This can be achieved by the means of prodrug or salt formation quoted in figure 1.
Figure 1: Different types of chemical modification

**Prodrug Approach**
In delivery of molecules with limited water solubility, prodrug approach is adopted so that therapeutic effect of drug can be achieved. Recent developments in prodrug design strategy are discussed below as:

- **Phosphate prodrugs**: The synthesis of phosphate esters is most commonly used approach in enhancement of aqueous solubility of hydrophobic drugs as they exhibit higher solubility than parent drug and are also ionizable.
- **Polymer prodrugs**: Hydrophilic polymers have been explored in preparation of prodrugs of poorly soluble drugs. Polymer bound prodrugs are capable of targeting by enhanced permeability and retention effect. Therefore poorly soluble anticancer drugs can be formulated like this. Hydroxylpropyl methacrylamide (HPMA) polymer has been extensively investigated for polymer prodrugs.

**Salt Formation**
The solubility of ionizable drug can be enhanced exponentially by alteration in the pH of the system. Ionizable drug should be either weak acid or weak base. There is little effect of change in pH on nonionizable drugs so solubility of these drug substances can be increased by altering dielectric constant of solvent by use of co-solvent. Salt formation is most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is adjusted by addition of acid the solubility of the base is increased. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water. Similarly the solubility of slightly soluble acid is increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates). At a given pH, the solubility of a drug is constant. The influence of salt formation on drug solubility can be explained by taking into account the pH of diffusion layer not the pH of the bulk solution.

**VESICULAR APPROACHES**
Recently lipid vesicles were found to be of very much use in membrane biology. These vesicles were first reported by Bingham in 1965 and thereby also called Bingham bodies. The vesicular approach basically takes into consideration the concept of micellar solubilization. Poorly soluble compounds which fit into the micelle structure are most appropriate. These micelles soak up the lipophilic substance in their lipophilic region and subsequently no dissolution of poorly soluble compound needed before absorption as the drug is already in solubilized form. They are easy to formulate and reproducible on large scale. They prolong the existence of drug in systemic circulation and also delays the elimination of rapidly metabolizable...
drugs. Various possible systems based on vesicular approach are quoted as

**Liposomes**
Liposomes are microscopic, synthetic cells used as sustained-action delivery vehicles for a wide variety of drugs, vaccines, enzymes, non enzyme proteins, and genetic material and now, for some nutritional supplements as well. The drug is encapsulated inside the liposomes, which eventually break down through natural processes and spill their contents into the bloodstream or into tissues to which they have migrated by diffusion through the walls of capillaries. The release of poorly water-soluble compounds occurs through diffusional or collisional transfer to other lipid components, such as lipoproteins, in the ‘lipid highway’ of blood. It has been reported that the liposome encapsulation efficiency of lipophilic drugs depends on both the physicochemical properties of the drug, such as its lipophilicity. Liposomes are a safe and effective way to introduce agents into system that are problematic for some reason when taken orally, as well as agents that cannot be taken orally at all (because they are degraded by digestive juices). In the lipid domain of bilayered membrane, lipophilic drugs can be dissolved. Availability of ready-for-use liposomes with defined particle size and instantaneous loading procedures with poorly watersoluble drugs liposomes are certainly useful options to increase the solubility of poorly water-soluble compounds. Liposomes offer a dynamic and adaptive technology for enhancing drug solubility. The main advantage of liposomal formulations in contrast to other carrier systems is generally regarded as safe (GRAS) status of phospholipid constituents. Ganciclovir liposomes were formulated and ocular bioavailability was shown to increase 1.7 fold higher than ganciclovir solution.

**Niosomes**
Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery. Niosomes of griseofulvin were prepared using different non ionic surfactants by thin film method and ether injection method. The in vivo study revealed that niosomal dispersion significantly improved the oral bioavailability of griseofulvin in albino rats after single dose. [47]

**Pharmacosomes**
Pharmacosomes having distinctive compensation over liposome and niosome vesicles, have emerged up as potential alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. [40] As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as pharmacosomes. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (- COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilic characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior. Pharmacosomes of aceclofenac were prepared using phosphatidylcholine (80%) in two different ratios in 1:1 and 2:1 by conventional solvent evaporation technique. Aceclofenac pharmacosomes showed improved dissolution profile than aceclofenac acid. [48]

