Review Article **ISSN: 2347-8322**

Asian Journal of Chemical and Pharmaceutical Research
AJCPR, 2014, Vol.2(2): 186-191
www.pharmaresearchlibrary.com/ajcpr

A Review on Liquisolid Technique

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Received: 10 July 2014, Accepted: 30 August 2014, Published Online: 12 September 2014

Abstract

Poorly soluble, highly permeable active pharmaceutical ingredients represent a technological challenge because their poor bioavailability is only caused by poor water solubility resulting in low drug absorption. Newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. Problem of solubility is a major challenge for formulation which can be solved by different technological approaches during the pharmaceutical product development and to improve water solubility and drug release respectively, among which the liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. 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. It has been speculated that such systems exhibit enhanced release profiles.

Keywords: Liquisolid technology, liquid load factor, solubility, carrier material, coating agent.

Contents

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Manuscript ID: AJCPR2205

PAPER-QR CODE

1. Introduction

The oral route is the most preferred route of drug administration due to the ease, high patient acceptance, and low cost production. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT) when given orally [1]. The solubility and dissolution behavior of a drug are the key determinants of its oral Bioavailability [2]. Advancements in the fields of biotechnology and drug discovery have led to the discovery of increasingly large number of active molecules. However, 40% of all newly developed drugs and identified via combinatorial screening programmes are poorly water soluble [3]. Different types of techniques are available to increase the solubility of poorly water soluble drugs i.e., Micronization, Lyophilisation, Solid dispersions, use of complexing agents, co solvency, chemical modification, pH adjustment, solubilisation by surfactants, solid solutions, inclusion of liquid drug into the soft gelatin capsules, salt formation, liquisolid technique, etc. These techniques have been introduced to increase the dissolution rate, there by absorption and bioavailability. But there are some practical limitations in this type of technique. Micronization is the process of size reduction in particle size the expected dissolution & absorption rates may not be achieved because the fine particles tend to form aggregates (or) agglomerates due to increased surface energy & Vander Waals attraction. Solid dispersions are important for

improving solubility, wettability, dissolution rate and further bioavailability of drugs. However, only few products are available commercially, because of their poor physical characteristics for dosage form formulation. Solid dispersions prepared by melting technique may leads to stability problems. Salt formation leads to hygroscopicity and May causes stability problems. By the use of co solvents precipitation may occurs upon dilution [4-11].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic drugs, or water-Immiscible solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medication may be converted into a dry, non-sticky, free flowing, and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-immiscible substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [12, 13].

The new €liquisolid• technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-immiscible solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation[14, 15]. 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, non-sticky, free- flowing, and readily compressible powders. The liquisolid technology gives best results with the low dose poorly water soluble drugs to enhance the solubility but with high dose drugs it poses certain problems of overweight tablets. If the dose of the drug is high we will require more amount of non-volatile liquid vehicle to make the drug water soluble consequently the amount of carrier and coating material will be increased so the total weight of the tablet will be increased above 1gm or so which will be difficult to swallow.

2. Concept of Liquisolid Technology

With the liquisolid technology as described by Spireas [16] a liquid may be converted into a free flowing, easily compressible and evidently dries powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid, a 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 glycerin are best suitable as liquid vehicles [17]. 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 evidently dry, free flowing, and easily compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients like lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts (Fig. 1). 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[16]. This approach is based on the flowable (, -value) and compressible (*f* -number) liquid retention potential introducing constants for each powder/liquid combination [18, 19].

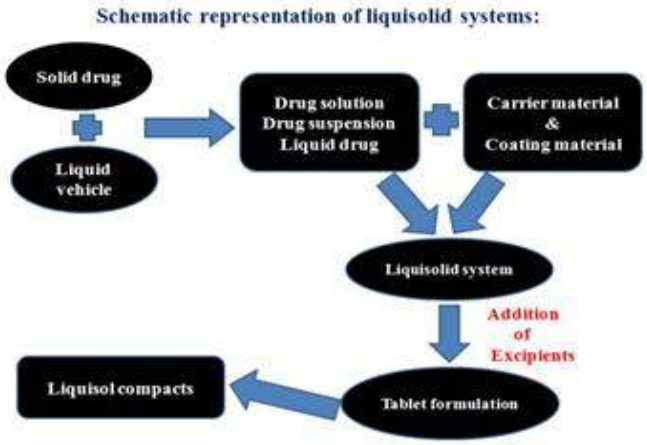

Figure 1: Schematic Outline of Steps Involved in Preparation of Liquisolid Compacts [20]

The , -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 flowability. The flow ability may be determined from the powder flow or by measurement of the angle of repose.

