Available online on 15.05.2016 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
An International Peer Reviewed Journal
Open access to Pharmaceutical and Medical research

REVIEW ARTICLE

VARIOUS TECHNIQUES OF BIOAVAILABILITY ENHANCEMENT: A REVIEW

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Received 04 April 2016; Review Completed 28 April 2016; Accepted 11 May 2016, Available online 15 May 2016

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 parameters which are required to achieve optimal concentration of drug in systemic circulation to show a pharmacological response. A drug which has poor bioavailability shows poor aqueous solubility, slow dissolution rate, poor stability of dissolved drug at physiological pH, poor permeation through biological membrane, extensive first pass metabolism. Drugs which are poorly water soluble require high doses to obtain therapeutic plasma concentrations after oral administration of drugs. Low aqueous solubility is the major problem encountered with formulation development of new drugs. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. This review deals with various techniques used for the improvement of the Bioavailability of drugs. The various techniques used are size reduction, solubilising excipients, colloidal drug delivery systems, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilisation, hydrotropy etc. The article describes about various techniques which can be utilized to enhance bioavailability of drugs enhancement for their effective absorption in the body.

Key-words: BCS class II drugs, Bioavailability, Solubility and Therapeutic Efficacy

INTRODUCTION

Bioavailability is one of the important pharmacokinetic properties of drugs which are used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a drug is administered intravenously, its bioavailability is 100%. However, if the drug is administered through other routes (such as oral), its bioavailability decreases because of incomplete absorption or first pass metabolism. The measurement of the amount of the drug in the plasma at fixed time intervals indirectly represents the rate and extent at which the active drug moiety is absorbed from the drug product and becomes available at the site of action. Bioavailability is an essential tool in pharmacokinetics, which is used for calculating dosages for non intravenous routes of administration. It is expressed as either absolute or relative bioavailability.[1]

The therapeutic efficacy of a drug depends upon the ability of the dosage form to deliver the active drug to the site of action at a rate and amount which is sufficient to show the desired pharmacological response. This property of the dosage form is referred to as physiologic availability, biologic availability or simply bioavailability. For almost all drugs, the pharmacologic response can be related directly to the plasma levels. 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. A drug with poor bioavailability is one which has poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biological membrane, extensive pre systemic metabolism. Bioavailability of poorly water soluble drugs is a major problem.

Oral route is the most suitable and commonly used route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, no sterility issues and flexibility in the design of dosage form.

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Therefore many drug companies are interested more to produce bioequivalent oral drug products. As new drug development requires high cost and time, many patents get expired; ease of manufacturing and ready availability of technology for the production of oral drug products leads many generic pharmaceutical companies towards the development of bioequivalent oral dosage forms. However, the major problem with the design of oral dosage forms is 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 mechanisms[2]

The usual cause of low oral bioavailability is because of poor solubility and low permeability[3]. The intensive pharmaceutical research to understand the causes of low oral bioavailability have led to the development of novel technologies to deal with these challenges. One of the technologies to improve the oral bioavailability is to design a prodrug with the required physico-chemical properties.[4] For example, the prodrug approach resulted in improved bioavailability of etilevodopa.[5] 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 interesting way for improving the oral bioavailability of BCS class II drugs, it requires detailed studies to establish the safety profile of prodrugs in humans, which ultimately may result in failure. Furthermore, the main 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-liming 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 class II drugs. They use already approved excipients and GRAS materials. This in turn reduces the cost and development time. The common technologies which are used to achieve the enhanced oral bioavailability of drugs with poor aqueous solubility are 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 liposomes.[7]

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 THE BIOAVAILABILITY

As per the definition the drug candidate which has the following properties is one with poor bioavailability.

- 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 biological membrane
- Extensive presystemic metabolism

There are three major approaches used to overcome the bioavailability problems.

A) Pharmaceutics approach:

It is done by modifying of formulation, manufacturing processes or physiochemical properties of the drug are done.

B) Pharmacokinetic approach:

Alteration of pharmacokinetic parameters by modifying its chemical structure.

C) Biological approach:

The route of administration is changed in this method. Solubility and rate of dissolution are very important factors in third approach.

