

**BIOAVAILABILITY ENHANCEMENT: A REVIEW****HIMANI BAJAJ*¹, SEEMA BISHT², MAYANK YADAV¹ AND VINOD SINGH³**¹Adarsh Vijendra Institute of Pharmaceutical Sciences, Gangoh, Saharanpur, India.²S.G.R.R.I.T.S, Patel Nagar, Dehradun, India.³Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences & Research, Balawala Dehradun, Uttarakhand, India.**HIMANI BAJAJ**

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ABSTRACT

Bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. A drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane, extensive presystemic metabolism. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. This review focuses on the various techniques used for the improvement of the Bioavailability of drugs including size reduction, solubilising excipients, colloidal drug delivery systems, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilisation, hydrotrophy etc. The purpose of this review article is to describe the techniques of Bioavailability enhancement for the attainment of effective absorption and improved bioavailability.



KEYWORDS

Bioavailability, Bioavailability enhancement, solubility.

INTRODUCTION¹

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This attribute of the dosage form is referred to as physiologic availability, biologic availability or simply bioavailability. For most drugs, the pharmacologic response can be related directly to the plasma levels. Thus the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It can also be defined as the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane, extensive presystemic metabolism. Bioavailability of poorly water soluble drugs is a major problem.

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. The high costs and time involved in new drug development, expiry of patents for a significant number of drug molecules, ease of manufacturing and ready availability of technology for the production of oral drug products are also driving the generic pharmaceutical companies towards the development of bioequivalent oral dosage forms. However, the major challenge with the design of oral dosage forms lies with their poor

bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms². The most frequent causes of low oral bioavailability is attributed to poor solubility and low permeability³. The tremendous pharmaceutical research in understanding the causes of low oral bioavailability has led to the development of novel technologies to address these challenges. One of the technologies is to design a prodrug with the required physico-chemical properties to improve the oral bioavailability⁴. For example, the prodrug approach resulted in improved bioavailability of etilevodopa⁵. For BCS class IV drugs with poor solubility and poor membrane permeability and BCS class III drugs with high solubility and low permeability, prodrug approach is the best option to enhance their bioavailability. Though prodrug approach is an exciting way of improving the oral bioavailability of BCS class II drugs, it requires extensive studies to establish the safety profile of prodrugs in humans, which ultimately may result in failure. Furthermore, the potential drawback of this approach is the reduced solubility of the prodrug. In today's market, more than 40% of oral drug products contain poorly soluble drugs, and among the pharmacopoeia, this share is more than 30%⁶. For these BCS class II drugs with low solubility and reasonable permeability, drug dissolution step is the rate-limiting process of drug absorption. When administered as oral dosage forms, the pharmaceutical formulation plays a critical role in the absorption of such drugs from gastrointestinal tract. A variety of pharmaceutical formulation technologies are used to enhance oral bioavailability of BCS



class II drugs. They use already approved excipients and GRAS materials. This in turn reduces the cost and development time. The main technologies to achieve the enhanced oral bioavailability of drugs with poor aqueous solubility include the use of micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles and other colloidal drug delivery systems such as microemulsions, self-emulsifying drug delivery systems, self microemulsifying drug delivery systems and liposomes⁷.

A brief review of the technologies along with a few reports is presented to emphasize their importance in enhancing the oral bioavailability of poorly soluble drugs.

Methods for enhancement of bioavailability

As far as the definition of bioavailability is concerned, a drug with poor bioavailability is the one with-

- Poor aqueous solubility and/ or slow dissolution rate in the biologic fluids,
- Poor stability of the dissolved drug at the physiologic pH.
- Inadequate partition coefficient and thus poor permeation through the biomembrane.
- Extensive presystemic metabolism.

There are three major approaches to overcome the bioavailability problems.

A) Pharmaceutics approach:

Modification of formulation, manufacturing processes or physiochemical properties of the drug is done.

B) Pharmacokinetic approach:

Pharmacokinetics of drug is altered by modifying its chemical structure.

