Journal of Pharmaceutics and Drug Research
JPDR, 2(1): 49-53
www.scitcentral.com

ISSN: 2640-6152

Original Research Article: Open Access

Liquisolid Technology: An Approach to Improve Solubility and Dissolution

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Received October 15, 2018; Accepted November 18, 2018; Published January 07, 2019

ABSTRACT

Solubility and dissolution are the key parameters for formulation of quick release dosage forms. Liquisolid technology is an efficient technique that can improve the dissolution rate of poorly soluble drugs. Liquisolid systems are formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, non-adherent, free-flowing and compactible powder mixtures by blending the suspension or solution with selected porous carriers and coating materials. This technique is effective in terms of its low-cost formulation, large scale production feasibility and improved dissolution rate similar to conventional tablets and capsules.

Keywords: Solubility, Dissolution, Excipients, Adsorption, Coating

INTRODUCTION

What is liquisolid technique?

These are free-flowing compressible powders containing a nonvolatile liquid vehicle and solid drug. The solid drugs are dissolved completely or partially by the non-volatile liquid, which are non-volatile and thus the drug is carried within the liquid system [1]. This liquid system is converted into a dry looking, free-flowing, non-adherent and compressible powder by mixing with suitable excipients termed as carrier and coating materials [2]. In liquisolid formulations, the adsorbents are used as carrier material which adsorb the liquid formulation and the coating material with very high surface area which usually covers the carrier surfaces containing liquid. The general method of preparation is presented in **Figure 1**.

Advantages

- Drugs with poor aqueous solubility can be formulated into a liquisolid system.
- It exhibits improved solubility and dissolution.
- Liquisolid systems can also be used for sustain release of water soluble drugs.
- Simple technique, low production cost and do not require any specialized equipment.
- Scale up is feasible.
- Liquisolid systems are stable for drugs exhibiting polymorphism. In these systems, the solution of drug in non volatile solvent is quickly converted to dry free flowing powder. A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.

Disadvantages

- Drug should have good solubility in non volatile liquid.
- Suitable for low dose drugs.
- Tableting of liquisolid formulations may be poor. Sometimes liquid may squeeze out of the compact during compression.

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Citation: Patra CN & Somesu M. (2019) Liquisolid Technology: An Approach to Improve Solubility and Dissolution. J Pharm Drug Res, 2(1): 49-53.

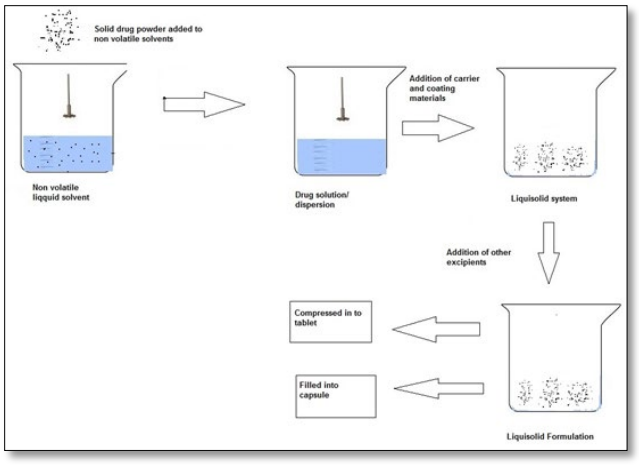

Figure 1. General method of preparation of liquisolid formulations.

THEORY

A carrier can retain certain amounts of liquid while maintaining adequate flow and compression properties. In order to determine the required amounts of carrier and coating materials, a mathematical approach for liquisolid formulations has been developed by Spireas and Sadu [3]. This approach is based on the flowable (Φ-value) and compressible (ψ-value) liquid retention potential.

The flowable liquid retention potential (Φ-value) of a powder represents the highest amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining an acceptable flowability. The flowability can be determined by angle of repose, Hauner's ratio and Carr's index. The compressible liquid retention potential (ψ-value) of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk (w/w) while maintaining acceptable compactability. The compact must have desired hardness without any liquid squeezing out during compression [4]. The compactability may be determined by pactisity, which describes the maximum (plateau) crushing strength of a 1 g tablet compacted at sufficiently high compression forces.