Co-solvency

The solubility of a poorly water soluble drug can be increased by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents[8]. Co-solvents are mixtures of water and one or more water miscible solvents used to prepare a solution with enhanced solubility for poorly soluble compounds. This is one of the most widely used techniques because of its simplicity.

Cosolvents can be easily produced and evaluated. 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.

Amit et al examined and compared the cosolvency using three different cosolvents which are PEG 400, PG, and glycerin on the aqueous solubility enhancement of a poorly aqueous soluble drug, etoricoxib, since solubilization of nonpolar drugs constitutes one of the important tasks in the formulation design of liquid dosage forms. The aqueous solubility of etoricoxib was 0.0767±0.0018 mg/mL, which was significantly enhanced by the addition of PEG 400, PG, and glycerin as cosolvents. It was analysed that the less-polar solvents increased the aqueous solubility by greater extent, thus emphasizing hydrophobic interaction mechanism. Among various solvent-cosolvent mixtures investigated, water-PEG 400 showed highest solubilization potential. Thus, the

study generated an important pattern of data to compare the effect of these cosolvents on the aqueous solubility of etoricoxib.[9]

Particle size reduction

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

Currently Particle size reduction can also 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 particle size,surface area increases which in turn improves the dissolution properties. 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.

Bansal et al studied that the dissolution rate is one of the limiting factors for achieving good bioavailability. In various formulations, the particle size of drugs and components may affect the processing and bioavailability. Many compounds that are investigated in pharmaceutical field have low aqueous solubility and fall in class II and IV of the biopharmaceutical classification system. Particle size reduction, leading to increase in surface area, is a leading tool to increase dissolution rate and in turn the bioavailability of poor water soluble compound

In this work it was attempted to improve dissolution profile of Norethindrone from the tablet dosage form by using micronization techniques to decrease particle size. Particle size reduction was achieved by Air Jet Milling. Micronization of Norethindrone caused enhancement in the dissolution rate to a significant extent when compared with unmicronized material. Norethindrone Oral Tablets which are commercially available in Indian market showed similar dissolution property as the tablets prepared with unmicronized Norethindrone, while those prepared with micronized Norethindrone showed higher dissolution rate. The result suggest that micronization technique can be used for the preparation of rapidly dissolving formulations of Norethindrone, and could potentially lead to improvement in the in vivo bioavailability of oral Norethindrone Tablets.[10]

Hydrotrophy

Currently number of techniques addressed the enhancement of solubility and dissolution rate of poorly soluble drugs. Hydrotropic solubilization is one of them.

Hydrotrophy is a solubilisation technique in which a large amount of second solute is added which results in an increase in the aqueous solubility of another solute. Solute which is used consists of alkali metal salts of various organic acids. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solution Hydrotropes are having the ability to increase the solubility of poorly water soluble drug and this tendency is greatest when concentration of hydrotropes is sufficiently enough to form the associated structures. [11].

Hydrotropic agents are ionic organic salts. The 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”[12] Hydrotropic solutions do not exhibit colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy leads to increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[13,14]

Maheshwari et al in their study employed hydrotropic solution of ibuprofen sodium (0.5M) as solubilizing agent to solubilize the poorly water-soluble drug, ornidazole from fine powder of its tablets for spectrophotometric determination. Ornidazole shows its maximum absorbance at 320 nm and Beer’s law was obeyed in concentration range of 5-25mcg/ml.[15]

Mixed Hydrotropy

It is a solubilization technique to increase the water solubility of poorly water soluble drugs by using different ratio of blends of hydrotropic agents which gives synergistic enhancement effect. The main advantage of this technique is that it reduces the concentration of individual hydrotropic agents which directly reduces the side effects of individual hydrotropic agent. A novel, safe and sensitive method of spectrophotometric determination of Hydrochlorothiazide in tablets was developed using mixed hydrotropic solubilisation technique and concluded that there is enhancement of solubility up to 25 folds by mixed hydrotropy. Hydrotropic solid dispersion of aceclofenac was formulated and evaluated by using six blends of hydrotropes (urea and sodium citrate) and concluded that solubility of aceclofenac increases synergistically by mixed hydrotropic solublization technique.[16] A further study was analyzed by using mixed hydrotropy on nitazoxanide, using sodium benzoate and sodium salicylate as hydrotropic agents and accomplished that there is enhancement of solubility up to 12 folds.[17]

Solid dispersions

The effective surface area is one of the important factors which govern the dissolution rate of poorly soluble drugs. Apart from micronization and nanosizing technologies, solid dispersion is the other way of enhancing the effective surface area available for dissolution.[18,19]

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix(carrier) and a hydrophobic drug. The matrix can be either crystalline or amorphous. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of bioavailability by solid dispersion[20].