C) Biological approach:

In this, route of drug administration may be changed such as parenteral form instead of oral form. Rate dissolution and its solubility are very important factors in third approach. The second approach of chemical modification has number of drawbacks such as being very expensive, time consuming, requires repetition of chemical studies, risk

of precipitation and adverse effects.. Moreover, the new chemical entity may suffer from another pharmacokinetic disorder or bear the risk of precipitating adverse effects. So generally only pharmaceuticals approach is considered here¹.

The attempts, whether optimizing the formulation, manufacturing process or physiochemical properties of the drug, are mainly aimed at enhancement of dissolution rate as it is the major rate limiting step in the absorption of most drugs. There are several ways in which the dissolution rate of the drug can be enhanced. Some of the widely used methods, most of which are aimed at increasing the effective surface area of the drugs, will be discussed briefly.

Co-solvency

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents⁸.

Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parentally. Parenteral formulations may require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co-Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilisation approaches.



However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. In this case, dissolution of this precipitate is required for oral absorption. Co-solvents may be combined with other solubilisation techniques and pH adjustment to further increase solubility of poorly soluble compounds. The use of co-solvents is a highly effective technique to enhance the solubility of poorly soluble drugs^{9, 10}. The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerine, and polyethylene glycol^{11, 12}. Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been widely used as cosolvents because of their large solubilisation capacity for poorly soluble drugs and their relatively low toxicity¹³⁻¹⁴.

Advantages:

Simple and rapid to formulate and produce.

Disadvantages:

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size. Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.
- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

Co-solvent products: Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir

Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

Particle size reduction

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

Nowadays Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size. In micronization the solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Nanosuspensions are produced by homogenization and wet milling process¹⁵.

Advantages:

- ✓ Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can



be converted into solids for later clinical development.

- ✓ Typically, low excipient to drug ratios is required.
- ✓ Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation.
- ✓ Generally, crystal forms are chemically and physically more stable than amorphous particles.
- ✓ A method to consider for stubborn compounds that defeat previous attempts to increase solubility.

Disadvantages:

- ✓ Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
- ✓ Developing a solid dosage form with a high payload without encouraging agglomeration may be technically challenging.
- ✓ Technically, development of sterile intravenous formulations is even more challenging.

Hydrotrophy

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”¹⁶. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak

interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs^{17, 18}.

Advantages of Hydrotropic Solubilisation Technique:

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

The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, *a* and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene¹⁹. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotropeaction may be due to the availability of interactive orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilisation of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and



polymers, etc. Other techniques that enhance the solubility of poorly water soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble prodrug, Application of ultrasonic waves, spherical crystallization²⁰.

Solid dispersions

The effective surface area is one of the important factors governing the dissolution rate of poorly soluble drugs. In addition to the micronization and nanosizing technologies, as described above, solid dispersion is the other way of enhancing the effective surface area available for dissolution^{21, 22}. Solid dispersion involves the dispersion of one or more active ingredients in an inert carrier or matrix at solid state. These are usually prepared by heating mixtures of the drug and carrier to a molten state, followed by resolidification by way of cooling. A solid dispersion of nitrendipine prepared by a *melt-mixing method* using silica particles as carriers showed remarkably improved dissolution properties compared with that of the original nitrendipine crystals²³. This melt method often requires relatively high temperatures (>100°C), which may lead to thermal degradation of the drug. Solvent evaporation method is another technique of preparing solid dispersions which involves dissolving the components in a mutual volatile solvent followed by evaporation. Sometimes, drug is dissolved in a solvent such as propylene glycol and the resulting solution is added to the molten carrier. Solid dispersions of spironolactone, itraconazole and prednisolone, prepared by *solvent evaporation method*, were shown to enhance their dissolution²⁴. The solvent evaporation method has several disadvantages. It is time-consuming and expensive because of long processing and drying times. Moreover, it is not environment-friendly due to the use of organic solvents, and may have toxic residual solvent(s) in the final product. As described under micronization approach, the *SCF technologies* involving mild processing

