Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

"LIQUISOLID TECHNOLOGY: A NOVEL CONCEPT"

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ABSTRACT:

Most of the drugs that have been invented are BCS Class II. This technique of delivering drugs is suitable mostly for lipophilic drugs and poorly water soluble drugs and enhance the immediate or sustain release formulations. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water soluble drugs. Therefore; dissolution rate enhancement is the key aspect for absorption of these drugs. Liquisolid technology is very efficient in the dissolution rate enhancement of these drugs. Moreover use of the other polymers such as Eudragit and Hydroxypropyl Methylcellulose in the Liquisolid approach can cause sustained release of drugs.Liquisolid system is evaluated by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in vitro release and in vivo evaluation. Liquisolid serve as a better technique in the controlled release formulations of poorly water soluble drugs.

KEYWORDS: *Liquisolid, Solubility Enhancements, Liquisolid Technology, Components, Evaluation.*

INTRODUCTION:

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition the oral route medication is generally considered as the first avenue investigated in the discovery a development of new chemical entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulation provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profile with an acceptable level of safety to the patient. Thus one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water.[1] nowadays, the synthesis of poorly soluble drugs increasing steadily. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.[2]

There are several methods for enhancing dissolution rate of poorly water-soluble drugs including:[3]

- Reducing particle size to increase surface area, thus increasing dissolution rate of drug.
- Solubilization in surfactant systems.
- Formation of water-soluble complexes.
- Drug dramatization such as a strong electrolyte salt forms that usually have higher dissolution rate.
- Manipulation of solid state of drug substance to improve drug dissolution, i.e. by decreasing crystallinity of drug substance through formation of solid solutions.

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SOLUBILITY ENHANCEMENT TECHNIQUES OF POORLY SOLUBLE DRUGS: [4]

For the past few years many has been developed to improve the solubility of the poorly soluble drugs like-

- Micronization
- Complexation With β- Cyclodextrins
- Eutectic Mixtures
- Spray Drying
- Use of salt form of the drugs (Derivatization)
- Alteration of pH of the drug Microenvironment by the addition of buffers
- Using Metastable Polymorphs
- Solute-Solvent Complexation
- Solvent Deposition
- Solid Dispersion (Co-Precipitation)
- Hydrotrophy
- Co-solvency
- Solid Solutions
- Lyophilization (Freeze Drying)
- Using Pro-drugs Approach
- Encapsulation of Solution form of drug in the Soft Gelatin Capsule Shell
- Microwave Induced Dissolution Rate improvement
- Adsorption on to the silica gel
- Steam aided granulation
- Lipid based formulations
- Solvent evaporation by ultra rapid freezing