**NANOTECHNOLOGY APPROACHES**

**Solid Lipid Nanoparticles**
Solid lipid nanoparticles (SLNs) are particulate systems with mean particle diameters ranging from 50-1000nm. They are derived in oil in water emulsions by replacing liquid lipid by solid lipid. The formulation components of SLNs include solid lipid, emulsifier and water. [49] They are used for controlled release, targeting of drugs, modification of dissolution rate and enhancement in bioavailability as they possess adhesive properties by which they get adhere to gut wall and release the drug wt the site of absorption. There are number of potential advantages associated with SLNs as lipid matrix of system is made from physiologically tolerated lipids components which reduces the risk of toxicity, they can be produced on large industrial scale by high pressure homogenization, they have
the ability of being stable for at least 3 years. SLNs formulation of vinopocetine was formulated using lipid matrix as glyceryl monostearate by ultrasonic solvent emulsification technique. The formulation showed remarkable enhancement in bioavailability compared to vinopocetine solution \(^{50}\). Other examples include quercitin \(^{51}\), lovastatin. \(^{52}\)

**Nanoparticles**

Nanoparticles have emerged as promising strategy for efficient delivery of poorly water soluble drugs because of their versatile features and unique advantages \(^{53}\) often referred as hydrosols, are very finely dispersed solid particles in aqueous vehicle, size distribution of solid particles is usually < 1 μm, with average particle size range of 200-600 nm. The overall bioavailability is improved by increase in surface area and saturation solubility aided by particle size reduction. They are prepared by precipitation, pearl milling and high pressure homogenization. Additionally, carrier related drawbacks, such as limitations in drug load, as well as side effects due to matrix components are bypassed by nanosuspension system.

**Nanocrystals**

The Nanocrystal technology for formulation of poorly water soluble drugs has been successful at commercial level in recent period of time. Generally nanocrystals are particles composed of 100% Active pharmaceutical ingredient (API) devoid of any carrier and form ultrafine dispersion in media.\(^{54}\)\(^{55}\) The term ‘nanocrystal’ is a misnomer, as these particles can subsist not only in crystalline state but also in the amorphous state, formation of which depends on the methodology of manufacturing and process conditions used. On administration of a nanocrystal, formulation particles are released in the nanorange, which is of paramount importance in imparting many advantages to the nanocrystals as fast dissolution, increased kinetic saturation solubility and adhesion to biological membranes, which ultimately results in enhanced solubility and permeability. \(^{56}\)

**CONCLUSION**

By this article it is accomplished that drug solubility is the most essential aspect in formulation development and also in therapeutic efficacy. For the drugs administered by oral route, solubility is one of the rate restrictive steps to achieve effective concentration in systemic circulation for the consequential pharmacological response. Number of techniques described here in this review unaccompanied or in combination can lead to enhancement in drug solubility resulting in increased bioavailability as well. With further investigations the development of new molecules as well as technologies, formulation tactics will become more capable.

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<tr>
<th>TECHNIQUE</th>
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<tr>
<td>Pearl Milling (Nanocrystals®)</td>
<td>It involves filling an aqueous suspension of drug in pearl mill containing glass or zirconium oxide pearls as milling media. (^{5}[6])</td>
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<tr>
<td>High Pressure Homogenization (Dissocubes®)</td>
<td>It involves dispersing a drug powder in an aqueous surfactant solution and passing through high pressure homogenizer. (^{7-8})</td>
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<tr>
<td>Solution enhanced dispersion by supercritical fluids (SEDS)</td>
<td>Drug in organic solvent solution mixed with compressed fluid carbon dioxide and made to flow in particle formation vessel through restricted orifice. (^{9})</td>
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<tr>
<td>Rapid Expansion from Supercritical to Aqueous Solution (RESAS)</td>
<td>It includes rapid nucleation of supercritical fluid dissolved drugs and surfactants resulting in particle size with desirable particle size distribution. (^{10})</td>
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<tr>
<td>Spray Freezing to Liquid (SFL)</td>
<td>It involves atomizing an aqueous organic cosolvent solution, aqueous organic emulsion or suspension containing drug and pharmaceutical excipients directly into compressed gas or cryogenic liquids. The frozen particles are lyophilized to obtain free flowing micronized powder. (^{11})</td>
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REFERENCES


51. Li, HL, Zhao, XB, Ma, YK, Zhai, GX, Li, LB. Enhancement of gastrointestinal absorption of


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