conditions of low temperatures (~ 30°C) and minimal or no organic solvents are considered the most promising to overcome the disadvantages associated with the melt and solvent evaporation methods of preparing solid dispersions²⁵. For example, the dissolution rate and stability profile of felodipine and carbamazepine prepared using SCF technologies were found superior to those prepared using conventional solvent evaporation method²⁶. Another interesting approach of producing solid dispersion without the use of organic solvents is the use of *melt extrusion technology*. In this process, heat is used to make thermoplastic materials pliable enough to incorporate drug particles in the polymer matrix. Intensive mixing is achieved through the shear stress created by the shear rate used. The decomposition of the drug and/ or carrier is unlikely with melt extrusion technology as the processing temperature is lower than the melting point of the drug and the softening temperature of the polymer (carrier). The dissolution profile and stability of several drugs including 17_estradiol, itraconazole and nitrendipine solid dispersions were improve when prepared using melt extrusion technology²⁷. The melt extrusion technology is considered to be an efficient technique in developing solid molecular dispersions and has been demonstrated to provide sustained, modified and targeted drug delivery resulting in enhanced bioavailability²⁸.

Sustained release tablets of verapamil prepared with melt extrusion technology were resistant to the effects of ethanol on *in vitro* dose dumping when combined with readily accessible ethanol concentrations. The vast number of reports on solid dispersion research could bring out the industrially feasible technologies such as melt extrusion technology and SCF technology for the production of solid dosage forms with improved oral bioavailability. This is highly beneficial to BCS class II drugs as the enhanced dissolution increases permeation through the gut wall. In contrast, BCS class



IV drugs may not gain from fast dissolution, as a lower permeation may cause the recrystallization of the drug after dissolution in the gut environment²⁹.

Micellar solubilisation

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium³⁰⁻³². They can also be used to stabilise drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles³³. This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved³⁴.

Micellar solubilisation is a widely used alternative for the dissolution of poorly soluble drugs³⁵. Examples of poorly soluble compounds that use Micellar solubilisation are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and androsiglitazone³⁶.

Complexation

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α , β , γ -cyclodextrin) bound in a 1, 4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non covalent inclusion complexes resulting in increased aqueous solubility and chemical stability³⁷.

Derivatives of β -cyclodextrin with increased water solubility (e.g. hydroxypropyl- β -cyclodextrin HP- β -CD) is most commonly used in pharmaceutical formulation. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide (DEET)³⁸ and the stability and photostability of sunscreens. Cyclodextrins are large molecules, with molecular weights greater than 1000Da, therefore it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase³⁹ and decrease skin penetration. In a recent review of the available data, Loftsson and Masson concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, while low cyclodextrin concentrations resulting in increased flux. As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug which is in excess of its solubility, an increase in flux might be expected. However, at higher cyclodextrin concentrations, the excess cyclodextrin would be expected to complex free drug and hence reduce flux. Skin penetration enhancement has also been attributed to extraction of stratum corneum lipids by cyclodextrins⁴⁰. Given that most experiments that have reported cyclodextrin mediated flux enhancement have used rodent model membranes in which lipid extraction is considerably easier than human skin⁴¹ the penetration enhancement of cyclodextrin complexation may be an overestimate. Shaker and colleagues recently concluded that complexation with HP- β -CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms⁴². Lipophilic drug- cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipient together, resulting in



enhanced drug solubilisation. Cyclodextrins (CD) are a group of structurally-related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. Cyclodextrins consisting of 6, 7 and 8 D- glucopyranosyl units connected to α -1, 4 glycosidic linkages are known as α , β , γ , cyclodextrins, respectively⁴³. Hydrophilic cyclodextrins are nontoxic in normal doses while lipophilic ones may be toxic; hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use. The solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents⁴⁴. CDs can also be used as nasal permeation enhancers acting by interaction with nasal epithelium by modifying tight junction & lipid and protein content of the membrane, which enhances the permeation of the membrane⁴⁵.

CDs can also be utilized as permeation enhancer in pulmonary drug delivery systems. Rifampicin is a so-called concentration-dependent antibiotic, the rate and extent of bacterial kill is related to the attainment of high maximum concentration relative to the minimal inhibitory concentration. The rifampicin-CD inclusion compound can improve the lung transport of drug when nebulized with compatible pulmonary deposition and achieve required concentration of drug in broncho-alveolar epithelium lining-fluid when administered as aerosolized solution⁴⁶⁻⁴⁸. 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 α -CD, (iii) Vander walls interactions, and (iv) hydrogen and hydrophobic bindings⁴⁹.