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.[21]

- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
- Able to preferably increase the aqueous solubility of the drug.

Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms[22] .

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles.

These are usually prepared by heating a mixture of the drug and carrier to a molten state, and then cooled for resolidification. A solid dispersion of nitrendipine prepared by a melt-mixing method in which silica particles were used as carriers showed remarkably improved dissolution properties compared with that of the original nitrendipine crystals.[23]

In an another study by, Ha et al, solid dispersion nanoparticles with a hydrophilic polymer and surfactant were developed using the supercritical antisolvent (SAS) process to improve the dissolution and oral absorption of megestrol acetate. The physical and chemical properties of the megestrol acetate solid dispersion nanoparticles were studied using scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction, and particle-size analyzer. The oral bioavailability and dissolution of the nanoparticles were also studied in rats. Hydroxypropylmethyl cellulose solid dispersion nanoparticles significantly increased the maximum dissolution when compared with polyvinylpyrrolidone K30 solid dispersion nanoparticles. The dissolution rate along with extent of megestrol acetate increased after the adding a surfactant into the HPMC solid dispersion nanoparticles. The most effective surfactant was Ryoto sugar ester L1695, followed by d-a-tocopheryl polyethylene glycol 1000 succinate. The results suggested that the preparation of megestrol acetate solid dispersion nanoparticles using the supercritical antisolvent process is a promising approach to improve the dissolution and bioavailability of megestrol acetate.[24]

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, \Abboft) from the market[25].

Micellar solubulisation

Various surfactants can also be employed to improve the dissolution performance of poorly soluble drug products. Surfactants lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium.[26,27,28] They are also 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, thus entrapping the drugs within the micelles.[29] This process is called as micellisation and causes enhancement of solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved.[30] Micellar solubilisation is a widely used alternative for the dissolution of poorly soluble drugs.[31] Examples of poorly soluble compounds that use Micellar solubilisation are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone androsiglitazone.[32]

Meenakshi et al studied solubility studies of Glipizide using different solubilization techniques. Different concentration (0.2. 0.4, 0.6, 0.8, 1.0 % w/v) o f surfactants (Sodium lauryl sulphate, cetrimide and t ween 80were prepared.An excess of glipizide was add ed to 10 mL each of the surfactant solution taken in 25 mL of stopperedflasks. The flasks were shaken for 24 h. At equilibrium samples were withdrawn and properl y diluted and filtered through filter of pore size of 0.22 mm and analyzed for concentration of glipizide spectr ophotometrically at 274 nm.The study also evaluated a nd compared solubility enhancement of glipizide using three different surfactants glipizide using three different surfactants i.e. sodium lauryl sulphate

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Tween 80 and cetrimide. Tween 80 was found to be the most efficient surface active agent, improving solubility by nearly to 36 folds. Thus from this comparative solubility analysis of glipizide using different solubilization techniques can further be successfully applied for development and formulation of liquid or semisolid dosage form of glipizide.[33]

Complexation

There are various approaches of complexation with cyclodextrins which have gained good acceptance in recent years in industry for enhancing the solubility and thus dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic external surface and lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a result of inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be effectively enhanced. Cyclodextrins are being increasingly applied in various pharmaceutical formulations in recent years. Cyclodextrins are produced from starch by means of enzymatic conversion. [34,35]

CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, mainly their aqueous solubility and rate of dissolution. Among the various approaches, preparation of inclusion complexes with cyclodextrin have found to be successful in enhancing the solubility of poorly water soluble drugs.[36,37,38] Among the three types of CDs β - Cyclodextrin is known to be more suitable for practical use because of the following three reasons.[38,39,40,41]

