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Liquisolid Dosage System: A Novel Approach for Dosage formulation

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ABSTRACT:

Liquisolid system is a novel concept of dosage formulation for water insoluble drugs and lipophilic drugs via oral route. 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. Liquisolid compacts are compressible powdered forms of liquid medications, and they are industrially applicable. 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. However, the formulation of high dose poorly soluble drugs is one of the limitations of this technique because of the high amount of liquid vehicle needed. Consequently, high amounts of carrier and coating material are required ultimately leading to an unacceptably high tablet weight.

Keywords: Liquisolids, solubility enhancement, carriers, coating materials, water in-soluble/ soluble drugs.

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INTRODUCTION:

The concept of liquisolid compacts as defined by Spireas et al, (1998) can be used to formulate liquid medication such as oily liquid drug and solutions or suspensions of water-insoluble solid drugs in non-volatile vehicles, into acceptably flowing and compressible powders[1]

Poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge because their poor bioavailability is only caused by poor water solubility resulting in low drug absorption. Numerous methods have been applied to improve water solubility and drug release, respectively, among which the liquisolid technology is one of the most promising approaches. 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.

Usually, microcrystalline cellulose and colloidal silica are used as the carrier and the coating material, respectively. Water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles[2-3.] Hence, the liquisolid technology allows the transformation of liquid systems into solid drug delivery systems such as tablets.

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 for different formulation systems, namely, "powdered drug solutions", "powdered drug suspensions", "powdered drug emulsions", and "powdered liquid drug". Furthermore, the older term of "powdered solutions" seems to be inadequate even in describing the original systems, since it has not been proven that the remains in solutions in the liquid vehicle after its deposition on the extremely large powder surfaces of silica used[4]

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.

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

REQUIREMENTS FOR LIQUISOLID SYSTEMS

Drug candidates

Examples of drug candidates include digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil, etc[5-6].

Non-volatile solvents

Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol[7].

Carrier materials

It Refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption. such as Avicel PH 102 and 200, Lactose, Eudragit RL and RS (to sustain drug delivery), etc[8].

Coating materials

It Refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder 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 nonvolatile liquid vehicles, is incorporated into the porous carrier material (Fig. 1)[9].

Disintegrants

Most commonly used disintegrant is sodium starch glycolate (Explotab, Pumogel, etc.)[9]

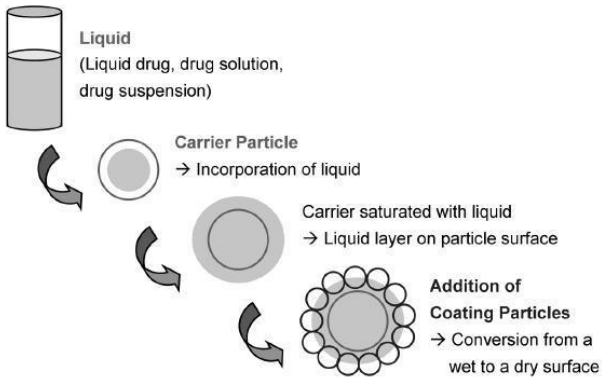

Figure 1: Schematic representation of liquisolid systems.

CLASSIFICATION OF LIQUISOLID SYSTEMS

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups[10].

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems. Simultaneously, based on the formulation technique used, liquisolid systems may be classified into two categories namely,

- Liquisolid compacts
- Liquisolid Microsystems

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively[10].

The term "liquisolid Microsystems" refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid compacts[10].

GENERAL METHOD OF PREPARATION

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. [11-12]

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. [13] 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 olutions 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.[14] 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. [15]

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.[16]

$$Lf = W/Q$$

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,[17] 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.

PROCEDURE :

As shown in figure 2, a liquid lipophilic drug (eg. Chlorpheniramine, clofibrate, 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[18].

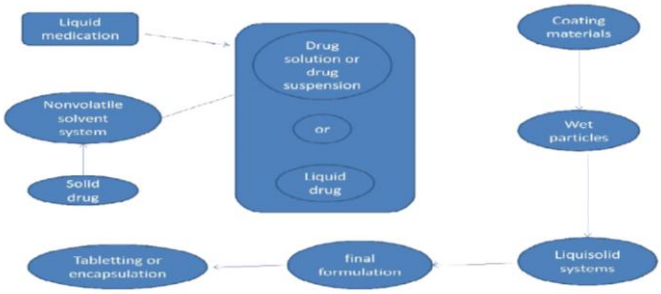

Figure. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts.

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.[19] Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems. [20]

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. [21]

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. [22-23, 21]

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.[24] 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.[25]

Scanning electron microscopy (SEM) Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.[25]

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.[24]

***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,[26] Prednisolone[15] Carbamazepine[23] Piroxicam.[23-24] Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

***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. [27]

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