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A REVIEW ON LIQUISOLID TECHNOLOGY

A.Swarupa*, J.V.C Sharma, P.Vishnu Priya, Shyamala

Joginpally B.R Pharmacy College, Yenkapally (V), Moinabad (M), Hyderabad, Telangana, India.

ABSTRACT

The "Liquisolid" technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability. This technique is based upon the admixture ofdrug loaded solutions with appropriate carrier and coating materials. Formulation concept of liquisolid technology involves water insoluble drugs dissolved in suitable non-volatile liquid vehicles, and converted in to compact by blending with selective powder excipients. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. The liquisolid technology allows the transformation of liquid systems into solid drug delivery systems such as tablets. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs.

Key words: Liquisolids, Carriers, Coating materials, Water in-soluble/ soluble drugs.

INTRODUCTION

The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation. With the liquisolid technology as described and patented by Spireas, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients.

Liquisolid technology is the next generation 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, non-adherent powder by mainly adsorbing the liquid onto silica having large specific surfaces. However, such preparations have been studied 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 developments on powdered solutions, compression enhancers and binders such as microcrystalline cellulose were incorporated in such systems to improve the compactability of the blend.In these investigations, however, large quantities of silica were being used and the flow as well as compression properties of the product were never validated and optimized to the industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they showed significant problems of liquid squeezing out and unacceptably soft tablets. Thus the industrial application of such systems was hindered.

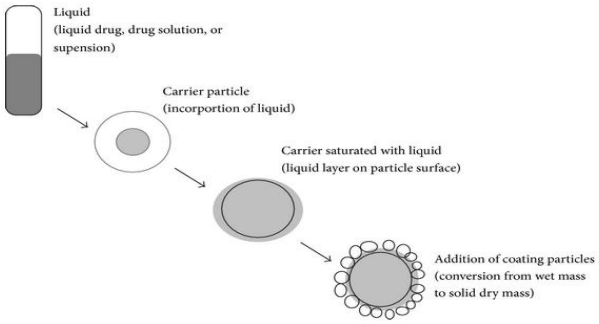
Liquisolid compacts, on the contrary, show acceptable flow and compressibility and deserve industrial application. In addition, the term „liquid medication" does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions or liquid oily drugs. Therefore, in contrast to powdered solutions, the term Liquisolid compacts is wider and more general and it may encompass four different formulation systems viz. powdered drug solutions, powdered drug suspensions, powdered drug emulsions and powdered liquid drugs.

CONCEPT OF LIQUISOLID SYSTEM:

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 such as celluloses, both absorption and adsorption take place. The liquid initially absorbed in the interior of the particles is captured by its internal structure. After the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. Then, the coating material having high adsorptive properties and large specific surface area provides the

***Corresponding Author A.Swarupa** E mail: rupa03arvapalli@gmail.com

liquisolid system the desirable flow characteristics . In liquisolid systems, the drug is already in solution form in liquid vehicle, while at the same time, it is carried by powder. The wettability of the compacts in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. 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. However, the drug release profile entirely depends on the characteristics of drug, carrier and vehicle used. Thus by altering these variables, liquisolid technique can be used for enhancing or retarding the drug release.



MERITS OF LIQUISOLID SYSTEMS

- Number of water-insoluble solid drug can be formulated into liquisolid systems.
- Can be applied to formulate liquid medication such as oily liquid drugs.
- Simplicity.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capules.
- Production of liquisolid system is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drugs.
- Exhibits enhanced in-vitro drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).
- Drug can be molecularly dispersed in the formulation.

DEMERITS OF LIQUISOLID SYSTEMS

- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
- Due to the high surface charge on discrete small paricles, there is a strong tendency for particle agglomeration.

COMPONENTS OF LIQUISOLID SYSTEM

The major formulation components of liquisolid compacts are:

Carrier Material

The carrier material should possess porous surface and closely matted fibers in the interior. Carriers are involved in the sorption process of liquid medication which improves the effective surface area for dissolution. These also assist the compression. Carriers due to relatively large, preferably porous particles, possess a sufficient adsorption property and matted fibers in interior contribute in absorption of liquid medication. e.g. various grades of cellulose, starch, lactose, sorbitol etc.

Coating Material

Coating material forms a uniform film around the particles of carrier. Thus they prevent the aggregation of particles as well as reduce the inter-particulate friction. This phenomenon improves the flowability as well as gives the liquisolid a dry looking appearance by covering the wet carrier particles and by absorbing any excess liquid.Coat materials are usually very fine (10 nm to 5,000 nm in 149 diameter) and highly adsorptive coating particles e.g. colloidal silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc.