Solubilizing excipients

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

The absorption largely dependent upon diffusion, which changes with the pKa of the drug and the pH of the individual regions within the gastrointestinal tract, and permeability, which is not only altered by the surface area of the region in which it is released, but also the regional pH effects when drug ionizes .While the importance of salt used and pH adjustment has been stressed as an important parameter of pre-formulation, the use of pH-altering excipients within drug delivery systems is also of great importance. Solubilised excipients that increase environmental pH in a dosage form, such as a tablet or capsule, to a range above that of pKa of weakly-acidic drugs increases the solubility of that drug. Excipients which act as alkalising agents may increase the solubility of weakly basic drugs. Another example is 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; after the hydration of dosage form , the electrolyte is wetted simultaneously with the active compound, creating a microenvironment independent of gastrointestinal pH. Micro environmental pH may be changed to enhance dissolution of poorly soluble drugs by salting-in effects through the inclusion of electrolytes of different hydrophobic character; oppositely, intra-dosage form pH may induce precipitation of highly soluble drugs, thereby decreasing the rate of dissolution through salting-out effects.

Colloidal drug delivery systems

The formulations containing lipids have been shown to enhance the bioavailability of orally administered drugs.[42,43,44,45] .As lipidic excipients are widely available with specific characteristics they offer various applications with respect to improve the bioavailability of poorly water-soluble drugs and changing their release profiles .[46]

Self-microemulsifying drug delivery systems (SMEDDS) are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability and thus the dose of the drug can be reduced. [47].

Self micro emulsifying drug delivery system (SMEDDS) are as isotropic 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 by agitating mildly followed by diluting in an aqueous media, such as GI fluids.[48] SMEDDS are advanced as compared to the other drug delivery systems due to their ability to deliver various macromolecules like peptides, hormones, enzyme substrates and inhibitors and protect them from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation.[49] These systems are formed spontaneously without aid of energy or heating thus suitable for thermolabile drugs such as peptides.

SMEDDS are generally prepared as liquid dosage forms that can be administrated as soft gelatin capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self emulsifying ingredients into a powder in order to create a solid dosage form

(tablets, capsules). Pellets of progesterone in SMEDDS have been prepared by the extrusion spheronization process to provide a better in vitro drug release .The similar dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C max and T max values.[50]

With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs

However, conventional SMEDDS are mostly prepared in a liquid form, which can have some disadvantages. Hence, **solid** SMEDDS (**S**-SMEDDS) prepared by solidification of liquid/semisolid self-micron emulsifying ingredients into powders, have gained popularity [51]

The nanosuspensions technology can be successfully utilized for overcoming problems associated with poorly soluble drugs or lipophilic drugs insoluble in both organic and aqueous media[52]. To enhance the bioavailability of curcumin different formulations have been made. Among them, nanoglobules based nanoemulsion formulation has been prepared to evaluate the potential for the solubility enhancement of curcumin. During *ex vivo* study, the release of curcumin from nanoemulsion was found much higher than curcumin suspension. This showed the increase in solubility of curcumin in aqueous solution.[53]Another study showed that encapsulating the curcumin into the hydrogel nanoparticles yielded homogenous curcumin dispersion in aqueous solution compared to the free form of curcumin. The *in vitro* release profile showed up to 95% release of curcumin from the developed nano-microparticulate systems.[54]

Akhgari et al prepared a nanosuspension formulation as a new vehicle for the improvement of the ocular delivery of vitamin A. Formulations were designed based on full factorial design. High pressure homogenization technique was employed to produce nanosuspensions. Fifteen formulations were prepared by using different combinations of surfactants Tween 80, benzalkonium chloride and Pluronic and evaluated for pH, particle size, entrapment efficiency, Differential scanning calorimetry (DSC), stability and drug release. Also, Draize test was used to evaluate the irritation of rabbit eye by formulations. All formulations showed a small mean size that is well suited for ocular application. Also it was observed that the particle size decreased with increase in the amount of surfactant. Drug entrapment increased with increasing amount of surfactant. It was shown that initial and final drug release can be controlled by the ratio and the total amount of surfactants, respectively. It was found that the use of Tween 80 and Pluronic in the formulations with a proper ratio does not show eye irritation and could be useful to prepare a suitable nanosuspension of vitamin A as a novel ocular deliver system.[55]

Liquisolid Technique

Liquisolid technique is also known as powder solution technology. Liquisolid is mainly composed of drug, non volatile solvent, carrier material, coating material, and disintegrant.[56] In liquisolid technique carrier and coating material which should be in the ratio of 20:1 is mixed into the non volatile solvent and then disintegrant is added and final material is compressed into tablets. Hence, the liquisolid technology allows the transformation of liquid systems into solid drug delivery systems. Both immediate and sustained release of drug can also be achieved with the help of liquisolid technique. For sustained release of drug hydrophilic polymer like Hydroxy Propyl Methyl Cellulose can be the best option. [57]

Classification of liquisolid systems

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups.