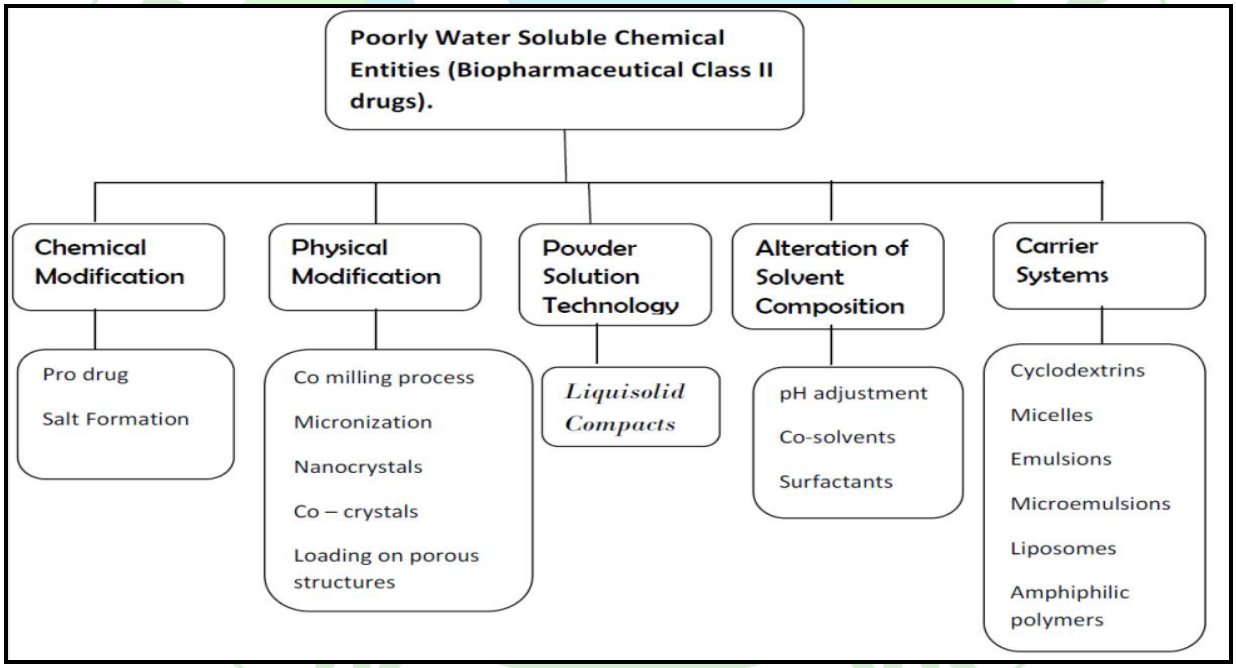

Fig. 1: Different Techniques for the improvement of solubility

Micronization is the common technique for increasing the effective surface area (which is exposed to the dissolution medium), but sometimes this is not suitable because it will cause changes in flow properties during tabletting. Salt formation leads to stability problems due to increase in hygroscopic nature. As we are using the strong acid sand bases palatability is also need to be considered. Co-solvents may precipitates upon dilution. Solubilization by surfactant or by micellar solubilization if the concentration of surfactant is more it leads to toxicity and there is a chance to interact with the preservatives. In case of complexation the release of drug from the complex is sometimes problematic. The drug load by this system is low and this works on the principle with drugs that fit into the cavities of the molecules of cyclodextrins. In solid dispersion technique one or more active ingredients dispersed in to hydrophilic carrier(s) by melt fusion or solvent evaporation method. In melt fusion method drug is added to molten carrier and mix them to form homogeneous

dispersion. In solvent evaporation method drug and carrier are dissolved in small amounts of carrier and finally evaporate the solvent, however the preparation also sometimes need special equipment like spray dryer and fluidized bed dryer. Solid dispersion prepared with polyethylene glycol (PEG) and polyvinylpyrrolidine (PVP) are sticky in nature which are difficult to formulate into tablets or to fill into the capsules, however the preparation of solid dispersion needs sometimes sophisticated equipments like fluidized bed dryer or spray dryer. Co-grinding process of poorly soluble drugs with hydrophilic carriers or excipients (I. e PVP, crospovidone, different types of silica) also leads to amorphization of drug thereby increase in solubility is observed. Adsorption on to the hydrophilic silica aerogels also found to enhance the dissolution of drug this can be enhanced by increasing the surface area of the drug. However the drug loading on to the carrier is very low and another disadvantage is that it involves complex manufacturing process i. e. the drug solution is loaded on to the silica gel by using supercritical carbon dioxide.

LIQUISOLID TECHNOLOGY: [5]

A more recent technique, **"**powdered solution technology" or "Liquisolid technology**"**, has been applied to prepare water-insoluble drugs into rapid release solid dosage forms. Powdered solutions are designed to formulate liquid medications in powdered form. The concept of powdered solutions enables one to convert a liquid drug or poorly water-soluble solid drug dissolved in a suitable non-volatile solvent into a dry, non-adherent, free flowing and readily compressible powder by its simple admixture with selected carrier and coating materials. In spite of formulating the drug in a tableted or an encapsulated dosage form, it is held in solution thus enhancing its release.

DEFINITION: [6]

***Liquid medication*:**

liquid lipophilic drugs and drug suspensions or solutions of solid water-insoluble drugs in suitable non volatile solvent systems are called Liquid medication.

***Liquisolid systems*:**

Refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

REQUIREMENTS FOR PREPARATION OF LIQUISOLID SYSTEMS: [7, 8]

Drug candidates:

Examples of drug candidates include Digoxin, Digitoxin, Prednisolone, Hydrocortisone, Spironolactone, Hydrochlorothiazide, Polythiazide, and other liquid medications such as Chlorpheniramine, water, insoluble vitamins, fish oil, etc.

Non-volatile solvents:

Inert, high boiling point, preferably water miscible and not highly viscous organic solvent systems e.g. Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol, fixed oil, glycerin.

Carrier materials:

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. These include grades of Microcrystalline cellulose such as Avicel PH 102 and 200 Lactose, Eudragit RL and RS (to sustain drug delivery), etc.

Coating materials:

These are flow enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles its include silica (Cab-O-Sil M5, Aerosil 200, Syloid, 244FP etc.)

Disintegrates:

Most commonly used disintegrates is sodium starch glycolate (Explotab13, Pumogel, etc.)

NECESSARY EQUIPMENTS: [9]

Shaking water bath, electric balance, ultraviolet spectrophotometer, single punch tablet press, tablet hardness tester, friability tester, thickness

tester, disintegrates tester, and dissolution apparatus.

