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THE LIQUISOLID TECHNIQUE: A REVIEW

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Abstract: Poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge because their poor bioavailability is only caused by poor water solubility resulting in low drug absorption. Numerous methods have been applied to improve water solubility and drug release, respectively, among which the liquisolid technology is one of the most promising approaches. With this technique liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material.

Keywords: Poorly soluble drugs, coating material, carrier, hydrophilic solvent, liquisolid compacts



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INTRODUCTION

Dissolution is the critical parameter of pharmaceutical dosage forms. It is recognized that *in vitro* dissolution testing is often relied upon in screening drug formulations during development and to ensure batch to batch quality control. Under certain conditions, it can be used for the assessment of bioequivalence^[1] and sometimes as a means to correlate *in-vitro* with *in-vivo* drug release characteristics. Dissolution remains an important factor for absorption of drugs especially in case of water insoluble drugs^[2]. For such type of drugs whose absorption is dissolution rate limited, suitable modifications should be done in the formulation design. To increase dissolution rates of such drugs, various methods have been described. These include the use of solid dispersions^[3], inclusion complexes using β cyclodextrin^[4], micronization^[5], microwave induced dissolution rate improvement^[6] and adsorption onto silica aerogels^[7]. A newly developed technique by Spireas et al.^[8, 9], liquid system, has proved to be important technique for the dissolution rate improvement of water insoluble drugs. The liquid systems show acceptable flow properties and compressibility. Liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free flowing, non adherent, dry looking, and readily compressible powders with use of carrier and coating materials. As the drug is in the form of liquid medication, it is in

either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquid tablets of water insoluble drugs show improved dissolution properties and in turn increase in bioavailability^[10]. Also the low costs incurred during the manufacture of liquid systems prove them useful with respect to industrial production using this technique.

DEFINITIONS

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.

Solubility: water insoluble drugs include those drugs that are “sparingly water soluble” (one part solute into 30-100 parts of water), slightly water- insoluble (one part solute into 1000 -10,000 parts of water) and practically “water-insoluble” or insoluble (one part solute into 10,000 or more parts of water). The liquid technique systems refers to powdered forms of liquid medications formulated by changing to liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems into dry-looking, non-adherent, free moderately flowing.

Liquid systems based on the type of liquid medication can be classified into three sub groups:

(i) "Powdered drug solutions"

(ii) "Powdered drug suspensions"

(iii) "Powdered liquid drug "

The first two groups may exist or be produced by changing drug solutions and drug suspensions while the third is produced from the formulation of liquid drugs into liquisolid systems.

"Liquisolid compacts": refers to immediate sustained-release tablets or capsules that are described under "liquisolid systems".

"Liquisolid Microsystems": refers to capsules prepared by "liquisolid systems" plus the inclusion of an additive resulting in a unit size that may be as much as five times less than that of a liquisolid compact.

Liquid load factor (Lf): defined as the ratio of the amount of liquid medication (W) over the quantity of carrier material (Q) in the system.

$$L f = \frac{W}{Q}$$

Carrier: Coating Material Ratio (R): Ratio between the quantities of carrier (Q) and coating materials (q) present in the formulation.

$$R = \frac{Q}{q}$$

"Carrier material": refers to a preferably porous material possessing sufficient absorption properties.

"Coating Material": refers to a material possessing fine and highly adsorptive particles.

ADVANTAGES

1. Large number of Bio – Pharmaceutical classification class 2 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 Bio-availability of an orally administered water insoluble drugs is achieved
3. This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.
4. 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.
5. In this technique, production cost is low compared to soft gelatin capsules.
6. This liquisolid system is specifically for powdered liquid medications.

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

8. These Liquisolid systems formulate into immediate release or sustained release dosage forms.

9. Optimized sustained release Liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (Zero Order Release).

DISADVANTAGES

1. This technique is only for water insoluble drugs.

2. However, for formulation of high dose insoluble drugs the liquisolid tablet is one of the limitations of this technique.

3. In order to achieve acceptable flow ability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Therefore, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50 mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

Formulation Design of Liquisolid Systems

To achieve good flow behavior and compressibility of liquisolid systems a mathematical model designed by Spireas et

al.^[8, 9] was used as formulation design model for the liquisolid tablets. Prerequisites for this include suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. The Spireas et al's model is based on new fundamental properties of powder called "flowable liquid retention potential" (Φ value) and "compressible liquid retention potential" (Ψ value) of powdered excipients used in the formulation. The Φ value is defined as the maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid/powder admixture while the Ψ value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably compressible liquid or powder admixture i.e. being able to yield tablets of satisfactory mechanical strength without presenting any liquid squeezing out of liquisolid mass during compression.

The excipients ratio (R) or the carrier: coating material ratio is represented as follows:

$$R = Q / q \quad (1)$$

where, R is ratio of carrier (Q) and coating materials (q). For, a successful formulation design, this ratio R should be suitably selected.

Another term called Liquid load factor (L_f) is defined as ratio of weight of liquid medication

(W) to weight of carrier material (Q) in system.

$$L_f = W / Q \quad (2)$$

The Φ value was used to calculate excipient quantities. Equation derived for this is as follows:

$$L_f = \Phi + \Phi (1 / R) \quad (3)$$

where, Φ and Φ are the constant Φ values of carrier and coating materials, respectively. By calculating L_f and W , we can calculate the amount of Q and q required for the liquid system.