Solubilisation by complexation is achieved through specific interaction rather than changes in the bulk solvent properties as in other solubilizing system such as cosolvents, emulsion and pH adjustments. The dissociation is very rapid, quantitative and therefore predictable. Another significant advantage of

complexation technique is that some commonly used complexing agents such as hydroxy propyl beta cyclodextrin and sulfobutyl beta cyclodextrin are less toxic compared to other solubilizing agents such as surfactant and cosolvents. Since most complexes formed is 1:1 complexes of the AL type, the dilution of complexes will not result in solution which is super saturated with respect to substrate. This can be important for very insoluble compounds that may precipitate upon injection when solubilized by other system such as cosolvents. Despite all the attractive advantage of complexation, there are disadvantages. First of all the compound has to be able to form complexes with selected ligand. For compounds with very limited solubility to start with, solubility enhancement can be very limited. The second limitation is the complexes of Ap type, dilution of system may still result in precipitation. This is also true for solubilisation via combined technique such as complexation with pH adjustment. Lastly the potential toxicity issue, regulatory and quality control issue related to presence of ligand may add complication and cost to the development process⁵⁰.

Solubilising excipients

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Surfactants are also often used to stabilise microemulsions and suspensions into which drugs are dissolved. The presence of surfactants within a drug product formulation may result in an incompatibility with drug delivery technologies which rely upon well-regulated hydration, dissolution and erosion of a matrix or coating to achieve controlled release. The influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals is well documented. The absorption of a drug is



largely dependent upon diffusion, which varies with the pKa of the drug and the pH of the individual regions within the gastrointestinal tract, and permeability, which is not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionisation. While the importance of salt selection and pH adjustment has been stressed as a critical parameter of pre-formulation, the use of pH-altering excipients within drug delivery systems is also of significant utility. Solubilised excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalising agents may increase the solubility of weakly basic drugs. One example of such a use of pH-inducing excipients is SCOLR Inc's self-correcting hydrogel systems. One or more electrolytes are included within the dosage form whose pKa is complementary to the drug; as the dosage form hydrates, the electrolyte is wetted simultaneously with the active compound, creating a microenvironment independent of gastrointestinal pH. Microenvironmental pH may be modulated to enhance dissolution of poorly soluble drugs via salting-in effects through the inclusion of electrolytes of varying hydrophobic character; conversely, intra-dosage form pH may induce precipitation of highly soluble drugs, thereby slowing dissolution through salting-out effects.

pH adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach

the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are⁵¹ best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds⁵². Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs^{53, 54}.

The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

Advantages:

- Simple to formulate and analyse.
- Simple to produce and fast track.



- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

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

Commercial products using pH adjustment : Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na⁺ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents.

Colloidal drug delivery systems

These include the emulsified systems as well as liposomes. Traditional emulsions, microemulsions, self-emulsified drug delivery systems and self-microemulsifying drug delivery systems belong to emulsified systems. The formulation of *emulsions* involves the use of digestible oils such as cottonseed oil and soybean oil. The enhanced drug absorption from an emulsion is a widely known concept. For example, the oral bioavailability of griseofulvin from a corn oil emulsion formulation was found to be twofold in humans when compared with either an aqueous suspension or commercial tablet formulation⁵⁵. However, emulsions are known for their thermodynamic instability. This drawback can be eliminated by converting the liquid emulsions into solid emulsion powder by means of a suitable technique such as spray

drying. These *dry emulsions* are cohesive and bulky, and hence formulated as tablets or capsules. Comparable bioavailability were obtained from dry emulsion powder and oral dosage form (tablet and capsule) when a model drug was formulated and administered to beagle⁵⁶. The emulsions are cloudy, thermodynamically unstable and requires high amount of energy for producing them.