PREPARATION OF LIQUISOLID TABLET: [10]

Calculated quantities of drug and non-volatile solvent is accurately weighed in 20 ml glass beaker and then heated to dissolve the drug in that solvent. The resulting hot medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps

- During the first stage, the system is blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder.
- In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particle.
- In the third stage, the powder is scraped off the mortar surfaces by means of aluminum spatula and then blended with sodium starch glycolate for another 30 seconds in a similar way to the first stage. This gives final formulation of Liquisolid tablets. Prepared Liquisolid.

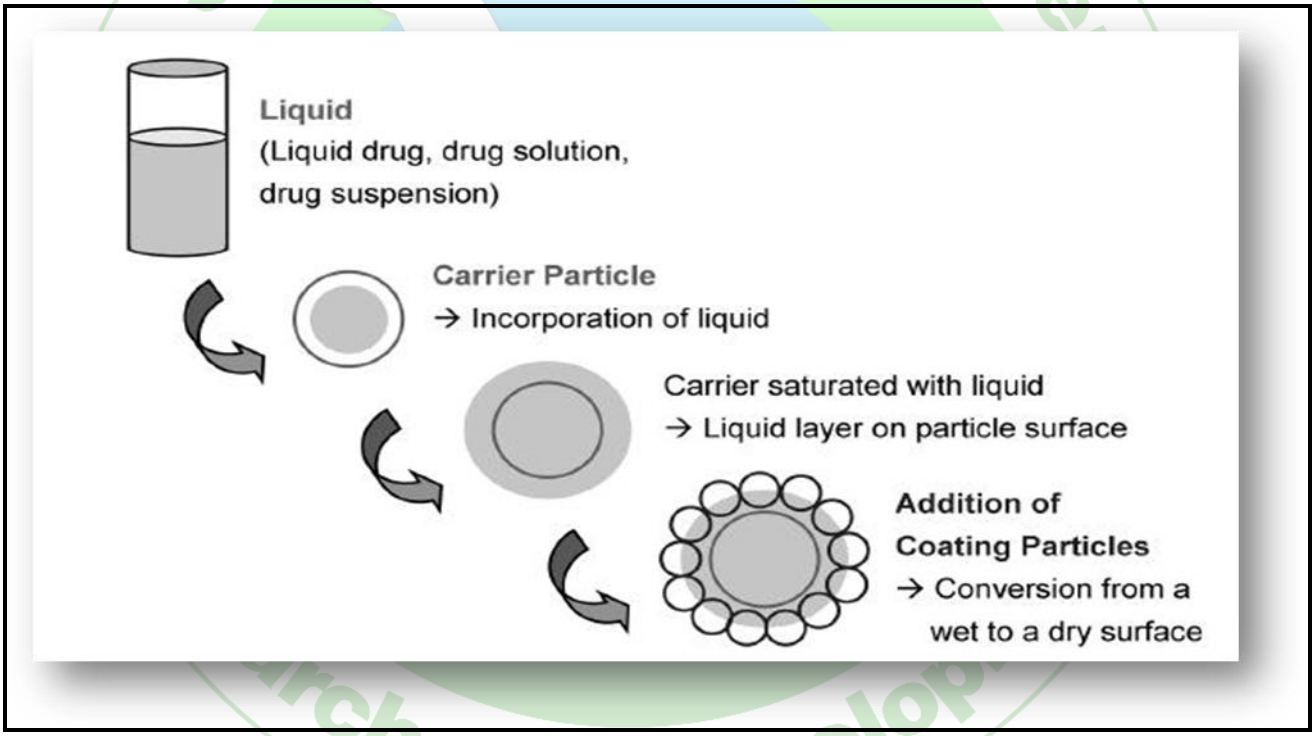

Fig. 2: Schematic representation of Liquisolid systems

CLASSIFICATION: [11]

A. Based on the type of liquid medication contained therein, Liquisolid systems may be Classified into three subgroups:

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e.g. Prednisolone Solution in propylene glycol) or drug suspensions (e.g. Gemfibrozil suspension in Polysorbate 80), and the latter from the formulation of liquid drugs (e.g. Clofibrate, Valproic acid, Liquid Vitamins, etc.), into Liquisolid systems.

B. Based on the formulation technique used, Liquisolid systems may be classified into

Two categories, namely,

- Liquisolid compacts
- Liquisolid Microsystems

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the Liquisolid Microsystems are based on a new concept which to produce an acceptably flowing admixture for encapsulations.

