Liquisolid Systems: A Review

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ABSTRACT: Liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles. 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.

KEYWORDS: Liquisolid compacts; Liquid medication; mathematical model; liquid load factor (Lf)

Introduction

Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility 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 (Charman SA et al., 2003). Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability (Darwish AM et al., 2001). Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced (Patel VP et al., 2008).

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug (Shinde AJ, 2007). Solid dispersion (Vanshiv SD et al., 2009; Shah TJ et al., 2007; Rane Y et al., 2007), micronisation (Li XS et al., 2007; Nighute AB et al., 2009), lyophilisation (Setty CM et al., 2008; Bhandari S et al., 2008), use of complexing agents (Munke AP et al., 2004; Gowrishankar P et al., 2007; Ghorab MM et al., 2004; El-Zein H et al., 1998), solubilization by surfactants (Nazzal S et al., 2006; Patil P et al., 2002; Nazzal S et al., 2006), solid solutions (Kapsi SG et al., 2001), inclusion of the drug solution or liquid drug into soft gelatin capsules (Cole ET et al., 2003) are some of the methods which have been used to enhance dissolution characteristics of water insoluble drugs.

Among them, liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs (Fahmy RH et al., 2008).

The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating (Spiras S et al., 2002; Spiras S et al., 2000; Spiras S et al., 1999).

Historical development

Historically, liquisolid compacts are descendants of ‘powdered solutions’, an older technique which was based on the conversion of a solution of a drug in a nonvolatile solvent into a dry-looking, nonadherent powder by mainly adsorbing the liquid onto silicas of large specific surfaces. Such preparations, however, have been investigated for their dissolution profiles while being in a powder-dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later studies on powdered solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems.

In these studies, however, large quantities of silicas were still being used, and the flow and compression properties of the products were never validated and standardized to industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they presented significant ‘liquid-squeezing out’ phenomena and unacceptably soft tablets, thereby hampering the industrial application of such systems.
Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and have industrial application. In addition, the term ‘liquid medication’ does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions, or liquid oily drugs. Therefore, in contrast to ‘powdered solutions’, the term ‘liquisolid compacts’ is more general and it may encompass four different formulation systems namely,

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

Furthermore, the earlier term ‘powdered solutions’ seems to be inadequate even in describing the original systems, since it has not been proven that the drug remains in solution in the liquid vehicle after its deposition on the extremely large powder surfaces of silicas used (Spireas S et al., 1998).

The new ‘liquisolid’ technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipients referred to as the carrier and coating powder materials, can yield dry-looking, nonadherent, free-flowing, and readily compressible powders (Spiras S et al., 1999).

**Concept**

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics (Fahmy RH et al., 2008).

In liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations.

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface (Javadzadeh Y et al., 2007). Figure 1 shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability.

![Fig. 1 Comparison of wettability between conventional tablet and liquisolid compacts.](image)

**Components**

The major formulation components of liquisolid compacts are:

**Carrier material**

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. E.g. various grades of cellulose, starch, (Spiras S et al., 2002) lactose (Javadzadeh Y et al., 2007), sorbitol (Javadzadeh Y et al., 2007) etc.
Coating material
These are flow-enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles (e.g., silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc.) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid (Spiras S et al., 2002; Spiras S et al., 2000; Spiras Set al.,1999).

Non-volatile solvents
Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems e.g., propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils, etc. are most suitable as vehicles.

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

Examples of drugs that can be incorporated into liquisolid systems
Chlorpheniramine, digoxin, nifedipine, clofibrate, gemfibrozil, etoposide, carbamazepine, hydrochlorothiazide, methylclothiazide, spironolactone, hydrocortisone, piroxicam, indomethacin, ibuprofen etc. (Spiras S et al., 2002; Spiras S et al., 2000).

Classification of liquisolid systems
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 (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, liquid vitamins, etc.), 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 are prepared using the previously outlined method to produce tablets or capsules, whereas the liquisolid microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive, e.g., Polyvinylpyrrolidone (PVP), in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation. The advantage stemming from this new technique is that the resulting unit size of liquisolid microsystems may be as much as five times less than that of liquisolid compacts (Spiras S et al., 2002; Spiras S et al., 2000; Spiras S et al., 1999).

Liquisolid system for controlled drug delivery
Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. 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 viability. Several methods have been developed to this end or to achieve this aim. It is suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. If hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained. The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. The presence of nonvolatile solvent reduces the glass transition temperature ($T_g$) of polymers and imparts flexibility. Therefore, reduction of $T_g$ of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the $T_g$, a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug thus, sustaining the release of drug from liquisolid matrices (Javadzadeh Y et al., 2008).

General method of preparation
As shown in figure 2, a liquid lipophilic drug (e.g., chlorpheniramine, clofibrate, etc.) can be converted into a liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g., hydrochlorothiazide, prednisone, etc.) is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.
Next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers. The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), are most suitable for this step. Before compression or encapsulation, various adjuvants such as lubricants and disintegrants (immediate) or binders (sustained-release) may be mixed with the finished liquisolid systems to produce liquisolid compacts i.e. tablets or capsules (Spiras S et al., 2002; Spiras S et al., 2000; Spiras S et al., 1999).

Application of the mathematical model for designing the liquisolid systems

The flowability and compressibility of liquisolid compacts are addressed simultaneously in the ‘new formulation mathematical model of liquisolid systems’, which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-number) of the constituent powders (Fahmy RH et al., 2008; Spiras S et al., 1999).

The Flowable Liquid Retention Potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability.