Basing 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 material is not exceeded. This liquid:carrier ratio is termed 'liquid load factor L_f (w/w) and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system.

$$L_f = W/Q \quad (1)$$

Excipient ratio (R) is the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation.

$$R = Q/q \quad (2)$$

The liquid load factor that ensures acceptable flowability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \Phi + \emptyset\,(1/R) \quad (3)$$

Where Φ and ∅ are the Φ values of the carrier and coating material, respectively.

Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \psi + \psi\,(1/R) \quad (4)$$

Where, ψ and ψ are the ψ numbers of the carrier and coating material, respectively.

Therefore, the optimum liquid load factor (L_o) required obtaining acceptable flowing and compressible liquisolid systems is equal to either $\Phi_{L\_}f$ or $^{\Psi}L_f$, whichever represents the lower value. As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows: coating (q_o) material required for converting a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q_0 = W/L_0 \quad (5)$$

$$q_0 = Q_0/R \quad (6)$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow [5] and compaction properties [6].

LIQUISOLID FORMULATIONS TO ENHANCE DRUG RELEASE

Preparation of liquisolid systems is based on the principles of conversion of the drug in the liquid state into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients, carriers and coating materials [7,8]. Liquid drug could be also sprayed into the carrier material in fluid-bed equipment for homogenous distribution of the active substance. Liquid drug is incorporated into the porous structure of a carrier material due to adsorption and absorption.

Mechanisms of enhancement of drug release

As the drug is present in the form of liquid medication, it is either in a solubilized or a molecularly dispersed state. This results in following changes:

- Increased surface area of drug available for drug release.
- Increased solubility and wettability of the drug.

Concentration of drug in liquisolid systems

The liquisolid technique has been applied successfully to low dose water-insoluble drugs. It is difficult to design a liquisolid formulation for high dose drugs as it requires a higher of amount of solvent and further this will also need high amount of carrier to convert to free flowing solid. But the use of modern carriers and coating materials with a large specific surface area and high absorption capacity (e.g. Neusilin®, Sylysia) is another way of incorporation of higher doses of water insoluble drugs into liquisolid systems.

Non-volatile solvent

Various non-volatile, high-boiling point, preferably water miscible and not highly viscous solvents are selected in the formulation of liquisolid systems. It was demonstrated in several studies that the solvent had a significant effect on drug release from liquisolid systems. For enhanced drug release from liquisolid preparations, a liquid vehicle in which the active ingredient is most soluble is usually selected. The most widely used non-volatile liquids used in the formulation of liquisolid formulations include polyethylene glycol 200, polyethylene glycol 400, propylene glycol, polysorbate 80, glycerin. Apart from these many researchers have also used novel liquid vehicles like caproyl 90, acrysol El 135, labrasol, etc. One of the prerequisite in the formulation of liquisolid systems is to determine the solubility of drug in different non-volatile solvents. Solvent with highest solubility is selected for formulation. Low solubility of drug candidate in solvents leads to insignificant improvement in dissolution rate.

Apart from solubility enhancement solvents can also impart compactness to liquisolid formulations. This was ascribed to hydrogen bonding owing to the presence of hydroxyl groups. In addition, non-volatile solvent can act as a binder in low concentration, and shows a negative effect on compaction properties of liquisolid compacts in higher concentrations. Excessive non-volatile solvent causes generation of the capillary state of powder aggregation and hence the surface tension effect becomes less significant in bringing the particles together, leading to poor bonding between powder particles. Also, decrease in tensile strength at high levels of solvent results in the formation of multilayer of solvent around the surface of the particles. These layers disturb or reduce intermolecular attraction forces and hence decrease tablet strength. Therefore, in higher concentrations, non-volatile solvent covers contact points between particles and acts as a lubricant and reduces the binding of particles. List of various non-volatile solvents for enhancement of dissolution rate are enlisted in **Table 1**.