1) Powdered drug solutions
2) Powdered drug suspensions
3) Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems.

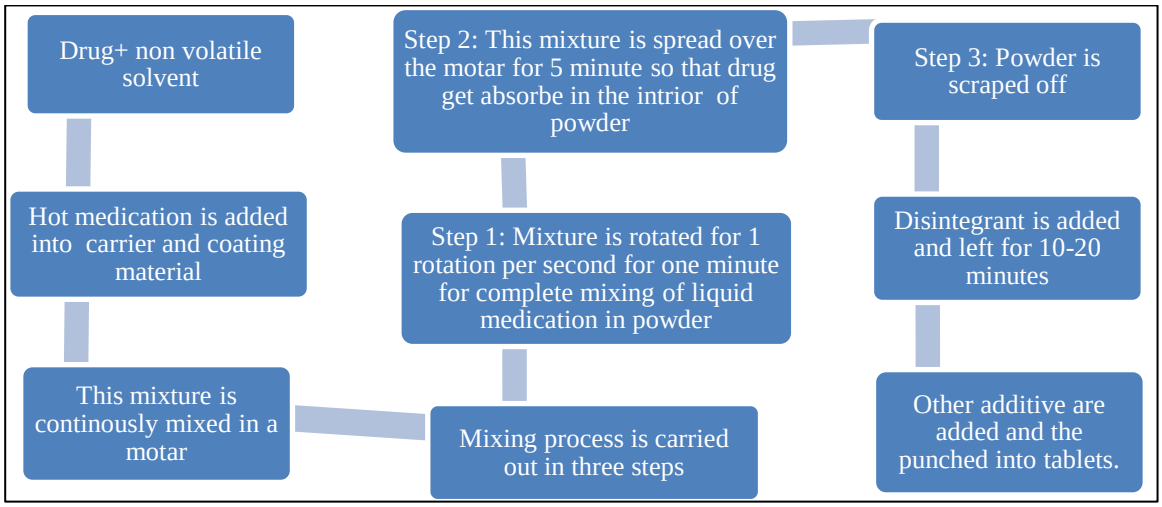

Figure 1: Steps of Liquisolid Technique [56]

Simultaneously, based on the formulation technique used, liquisolid systems may be classified into two categories namely,

1) Liquisolid compacts
2) Liquisolid microsystems

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared and combined with the inclusion of appropriate adjuvant required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders.

The term "liquisolid Microsystems" refers to capsules prepared by combining the drug with carrier and coating materials with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid compacts.[58]

Co-crystalization:

Co-crystals are known as crystalline complexes of two or more neutral molecular constituents, bound together in crystal lattice through non covalent interaction. Co-crystals can be prepared with several methods such as solution evaporation, solid grinding, and solvent drop grinding and sonocrystallization method. The pharmaceutical co crystal are prepared by combination of API and coformer i.e. pharmaceutically acceptable molecule inside a crystal lattice. As a matter of fact co-crystals increase the diversity of API form. Co-crystallization is molecular association of similar or different molecules, the network of hydrogen bonds results in generation of families in the molecular network.

Co-crystallization involves alteration in molecular assemblies and composition of pharmaceutical substance and which ultimately results in enhancing physical properties. Cocrystals are molecular complex brings about changes in solubility, bioavailability and stability in pharmaceutical designing without interacting with therapeutic utility. The major factor which affects cocrystal preparation is its thermodynamic stability. As concern with the therapeutic utility, cocrystals will play major role in development of formulation[59].

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How to cite this article:
Khan AD, Singh L, Various techniques of bioavailability enhancement: a review, Journal of Drug Delivery & Therapeutics. 2016; 6(3):34-41

 ISSN: 2250-1177 CODEN (USA): JDDTAO