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A Review: Innovational Approach to Enhanced Dissolution by Using Liquisolid Compact Technique

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ABSTRACT

The slow dissolution rate of water-insoluble drugs is still a major problem facing the pharmaceutical industry. Several methods have been used to enhance the solubility of drugs, among which the liquid-solid compaction technology is a novel one in which the solubility of insoluble drug moieties is increased with the help of non-volatile solvents. A new and promising addition to Target. Better resolution and bioavailability. Oral drug administration is one of the most convenient and widely accepted routes of administration for most therapeutic agents. It is one of the most commonly used drug delivery routes due to its obvious advantages of ease of administration, improved patient compliance, and convenience. Improving the oral bioavailability of poorly water-soluble drugs is one of the most challenging aspects of drug development. A newer technology, "powder solution technology" or "liquid solid technology", is used to produce water-insoluble drugs in immediate-release solid dosage forms. Limited drug solubility presents a challenge for the industry in developing the ideal solid dosage unit. This technology is based on dissolving an insoluble drug in a non-volatile solvent and mixing the drug-containing solution with a suitable carrier and coating material to transform it into an acceptable free-flowing and compressible powder.

INTRODUCTION:

Liquisolid technology is a promising new method that can alter the dissolution rate of drugs. It was used to improve the dissolution rate of poorly water-soluble drugs. For poorly soluble drugs (class II) and class drugs (class IV), the oral absorption rate is often controlled by the rate of dissolution in the gastrointestinal tract. The new "Liquisolid" technology formulates liquid drugs (i.e. solutions, suspensions, or emulsions of oily liquid drugs and water-insoluble solid drugs transported in a non-volatile liquid carrier) into powders suitable for tableting or encapsulation. can be applied Because liquid tablets contain a solution of drug in a suitable solvent. [1]

The concept of "liquid-solid tablet" was born from "powder dissolution technology" that prescribes "liquid". The term "liquid drug" refers to a solid drug dispersed in a suitable non-volatile liquid carrier. Simply mixing these "liquid drugs" with the carrier and coating material of choice produces powdered excipients that are dry in appearance, non-sticky, highly flowable, and well tolerated. Spireas and Bolton suggested that particles with highly absorbent porous surfaces, such as cellulose, starch, and lactose, could be used as carrier materials. As the water content of the carrier increases, the flowability of the powder decreases. A surface coating is required to keep the powder flowing. Therefore, the coating material should be a very fine and highly adsorptive silica powder. [2]

The Liquisolid system was developed by Spireas. Excipients and coating materials must be proportioned to maintain an acceptable amount of liquid converted to a solid. The powder excipient ratio R is the weight fraction of carrier (CR) and coating material (CO) present in the formulation, R = CR/CO. The maximum liquid load on the board is called the liquid load factor (Lf). Lf is defined as the weight ratio of liquid (w) to carrier powder (CR) in the system, Lf=w/CR, which must be provided by an acceptable liquid and compressible formulation. The φ value of a powder is the maximum amount of a given non-volatile liquid that can be held in bulk (w/w). The ψ number of the powder should be such that the powder is at its mass (w/w) while maintaining acceptable compatibility so that the "liquid squeeze" phenomenon does not occur when producing cylindrical compacts of sufficient strength. The maximum amount of liquid that can be absorbed and retained. The φ and ψ values of powders can be determined using the Liquisolid compressibility test (LSC). For liquid-solid systems, several mechanisms have been

postulated for the increase in solubility. The three main mechanisms proposed include increasing the surface area of drug particles, increasing water solubility, and improving the wettability of drug particles.[3]

Concept of liquisolid system:

Both absorption and adsorption occur when a drug dissolved in a liquid vehicle is incorporated into a carrier material, such as cellulose, which has a porous surface and densely entangled fibers inside. Liquid initially absorbed within the particle is captured by the internal structure of the particle. After this process is saturated, liquid adsorption occurs on the inner and outer surfaces of the porous carrier particles. Second, coating materials with high adsorption properties and large specific surface areas impart desirable flow properties to liquid-solid systems. In the Liquisolid system, the drug is already dissolved in the liquid vehicle and is carried by the powder. The wettability of pellets in dissolution media is one of the mechanisms proposed to explain the increased dissolution rate from liquid pellets. The non-volatile solvent present in the Liquisolid system facilitates the wetting of the drug particles by lowering the interfacial tension between the dissolution medium and the tablet surface. Therefore, liquid solids can be expected to exhibit improved release profiles for water-insoluble drugs, as the effective surface area for wettability and dissolution is greatly increased. [4]

The need for the liquisolid system

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance, and low drug manufacturing costs. For a drug to be absorbed into the systemic circulation after oral administration, it must dissolve in gastric juice. Therefore, one of the major challenges in drug development today is poor solubility, with an estimated 40% of all newly developed drugs being poorly soluble or insoluble in water. Additionally, up to 50% of orally administered drug compounds have formulation problems related to poor solubility and high lipophilicity. The bioavailability of poorly water-soluble hydrophobic drugs (class II of the biopharmaceutical classification system) is limited by their solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing surface area. Several studies have been performed to increase the drug dissolution rate by reducing the particle size and creating nanoparticles and microparticles.