Method of determining solubility of drug in non-volatile solvent

Solubility studies are carried out by preparing a saturated solution of the drug by adding an excess amount of drug into non-volatile solvents by using rotary shakers till equilibrium is attained. After this step, the saturated drug solution is filtered, dissolved in a specific solvent and evaluated by a suitable analytical technique. Solvents with greater ability to solubilize the drug are selected for the formulation of liquisolid systems for enhancement of drug release.

Carrier materials

In liquisolid formulations, role of carriers is vital in obtaining the dry form of powder from the drug in liquid state. Carriers should be a porous material possessing high liquid absorption capacity. Specific surface area of the carrier is an important factor in the formulation of liquisolid systems. In general an ideal carrier should have the following properties:

- High loading capacity
- Facilitates easy processing with standard processes of solid dosage forms like tablets and capsules
- High storage stability
- No negative impact on drug stability
- Complete drug release in the body
- No toxicity

Usually various carriers like microcrystalline cellulose [MCC (PH 102, PH 101 and PH 200)], lactose, mannitol are used. It was observed that Avicel is a better carrier because of high specific surface area. Apart from these other porous carriers with high specific surface area such as Neusilin US2, sylysia, anhydrous fujacalin are also used in liquisolid systems. The carriers like Neusilin US2 [9,10] and Sylysia [11] are also reported for conversion of melt dispersions into powder formulations. It was reported that large size particles of carrier (MCC 200) showed lower dissolution rate, poor flowability and lower tensile strength of tablets compared to smaller size particles of MCC 101.

Coating materials

Materials used as coating material must be of fine size (0.01 to 5 μm) with good absorbing capacity. Coating material should cover the wet carrier particles adsorbing excess liquid to ensure good flowability. In liquisolid formulations, this role is played by materials with a large specific surface area and high absorption capacity. At present, the coating materials used in liquisolid formulations are colloidal silicon dioxide (Aerosil®, Cab-O-Sil® M5), amorphous silica gel (Syloid®, Sylysia®), granulated silicon dioxide (Aeroperl®), silica aerogel, magnesium alumino metasilicates (Neusilin®), calcium silicate (Florite®) and ordered mesoporous silicates can be also used to prepare liquisolid system with suitable flowability and compressibility.

Table 1. Literature on liquisolid formulations.

Drug	BCS	Oral bioavailability (%)	Non-volatile Solvent	Carrier	Coating	Objectives	References
Clonazepam	4	90	Propylene glycol (PG)	MCC PH 102	Aerosil 200	Solubility Improvement	[12]
Glyburide	2	55	Polyethylene glycol (PEG)	MCC	Sillica	Improving The Dissolution	[13]
Irbesartan	2	60-80	PEG 400	MCC PH 102	Cab-o-sil	Improve Dissolution	[14]
Mosapride citrate	2	47	Glycerol, PG	Mannitol, Lactose, MCC	Colloidal silicon dioxide	Use of biorelevant media in evaluation of liquisolid compacts	[15]
Olmesatran	2	26	PG, PEG polysorbate fixed oil, glycerine	Fujicalin and neusiliin	Aerosil	Improve dissolution rate and bioavailability	[16]
Rosuvastatin	2	20	PG, PEG 200, PEG400	MCC PH 102	Aerosil 200	Enhance solubility and dissolution	[17]
Felodepine	2	15	PEG400	MCC PH 102	Aerosil 200	Enhance solubility and dissolution	[18]
Ezetimibe	2	35-65%	PEG4000 Transcutol HP Labrasol Tween 80	Avicel PH101 Avicel PH200	Aerosil 200	Improve the dissolution rate	[19]

CONCLUSION

Poor water solubility of newly developed drugs is a challenge to formulation scientists. Conventional formulation approaches often fail to achieve the desired dissolution and bioavailability for such drugs. The liquisolid technology has demonstrated improvement in solubility and bioavailability. The commercial product is yet to be launched by using this technique. It is an efficient technology in terms of large scale production capability similar to that of tablets with low cost of formulations.

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