The Compressible Liquid Retention Potential (Ψ) of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness and friability, with no liquid squeezing out phenomenon during the compression process.

The Φ value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ψ number of powders may be determined using a new method termed the liquisolid compressibility (LSC) test.
which employs the ‘pactisity theories’ to evaluate the compaction properties of liquid/powder admixtures (Spiras S et al., 2002; Spiras S et al., 2000; Spiras S et al., 1999).

According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where,

\[ R = \frac{Q}{q} \quad \ldots(1) \]

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor \( L_f \) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

\[ L_f = \frac{W}{Q} \quad \ldots(2) \]

The powder excipients ratios R and liquid load factors \( L_f \) of the formulations are related as follows:

\[ \Phi L_f = \Phi + \Phi \left(\frac{1}{R}\right) \quad \ldots(3) \]

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (\( \Phi \)-values) of powder excipients were utilized (Fahmy RH et al., 2008; Spiras S et al., 1999).

So to calculate the required weights of the excipients used, first, from Eq. (3), \( \Phi \) and \( \Phi \) and are constants, therefore, according to the ratio of the carrier/ coat materials (R), \( L_f \) was calculated from the linear relationship of \( L_f \) versus 1/R. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both \( L_f \) and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equations (1) and (2).

**Determination of flowable liquid retention potential (\( \Phi \)-value)**

The liquisolid flowability (LSF) test is employed to determine the flowable liquid retention potential (\( \Phi \)-value) of several powder excipients likely to be included in liquisolid compacts. The test is basically a titration-like procedure in which 25 to 30 grams of mixtures of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e., liquid/solid weight composition), such as, for example, polyethylene glycol, light mineral oil and clofibrate, are prepared using a standard mixing process which ensures uniformity, and their flow rate and consistency are assessed using a recording powder flow meter (RPF). The liquid/solid weight composition (w/w) in that admixture, which just complies with a desired and pre-selected limit of acceptable flowability, is taken as the \( \Phi \)-value of the excipient. The non-volatile solvent used in the LSF test should be the one selected to be included in the liquid medication (drug solution or drug suspension) of the targeted liquisolid product; where a liquid drug is formulated, then the LSF test should be conducted with the liquid drug itself. This value will change when different solvent or solvent system is employed (Spiras S et al., 2002; Spiras S et al., 2000; Spiras S et al., 1999).

**Solubility studies**

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies are carried out by preparing saturated solutions of drug by adding excess of drug into non-volatile solvents and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectrophotometrically.

**Preparation of liquisolid tablets**

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 as described by Spireas et al. 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 particles. 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 liquisolid formulation to be compressed.

**Evaluation of liquisolid systems**

**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 (Staniforth J et al., 2002; Wells J et al., 2002). Angle of repose, Carr’s index and Hausner’s ratio were used in order to ensure the flow properties of the liquisolid systems.
Precompression studies of the prepared liquisolid powder systems

In order to ensure the suitability of the selected excipients, differential scanning calorimetry, X-ray diffraction, and scanning electron microscope studies are performed. In addition, flowability studies are also carried out to select the optimal formulae for compression. Prior to the compression of the formulations into tablets.

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, as well as the liquisolid system prepared.

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 (Fahmy RH et al., 2008).

X-ray diffraction (XRD)

For characterization of the crystalline state, the X-ray diffraction (XRD) patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared liquisolid system (Javadzadeh Y et al., 2007).

Absence of constructive specific peaks of the drug in the liquisolid X-ray diffractogram indicate 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 system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of the drug (Fahmy RH et al., 2008).

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug–carrier systems (Fahmy RH et al., 2008).

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 (Figure 3) (Javadzadeh Y et al., 2007).

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 (Spireas S et al., 1998), prednisolone (Spireas S et al., 1998), carbamazepine (Javadzadeh Y et al., 2007; Tayel SA et al., 2008), piroxicam (Javadzadeh Y et al., 2008; Javadzadeh Y et al., 2005; Rakshit P, 2007), etc. Also several water insoluble drugs, namely, nifedipine, gemfibrozil, and ibuprofen, have exhibited higher bioavailability in rats as compared to their commercial counterparts.

Fig. 3 Schematic representation of contact angle measurement using imaging method.
The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium (Fahmy RH et al., 2008; Spireas S et al., 1998). The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs.

Drug release is decreased with an increase in concentration of drug or reduction in the concentration of nonvolatile solvent. Such differences in the drug release may be justified by differences in the amount of soluble form of drug or molecular dispersion states of the drug in the formulation (Javadzadeh Yet al., 2005).

Liquisolid compacts with lower R-values (carrier: coating ratio) contain relatively smaller amounts of carrier powder (microcrystalline cellulose), and larger quantities of fine drug loaded silica particles, and the ratios of the amounts of their liquid medication per powder substrate are relatively higher. On the other hand, liquisolid compacts with higher R-values contain low liquid/powder ratios, high presence of cellulose and low presence of silica. This could be directly associated with enhanced wicking, disintegration and deaggregation properties. Therefore, the liquisolid tablets with low R-values showed relatively poor dissolution (Spireas S, 1998).

**In vivo evaluation**

The in-vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs showed that the absolute bioavailability of the drug from liquisolid tablets was 15% higher than from commercial tablets (Khaled KA et al., 2001).

**Advantages of liquisolid systems**

- Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Simplicity.
- Better availability of an orally administered water-insoluble drug.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid systems is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drugs.
- Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.

**Conclusion**

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. 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 certain agents cause sustained release of drugs from the liquisolid tablets.

**References**