Non-Volatile Solvent

The solvent selected should possess ability to dissolve adequate amount of the drug candidate. Inert, preferably water-miscible and not highly viscous organic solvent systems having high boiling point e.g. propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils etc. are the suitable vehicles.

Disintegrant

The use of disintegrant, its type and concentration in the formulation will be mainly based on the objective of the investigation. For solubility enhancement studies, incorporation of super-disintegrant is encouraged. Most commonly used disintegrant is sodium starch glycolate (Explotab13, Pumogel etc.). While for matrix type of systems intended for sustained release, disintegration is not required.

CLASSIFICATION OF LIQUISOLID SYSTEMS

A. Based on the Type of liquid Medication

Based on type of liquid medication used in the formulation, liquisolid systems may be classified into four subgroups:

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

The first three may be produced from the conversion of drug solutions or drug suspensions and emulsions, the later from the formulation of liquid drugs 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 carried within the liquid system, remains dispersed throughout the final product.

B. Based on the Formulation Technique

Depending on the technique used, liquisolid systems may be classified into two categories:

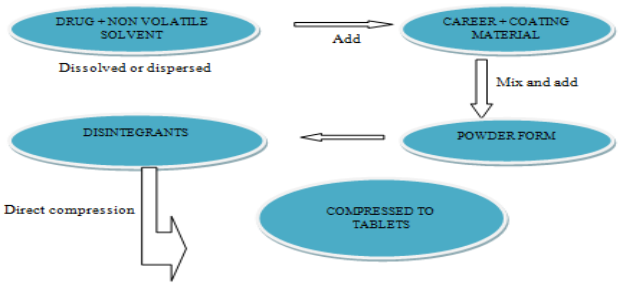
1. Liquisolid compacts
2. Liquisolid microsystems

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. 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.

METHOD OF PREPARATION OF LIQUISOLID SYSTEM

A liquid drug can be converted into a dry-looking liquisolid system without being further chemically modified. If liquisolid system of a solid water-insoluble drug is to be 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 a 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. 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 are suitable for this step.

Before compression or encapsulation, various adjuvant like lubricants and disintegrants (immediate release) or binders (sustained release) may be added to final liquisolid system to produce liquisolid compacts i.e. tablet or capsules.



Schematic outline of the steps involved in the preparation of liquisolid compacts

Preformulation

The Preformulation studies include,

1. Determination of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Ø value)
4. Calculation of liquid load factor (Lf)
5. Liquid solid compressability test (LSC)

The flowability and compressibility of liquisolid compacts are addressed concurrently 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.

Determination of drug in different non-volatile solvents

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

Determination of angle of slide: The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. It was used to measure the flow properties of powders. The angle of 33° is optimum for flow of powders.

Determination of liquid flowable liquid retention potential (Φ): –It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture. This Φ –value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ø value was used to calculate excipients quantities. Equation for this is as follows:

$$Lf = Ø + Ø\,(1 / R)$$

Where Ø and Ø are the constant Ø values of carrier and coating materials, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for liquisolid systems.

Calculation of liquid load factor (Lf)): It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Differnt concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

$$Lf = W/Q$$

W=ratio of weight of liquid medication

Q= weight of carrier material
The liquid load factor that ensures acceptable flowability (Lf), and can be measured by:

Lf= (1/R)

Liquisolid compressability test (LSC):

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture Systems, preparing several uniform liquid/powder admixtures to tablets, determining average hardness,measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value and Lf.

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. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Pre compression studies of the prepared liquisolid Powder systems: In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules.

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 background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm-1 at spectral resolution of 2cm-2 and ratio against background interfereogram. Spectra are analyzed by software.

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 of the liquisolid system. 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.

X-ray diffraction (XRD): For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify 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 compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.

Scanning electron microscopy (SEM): Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.

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.

In vitro dissolution studies: Works of many researchers revealed that toechnique 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, Prednisolone, Carbamazepine, Piroxicam. Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial
counter parts.

In vivo evaluation of liquisolid systems: This liquisolid technology is a promising tool for the enhancement of drug release of poorly 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. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.

List of Drugs that can be incorporated into liquisolid systems

- Antihistaminic: chlorpheniramine
- Antiarrthymic: digoxin, digitoxin
- Antihypertensive: nifedipine
- Antilipidemics: clofibrate, gemfibrozil
- Antiepileptic: Carbamazepine, valproic acid.
- Chemotherapeutic agent: etoposide.

- Diuretics:Hydrochlorothiazide, methylchlorthiazide,polythiazide, spironolactone.
- Glucocorticoids: prednisolone, hydrocortisone prednisone.
- NSAIDS: piroxicam, indomethacin, ibuprofen.
- Water-insoluble vitamins: vitamin A, D, E, and K

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