Microemulsions are novel pharmaceutical formulations designed to overcome the above disadvantages. They are thermodynamically stable, transparent, low viscosity, easy to prepare and isotropic dispersions consisting of oil and water stabilized by an interfacial film of surfactant molecules, typically in conjunction with a cosurfactant. It is possible to incorporate water-soluble, oil-soluble and amphiphilic drugs into microemulsions. For example, while formulating a microemulsion, water-insoluble lipophilic drugs can be incorporated into the disperse oil phase and/or hydrophobic tail region of the surfactant and the hydrophilic drug can be incorporated into disperse aqueous phase of water-in-oil droplet. For enhancing the solubility and dissolution rate of poorly soluble drugs, it is preferable to formulate them as oil-in-water microemulsions instead of water-in-oil microemulsions⁵⁷. This is because the droplet structure of oil-in-water microemulsions is often retained on dilution by aqueous biological fluid thereby enhances oral bioavailability. In contrast, if formulated as water-in-oil microemulsions, the droplet size increases on dilution in GI tract, and ultimately results in dose dumping due to phase separation. Microemulsion systems are widely used to improve the solubility and absorption of poorly water-soluble drugs. In one of the studies, microemulsions with varying weight ratios of surfactant to co surfactant were prepared using caprylic/capric triglyceride oil, polyoxyethylated castor oil as a surfactant, Transcutol® as a co surfactant and saline⁵⁸. The absolute bioavailability of cyclosporine loaded in this microemulsion system was increased about



3.3 and 1.25 fold enhanced bioavailability of cyclosporine loaded in this microemulsion system were considered due to the reduced droplet size of microemulsion systems. A microemulsion system of docetaxel was prepared and evaluated for its solubilisation capacity and oral bioavailability improvement⁵⁹. The oil-in-water microemulsion formulation composed of Capryol 90 (oil), Cremophor EL (surfactant) and Transcutol (co-surfactant) enhanced the solubility of docetaxel up to 30 mg/mL, which maintained solubilisation capacity for 24 h even after it was diluted 20 times with normal saline. The oral bioavailability of the microemulsion formulation in rats (34.42%) rose dramatically compared to that of the orally administered Taxotere® (6.63%). The studies showed that combined effect of the enhancement in solubility, the inhibition of P-gp efflux system and the increase in permeability might have increased the bioavailability of docetaxel. In another study, microemulsion formulation of puerarin, prepared with soybean oil, soybean lecithin/ethyl lactate (1:1) and 1,2-propanediol/water, was shown to be stable with enhanced oral bioavailability when compared to suspension formulation⁶⁰.

Self-emulsifying drug delivery systems (SEDDS) and *self microemulsifying drug delivery systems (SMEDDS)* are isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water⁶¹. The poorly soluble drug can be dissolved in a mixture of surfactant and oil which is widely known as pre-concentrate. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions. Compared with ready-to-use microemulsions, the SEDDS and SMEDDS have been shown to improve physical stability profile in long term storage. SEDDS have been reported to enhance the oral bioavailability of paclitaxel, griseofulvin and dexibuprofen^{62, 63}. *Solid SEDDS* are the advanced formulations that can be filled directly into soft or hard gelatin capsules for conventional drug delivery⁶⁴. For example, solid SEDDS of dexibuprofen,

prepared by spray drying of liquid SEDDS with an inert solid carrier Aerosil 200, showed twofold increase in the oral bioavailability when compared to the powder form⁶³. One of the challenges in formulating microemulsions, SEDDS or SMEDDS is the limited availability of formulation components with GRAS status. In this context, liposomal formulations may be preferred over the above colloidal drug delivery systems for solubilizing the drugs and thereby to enhance oral bioavailability⁶⁵. This is because of the GRAS status of phospholipid constituents used in liposomal formulations.

Liposomes are phospholipid vesicles, comprising a phospholipid bilayer surrounding an aqueous compartment. In the lipid domain of the bilayer membrane, lipophilic drugs can be dissolved. Due to their biphasic characteristic and diversity in design, composition and construction, liposomes offer a dynamic and adaptable technology for enhancing drug solubility⁶⁶. 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, and on factors including bilayer composition and the method of preparation⁶⁷.

A fenofibrate liposomal formulation was prepared by a dry-film dispersing method coupled with sonication and homogenization using soybean phosphatidylcholine and sodium deoxycholate or cholesterol⁶⁸. *In vivo* measurements of pharmacokinetics and bioavailability demonstrated higher rates of fenofibrate absorption from the liposomal formulations than micronized fenofibrate.

CONCLUSION

By this article we conclude that, bioavailability of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the



poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can

be used to enhance the bioavailability of the drug. It is now possible that to bioavailability of drugs with the help of various techniques as mentioned above.

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