The *f* -number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called „pactisity…, which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces [20].
The terms „acceptable flow and compression properties… imply the desired and thus preselected flow and compaction 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 material is not exceeded[16, 21]. This liquid/carrier ratio is termed „liquid load factor Lf… [w/w] and is defined as the weight ratio of the liquid formulation (W) and thecarrier material (Q) in the system:

$$Lf = W/Q \qquad \text{Eq. (1)}$$

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

$$R = Q/q \qquad \text{Eq. (2)}$$

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

$$\dagger Lf = \dagger CA + \dagger C \quad O\ (1/R) \qquad \text{Eq. (3)}$$

Where, †CA and †CO are the , -values of the carrier and coating material, respectively [22]. Similarly, the liquid load factor for production of Liquisolid systems with acceptable compactability (*f*Lf) can be determined by:

$$f\text{Lf} = f\text{CA} + f\text{CO}\ (1/R) \qquad \text{Eq. (4)}$$

Where *f*CA and *f*CO are the *f* -numbers of the carrier and coating material, respectively.
Therefore, the optimum liquid load factor (Lf) required, to obtain acceptably flowing and compressible liquisolid systems is equal to either †Lf or *f*Lf, whichever represents the lower value.
As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q) and coating (q) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q = W/Lf \qquad \text{Eq. (5)}$$

And

$$q = Q/R \qquad \text{Eq. (6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties [16, 23, 24].

Formulation and Designing of Liquisolid Systems

There are mainly five components of liquisolid compact, as follows:

Drug candidates

This technique have been successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate. Examples of drug candidates include carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen and prednisolone, digoxin, digitoxin, spironolactone, hydrochlorothiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc[25].

Non volatile Liquid

Non volatile liquid may be hydrophilic or lipophilic in nature and they should be inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilize the drug. It acts as a binding agent in the liquisolid formulation. Various solvents used for the formulation of liquisolid systems include polyethylene glycol 200 and 400, liquid paraffin, tween 80, 20, span 80, 20, glycerin, polysorbate 80 and cremophore L[26-29].

Carrier Materials

These are preferred to be coarser and granular for acceptable flow and these are compression enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. Eg. Various grades of cellulose such as avicel PH 102 and avicel PH 200, lactose, eudragit RL and eudragit RS12 (to sustain drug delivery) etc.[30, 31]

Coating Materials

It is a material of size range of about 10 to 5,000 nm in diameter, possessing fine and highly adsorptive properties which contribute in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid thus maintaining its flowability e.g. silica (Cab-O-Sil), Aerosil 200, Syloid[32].

3. 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[33]. The flow properties of powders are affected by Angle of repose, Carr•s index and Hausner•s ratio [34].

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 each spectrum is derived from single average scans collected in the region 400 - 4000cm-1 at spectral resolution of 2cm-2cm and ratio against background interfereogram [35].

Differential scanning calorimetry (DSC)

The themotropic properties of the drug, excipients prepared and determined by DSC. It is also given any possible interaction between excipients used in the formulation [34]. If the drug is in the form of solution in liquisolid formulation, i.e., the drug is molecularly dispersed within the liquisolid matrix, then the characteristic peak for the drug is absent in the DSC thermogram[36].

X- Ray diffraction (XRD)

To get justification that the drug is in the solubilised state or converted into amorphous form because of disappearance of characteristic peaks belongs to drug and their by appearance of peaks which belongs to carrier is absorbed [37].

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems[38]. This study confirms if there are any crystals present, or else drug is present in completely solubilised form by absence of crystals of drug [36].

In vitro dissolution studies

A Liquisolid compact has been successfully employed to improve the in-vitro release of poorly water soluble drugs as Prednisolone [39] Carbamazepine [40] Piroxicam [41, 42, 43]. Also several water insoluble drugs nifedipine, gem fibrozil, and ibuprofen, have shown higher bioavailability.

In vivo dissolution studies

This liquisolid technique is an encouraging tool for the enhancement of drug release of poorly water 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. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation [44].

4. Conclusion

This technique is a latent alternative for formulation of water-insoluble/soluble drugs. Liquisolid compact formed by conversion of solid state to liquid state, drug suspensions or drug solution in non-volatile solvents into dry looking, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents in such ratio. It can formulate into immediate release or else sustain release by selection of suitable solvent and carrier. Hence liquisolid technique can be used as a latent tool for design of suitable dosage forms for water insoluble/soluble drugs.

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