Requirements for Preparation of Liquid Systems

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. [8, 9]

Non-volatile Solvents

Various non-volatile solvents used for the formulation of liquid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol. [11]

Carrier Materials

These include grades of microcrystalline cellulose such as Avicel PH 102 and 200, [8, 9]

Lactose^[11], Eudragit RL and RS^[12] (to sustain drug delivery), etc.

Coating Materials

Coating material include silica (Cab-O-Sil M5 [8, 9], Aerosil 200^[13], Syloid, 244FP^[8, 9], etc.)

Disintegrants

Most commonly used disintegrant is sodium starch glycolate (Explotab^[13], Pumogel, etc.)

Pre-formulation Studies

These include solubility determination of drug in different non-volatile solvents, determination of angle of slide, determination of Φ values, calculation of liquid load factor (L_f), liquid compressibility test (LSC), etc.

Solubility studies

These are carried by preparing saturated solutions of drug in non-volatile solvents and analyzing them spectrophotometrically. [14] Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectrophotometrically [11].

Determination of angle of slide

Required amount of carrier is weighed and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to

slide. This angle is known as angle of slide. It was used as a measure of the flow properties of powders. Angle of 33° is regarded as optimum.^[15]

Determination of flowable liquid retention potential (Φ value)^[15]

Increasing amounts of liquid paraffin is added to a powdered material and mixed well. The powder absorbs or adsorbs only the liquid paraffin giving a change in flow properties. At each concentration of the liquid paraffin added, the angle of slide is redetermined according to previously described procedure. The Φ values are calculated according to equation:

Φ value = weight of liquid / weight of solid
(4)

Calculation of liquid load factor (Lf)^[11]

Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier-coating material admixture and blended. Using equation (2), drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

Liquisolid compressibility test (LSC)^[8, 9]

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures, compressing each liquid/powder admixtures to tablets, assessing average hardness, determination

of average liquid content of crushed tablets, as well as determining plactisity, sponge index and Ψ value and Lf .

Precompression studies

1 Flow properties: Flow properties of liquisolid formulation were studied by angle of repose, Carr's index, and Hausner's ratio^[16]. Each analysis was carried out in triplicate. Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied.

Pre-formulation Studies

Pre-formulation Studies includes

1. Determination solubility of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flow able liquid retention potential (Φ value)
4. Calculation of liquid load factor (Lf)
5. Liquisolid compressibility test (LSC)^[17]

Pre Compression Evaluations

The flow ability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur. In order to ensure the flow properties of the liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of

repose measurements, Carr's index and Hausner's ratios were adopted.

Post compression Evaluations

- a) Content of uniformity
- b) Hardness
- c) Weight variation
- d) Friability
- e) Disintegration
- f) In - vitro dissolution studies

These are should be in the official limits prescribed by official pharmacopoeia.^[18]

Evaluation of Liquisolid Systems

Flow behavior

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose $\geq 40^\circ$ indicate powders with poor flow ability.

Differential Scanning Calorimetry (DSC)

It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies^[19]. If the characteristic peak for the drug is absent in the DSC thermo gram, there is an indication that the drug is in the form of solution in liquisolid formulation and hence it is molecularly dispersed within the system.

X-ray diffraction (XRD)

Generally, disappearance of characteristic peaks of drug in the liquisolid formulation and retaining peaks of carrier material is observed. This indicates that drug gets converted to amorphous form or in solubilized form in the liquisolid formulation.

Scanning Electron Microscopy (SEM)

After SEM study, complete disappearance of crystals of drug which confirms that drug is totally solubilized in liquisolid system and this ensures the complete solubility.

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.^[20]

Estimation of drug content:^[21]

The liquisolid compacts are powdered well and powder equivalent to 10 mg of the drug is accurately weighed and suitably diluted using methanolic sulphuric acid. The drug content is calculated by at wavelength using UV-Visible spectrophotometer.

In-vitro drug release study:^[21]

The *in-vitro* dissolution study is carried out for a period of 1 hour using USP XXIV type-II (paddle) method with 900 ml of 0.1 N HCl

and distilled water as the dissolution media at required rpm and $37^{\circ}\text{C}+0.5^{\circ}\text{C}$. 10 ml of the sample is withdrawn and filtered at periodic time intervals in minutes. 10ml of fresh dissolution fluid is replaced to the baskets to maintain the constant volume (sink condition). The filtered samples are analyzed at wavelength by UV/Visible spectrophotometer. The mean of $n=3$ determination is used to calculate the percentage drug release from each formulation.

Applications^[22,23]

1. It gives rapid release and sustained release of drugs are obtained in liquisolid formulations.
2. Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
3. Solubility and dissolution enhancement.
4. Designing of controlled release tablets.
5. Application in probiotics.

Conclusion

This novel technique is found to be efficient method for formulation of water insoluble solid drugs and liquid lipophilic drugs. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of nonvolatile solvent in the formulation causes increased wettability of water

insoluble drugs and ensures molecular dispersion of drug in the formulation. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid tablets. Liquisolid Formulations shows better Flowability, Compressibility, improves solubility, Dissolution and hence better absorption.

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