LIQUISOLID COMPACT A REVIEW

Snehal P. Patil*, N. A. Gujrathi, B. R. Rane

P.S.G.V.P.Mandal’s College of Pharmacy, Shahada, Dist: Nandurbar, 425 409. (M.S)

ABSTRACT
Liquisolid technology has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. With Liquisolid 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. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs. Liquisolid system is characterized 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. By using this technique, solubility and dissolution rate can be improved, sustained drug delivery systems be developed for the water soluble drugs.

KEYWORDS: Liquisolids, carriers, coating materials, water in-soluble drugs, poorly soluble drugs.

INTRODUCTION
Bioavailability is affected by the dissolution properties of a drug and its release from a dosage form. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies have demonstrated that particle size reduction to the sub-micron range of poorly soluble drugs can lead to an increase in dissolution rate and higher bioavailability. The process by which a solid substance goes into solution is termed as dissolution. The extent to which the dissolution proceeds, under a given set of conditions are referred to as the solubility of the substance in the solvent i.e. rate of solution (dissolution) and amount that can be dissolved (solubility) are not same. As per Noyes-Whitney equation the rate of dissolution of a drug is directly proportional to its solubility and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually. The various properties of drug like solubility, particle size, polymorphism, salt form, complexation,
wettability affect drug dissolution and its rate and can be targeted to enhance dissolution of poorly water soluble drugs. Spireas described the method for promoting dissolution i.e. the formation of liquisolid compacts. A liquid may be transformed into a free flowing, readily compressible and apparently dry powder with the liquisolid technology by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material.

**Theory of Liquisolid Systems**

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flow ability. The flow ability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compatibility resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called “plasticity” which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms “acceptable flow and compression properties” imply the desired and thus As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Qo) and coating (qo) material properties which must be met by the final liquisolid formulation. Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only
if a maximum liquid load on the carrier defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

\[ Lf = \frac{W}{Q} \]  

(1)

\( R \) represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

\[ R = \frac{Q}{q} \]  

(2)

The liquid load factor that ensures acceptable flowability (Lf) can be determined by:

\[ Lf = \Phi + \phi \times \left( \frac{1}{R} \right) \]  

(3)

Where \( \Phi \) and \( \phi \) are the \( \Phi \)-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compact ability (\( \Psi Lf \)) can be determined by:

\[ \Psi Lf = \Psi + \psi \times \left( \frac{1}{R} \right) \]  

(4)

Where \( \Psi \) and \( \psi \) are the \( \Psi \)-numbers of the carrier and coating material, respectively. In liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed. Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liquisolid systems are equal to either \( \Phi Lf \) or \( \Psi Lf \), which ever represents the lower value. required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

\[ Q0 = \frac{W}{Lo} \]  

(5)

And \( q0 = \frac{Q0}{R} \)

(6)

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties.

**Determination of solubility:**

Saturated solutions were prepared by adding excess drug to the polyethylene glycol and shaking on a shaker for 48 h at 25°C with constant vibration. The solutions were filtered through a 0.45 micron filter, diluted with water, and analyzed with a Shimadzu1700 UV-Vis spectrophotometer at specific wavelength with respect to a blank sample (the blank sample was a solution containing the same concentration used without the drug). Determination was carried out in triplicate for each sample to calculate the solubility.

**MATERIALS AND METHODS**

1. **Non volatile Solvent**

Non volatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug.
The non volatile solvent acts as a binding agent in the liquisolid formulation. Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.

2. Disintegrant
Super disintegrant increases the rate of drug release, water solubility and wet ability of liquisolid granules. Mostly super disintegrates like sodium starch glycolate and crospovidone.

3. Carrier Materials
Carrier material should be porous material possessing sufficient absorption properties which contribute in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier’s results in decreased powder flow ability. These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200.

4. Coating Materials
Coating material should be a material possessing fine and highly adsorptive particles which contribute in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability. Coating material includes silica (Cab-O-Sil) M520, Aerosil 200, syloid.

5. Drug candidates
Examples of drug candidates include digoxin, digitoxin, prednisolone hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil.

PREPARATION OF LIQUISOLID COMPACT
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.

(1) 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.

(2) 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 1: Schematic representation of liquisolid systems**

### CLASSIFICATION

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three Subgroups:

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

The first two may be produced from the conversion of drug solutions or drug suspensions and the latter from the formulation of liquid drug into liquisolid systems. Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn is dispersed throughout the final product.

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

1. Liquisolid compacts
2. Liquisolid Microsystems

**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.
EVALUATION OF LIQUISOLID SYSTEMS

Precompression Studies Of Prepared Liquisolid Powders

In order to ensure the suitability of selected excipients Differential Scanning Calorimetry (DSC), X-ray diffractation (XRD) & Scanning Electron Microscopy (SEM) studies are performed. In addition flowability studies are also carried out to select the optimal formulae for compression prior to compression of the formulation to tablets.

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 flowability.¹⁶

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. If the characteristic peak for the drug is absent in the DSC thermogram, 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.¹⁷

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 solubilised form in the liquisolid formulation.¹⁸

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. After complete formulation, Tablets are evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, humidity content using karl fisher method, friability, hardness, disintegration, dissolution, and content uniformity. All these tests are carried out in triplicate and according to the compendial specifications. For content uniformity test tablets should contain not less than 95% and not more than 105% of the labelled potency. The disintegration test was carried out on six tablets in distilled water at 37 ± 2 °C using the SP disintegration apparatus.¹⁹

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 solid, the so called imaging method. A saturated solution of
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 the diameter of sphere drop on the tablet. Figure 5 represents the measurement of contact angle using imaging method.\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Schematic Representation of Contact Angle Measurement Using Imaging Method}
\end{figure}

**Dissolution studies of Liquisolid tablet**

Generally Dissolution studies of liquisolid tablet are carried out using dissolution apparatus USP II at 37°C ± 2°C. Many researchers revealed that at low drug concentrations in liquid medication, more rapid release rates are observed. The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from gastrointestinal tract.

**In vivo evaluation of Liquisolid tablets**

The improvement in oral bioavailability was confirmed by estimating the pharmacokinetic parameters in various animals such as rabbit, beagle dog. Results show that absolute bioavailability of drug from liquisolid tablets was much higher than marketed tablets\textsuperscript{21}.

**ADVANTAGES OF LIQUISOLID COMPACT**

1. A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems using the new formulation mathematical mode.
2. This technique is successfully Applied for low dose water insoluble drug.
3. The absolute bioavailability of the drug from the liquisolid tablet is 15% higher than that commercial one.
4. There production cost is lower than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets.
5. Drug dissolution from liquisolid compact is independent to the volume of dissolution media.
6. Most of liquid or solid ‘water insoluble drug’ may be formulated into immediate release or sustained release ‘Liquisolid compact’ or ‘Liquisolid microsystem’.

LIMITATIONS
1. This techniques is not applicable for high dose insoluble drug.
2. Mathematical calculation require.

APPLICATIONS
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
In conclusion, liquisolid compact refers to formulations formed by conversion of solid state to liquid state, 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 and coating agents. The formed liquisolid tablets dosage form showed significantly greater extent of absorption due to their solubility and dissolution improvement. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. Therefore, this formulation of the drug has the potential to be considered for human study in order to be manufactured on large scale.

REFERENCES


For Correspondence
Snehal Patil
Email: snehalppatil24@gmail.com