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LIQUISOLID TECHNIQUE: ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE: A MODERN REVIEW

PATEL KANU J., PATEL Y.K.
Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat, India.
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Abstract: Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. Liquisolid technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. Liquisolid compacts demonstrated a considerably higher drug dissolution rates than those of conventionally made capsules and directly compressed tablets. This was due to the increased wetting properties and surface of drug available for dissolution. This review mainly focus on the advantages, disadvantages, mechanism of enhanced drug release, classification, evaluation and application of liquisolid technique. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. Modification of formulation by use of some excipients cause sustained release of drugs from the liquisolid tablets.

Keywords: Solubility, Liquisolid technique, Carriers, bioavailability, Coating materials

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Corresponding Author: MR. PATEL KANU J

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INTRODUCTION

Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water[1, 2].

Liquisoild technique is a novel concept for delivery of drugs through oral route. This approach of delivering drugs is suitable mostly for lipophilic drugs and poorly or water insoluble drugs. This approach is suitable for immediate or sustain release formulations. Design and formulation of this approach is prescribed according to new mathematical model given by Spires. The liquisolid technique as described by Spireas is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term 'liquid medication' refers to liquid lipophilic drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle[2, 3].

This non-volatile solvent with drug dissolved may be existing in solution or else suspension nature known as 'liquid medicament'. The liquid medicament is converted into free flowing, non-adhere, dry form and readily compressible powders with the help of different compressible carriers like (cellulose, starch and lactose etc.) and else coating materials like (talc and collidol silica). Because of drug present in the liquid medicament as solubilised or moleulary dispersed state, as the dissolution is enhanced due to increased surface area as well as wetting area. Their by the Liquisolid technique is applied for water insoluble drugs to enhance dissolution rate and may also increase bioavailability[1, 4, 5]. Liquisolid technique is a new and promising method that can enhance the dissolution rate of drugs. By using this technique, solubility and dissolution rate can be improved, sustained drug delivery systems be developed for the water soluble drugs[3, 6].

Advantages[1, 7, 8]:

1. Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.

2. Improvement of bioavailability of an orally administered water insoluble drugs is achieved.

3. In this technique, production cost is low compared to soft gelatin capsules.

4. These liquisolid systems formulate into immediate release or sustained or controlled release dosage forms.

5. Greater drug surface area is exposed to the dissolution medium.

6. 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.

7. Capability of industrial production is also possible.

8. Omit the process approaches like nanonisation, micronization techniques.

Disadvantages[8, 9]:

1. The liquisolid systems requires more efficient excipients which have higher adsorption capacities which provide faster drug release with a smaller tablet size to improve liquisolid formulations.

2. To maintain acceptable flowability and compatibility for liquisolid powder formulation high levels of carrier and coating materials are require and that in turn will increases the weight of each tablet above 1 gm which is very difficult to swallow.

3. The liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.

Mechanisms of Enhanced Drug Release from Liquisolid Formulation

A. Increased aqueous solubility of the drug[6, 10]

In addition to the first mechanism of drug release enhancement it is expected that *Cs*, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co solvent.

B. Increased drug surface area[11, 12]

When the drug within the liquisolid system is absolutely dissolved in the liquid vehicle it is positioned in the powder substrate in a solubilized, molecularly dispersed state. Therefore, the

surface area of drug available for release is much greater than that of drug particles within directly compressed tablets. Consequently, with increasing drug content beyond the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. It has been pragmatic with various drugs that therelease rates are directly proportional to the fraction of themolecularly dispersed drug (*FM*) in the liquid formulation. *FM* is defined by Spireas as the ratio between the drug's solubility (*Sd*) in the liquid vehicle and the actual drug concentration (*Cd*) in this vehicle carried by each system.

$FM = Sd/Cd$

Where FM =1 if Sd ≥ Cd

C. Improved wetting properties[5, 13]

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been confirmed by measurement of contact angles and water rising times.

Materials Used in Liquisolid Technique Formulation[3, 14, 15]:

1. Non volatile solvent:

They may be hydrophilic or lipophilic in nature based on selection of type of formulation like immediate or control release. Some of them are propylene glycol, span 80, span 20, polyethylene glycol, liquid paraffin, tween 80, tween 20, cremophore L.

2. Drugs:

They are poorly soluble or insoluble in water.

3. Coating material:

Nano meter sized silica mostly preferred, like talc, Aerosil.

4. Carrier material:

They are preferred to be coarser granular for acceptable flow, Methyl cellulose, Ethyl cellulose, Avivel PH 200, Starch 1500, Ethocel and Avicel PH 102.

5. Disintegrant:

Superdisintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintigrants like sodium starch glycolate and crosspovidone are used.

Classification[16, 17]:

1. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups.

a. Powdered drug solutions

b. Powdered drug suspensions

c. Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e.g. prednisolone solution in propylene glycol drug suspensions (e.g. gemfibrozil suspension in polysorbate 80, and the latter from the formulation of liquid drugs (e.g. clofibrate, liquid vitamins, etc.) into liquisolid systems.

2. Based on the formulation technique used, liquisolid systems may be classified into two categories

a. Liquisolid Microsystems

b. Liquisolid compacts

General Method of Preparation[18, 19]:

A drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio. Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties. To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives were added according to their application and mixed for a period of 10 to 20 minutes in a mortar. The final mixture was compressed using the manual tableting machine to achieve tablet hardness. Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

Characterization of Liquisolid Technique[20-23]:

1. Flow behavior

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

2. *In vitro* dissolution studies

Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the *in-vitro* release of poorly water soluble drugs as hydrocortisone, Prednisolone, Carbamazepine, Piroxicam. Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

3. Fourier Transform Infra Red Spectroscopy (FT-IR)

FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm^{-1} against background interfereogram. Spectra are analyzed by software.

4. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix.

5. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.

6. X-ray diffraction (XRD)

For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.

7. Contact angle measurement

For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet.

8. *In vivo* evaluation of liquisolid systems

This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.

9. Stability studies

Drug content was determined there after the crystals were charged for accelerated stability studies according to ICH guidelines. Samples were taken and analysed for specified intervals.

Application:

1. Bioavailability improvement[22]

In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water- insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability.

2. Solubility and dissolution improvement[23, 24]

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 waterinsoluble 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, 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.

3. For designing of sustain release tablet[25]

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.

4. Flowability and compressibility [26, 27]

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 silicas 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 1 gm. 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.

CONCLUSION:

liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers. Liquisolid formulations are designed to contain liquid medications in powdered form and hence possess drug delivery mechanisms similar to that of soft gelatin capsule preparations, containing liquids. Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bioavailability of a poorly soluble, insoluble or lipophilic drug and to formulate them into immediate release or sustain or control release by selection of suitable solvent and carrier. Due to this formulation of the drug has the potential to be considered for human study in order to be manufactured on a large scale.

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