ADVANTAGES OF LIQUISOLID SYSTEM: [12, 13, 14]

- A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drug can be formulated into Liquisolid systems using the new formulation-mathematical mode
- This technique is successfully applied for low dose water insoluble drug.
- The absolute bioavailability of the drug from the Liquisolid tablet is 15% higher than that commercial one.
- There production cost is lower than that of soft gelatin capsules because the production of Liquisolid systems is similar to that of conventional tablets.
- Drug dissolution from Liquisolid compact is independent to the volume of dissolution media.
- Most of liquid or solid 'water-insoluble drug' may be formulated into immediate release or sustained release 'Liquisolid compact' or 'Liquisolid Microsystems.
- Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
- Capability of industrial production is also possible.
- Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.
- This Liquisolid system is specifically for powdered liquid medications.

DISADVANTAGES: [15,]

- The Liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile and liquid vehicles.
- To maintain acceptable flowability and compatibility for Liquisolid powder formulation high levels of carrier and coating materials are require and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow.
- It requires more efficient excipients which have higher adsorption capacities which provide faster drug release with a smaller tablet size to improve Liquisolid formulation.

APPLICATION OF LIQUISOLID TECHNIQUES: [16]

Solubility and dissolution improvement:

In order to overcome the limited solubility of the pharmaceutical, pharmaceuticals were formulated as Liquisolid tablets. The method of preparation of Liquisolid tablets as well as the effect of various formulation and processing variables on the preparation and the release properties of the tablets were studied y number of scientists. This technique was successfully applied for low dose water insoluble drugs. However, formulation of the high dose insoluble drugs as Liquisolid tablets is one of the limitations of the Liquisolid technique. In fact, when the therapeutic dose of drug is more than 50 mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant. But by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication (Microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain dry powder with free flowability and good compatibility.

Flowability and compressibility:

Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, whereas silica's of very fine particle size can be used as coating materials. In order to have acceptable flowability and compactability for

Liquisolid powder formulation, high levels of carrier and coating materials should be added and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow. Therefore, in practice it is impossible with conventional method to convert high dose drugs to Liquisolid tablet with the tablet weight of less than 1gm. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, on-adherent, dry looking powders. In further studies, compression enhancers were added to these powdered solutions like microcrystalline cellulose. However, the compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon. In this system liquid medication is to be mixed with the excipients and then compressed to tablets. It was proved that the smaller the drug concentration in the liquid medication, the more rapid the release rates, since drugs in a high concentration tend to precipitate within the polymers pores. Polymers possessing large surface areas, and diluents like microcrystalline cellulose of fine particle size and granular grades produced good flow and compression properties, resulting in Acceptable tablets.

For designing of sustain release tablet:

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its simplicity and low-cost. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in Liquisolid systems, sustained release systems can be obtained. Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems.

PRE-COMPRESSION STUDIES: [17]

Flow property:

Flow property is important in formulation and industrial production of tablet dosage form. Angle of repose, Carr's index, compressibility index, tapped density etc., have to be performed.

Differential scanning calorimetry (DSC):

It is used to determine the interactions between drug and excipients, which indicates the success of stability studies. The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation and it is molecularly dispersed within the system.

Fourier transform infrared spectroscopy (FTIR):

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates there is no chemical interaction.

X-ray diffraction (XRD):

XRD studies are used to determine the whether the drug is solubilised or in amorphous form. The disappearance of characteristic peaks of drug and their by appearance of peaks which belongs to carrier is observed.

In vitro release studies (USP 2005): [18]

Works of many researchers revealed that dissolution rate improvement is observed in case of Liquisolid formulation. It was also proved that at low drug concentration in liquid medication, more rapid release rates are observed. This may be due to the precipitation of drug within silica pores at high drug concentration. The in vitro release studies were performed by using the dissolution apparatus and compared the formulated Liquisolid tablets with direct compression tablets. The percentage drug release was estimated.

Scanning electron microscopy (SEM):

SEM analysis was performed to determine the crystallinity of drug in Liquisolid system. The disappearance of crystalline nature of drug indicates that the drug is solubilised in the system.

CONCLUSION:

Nowadays, new chemical entities often possess a high molecular weight and a high lipophilicity. Especially poorly soluble and highly permeable active pharmaceutical ingredients represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility, which may result in low drug absorption. This technique is a promising alternative for formulation of water-insoluble solid drugs and liquid lipophilic drugs. The enhanced rate of drug dissolution from Liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles available for dissolution. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in Liquisolid systems. Therefore, Liquisolid delivery of the drug has the potential to be considered for further clinical studies in order to be manufactured on a large scale.

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