However, fine drug particles are more prone to aggregation due to van der Waals attraction or hydrophobicity, both of which decrease surface area over time. Another way to increase the dissolution rate is to adsorb the drug to a high surface area support. In this technique, the drug is dissolved in an organic solvent, and the solution is subsequently transferred to a high surface area carrier, such as B. silica. Aggregation of the drug particles due to the binding of the drug to the carrier is prevented here. However, the use of toxic solvents is disadvantageous due to the presence of residual solvents in drug formulations. To solve this problem, a technology called 'Liquisolid Compacts' is a new promising approach for increasing resolution. Liquid pellets have acceptable flowability and compressibility.is made by simply mixing a carefully selected powdered excipient called a carrier and a coating material.[5]

Classification of liquisolid systems

A. Based on the types of liquid medication contained, Liquisolid systems can be divided into three groups.

1. Powdered drug solutions

2. Powdered drug suspensions

3. Powdered liquid drugs

The first two result from the conversion of drug uspensions (e.g., gemfibrozil suspensions in polysorbate 80), the latter resulting from the conversion of liquid drugs (e.g., clofibrate, liquid vitamins, etc.). to a liquid-solid system Because a non-volatile solvent is used to prepare the drug solution or suspension, the liquid vehicle does not evaporate, thus the drug is carried within the liquid system and dispersed throughout the final product.

B. Based on the formulation technology used, Liquisolid systems divide into two categories.
1.Liquisolid Compact
2.Liquisolid Microsystems

Liquisolid Pellets are manufactured according to the tablet or capsule manufacturing process described above, but Liquisolid Microsystems is a new concept that uses a similar methodology combined with Addition. It is based on. additives, e.g. Polyvinylpyrrolidone (PVP) in liquid drugs. It is incorporated into carriers and coating materials to produce acceptable fluid mixtures for encapsulation. The advantage of this

new technology is that the unit size of Liquisolid microsystems is up to five times less than Liquisolid Compact. [5]

Design the formulation and preparation of the liquisolid system:

1 Component of liquisolid system Formulation

1.1 Liquid Vehicle

The liquid vehicle used in the Liquisolid system should be orally safe, inert, not highly viscous, preferably water-miscible, and non-volatile, such as propylene glycol, glycerol, PEG 200 and 400, polysorbate 20 and 80. Must be an organic solvent. The solubility of a drug in a non-volatile solvent has a significant impact on tablet weight and dissolution profile. Higher drug solubility in the solvent allows for lower amounts of carrier and coating materials, thus reducing tablet weight. On the other hand, the higher the drug solubility in the solvent, the higher the FM value (fraction of molecularly dispersed drug) and the faster the dissolution rate. The choice of liquid vehicle primarily depends on the research objective. That is, in the case of dissolution improvement, a liquid vehicle with high drug solubilization ability is selected. However, if the goal is to prolong drug release, a liquid vehicle with the lowest ability to solubilize the drug can be chosen. In addition to drug solubility in liquid carriers, several other physicochemical parameters such as polarity, lipophilicity, viscosity, and chemical structure also have a significant impact on drug release profiles. Additionally, the low concentration of liquid vehicle is claimed to act as a binder and contribute to the compactness of the Liquisolid tablet. The reason may be the presence of hydroxyl groups in the molecular structure of the liquid vehicle, leading to hydrogen bonding between the solvent and other excipients in liquid formulations.[6]

1.2. Carriers

The carrier should have a porous surface and high liquid absorption capacity. Carrier properties, specific surface area (SSA) and liquid absorption capacity, are of critical importance when designing the formulation of the Liquisolid system, as the carrier allows large amounts of liquid drug to be incorporated into the liquid body structure. The primary factor influencing the liquid adsorption capacity is the SSA value. It is also affected by the type of coating material and the physicochemical properties of the liquid vehicle such as polarity, viscosity, and chemical structure. Currently, the most commonly used carrier is microcrystalline cellulose (MCC) with an SSA of

1.18 m^2/g.studied the effects of three grades of MCC (ie, PH 101, 102, and 200) on the flowability and compressibility and dissolution rate of piroxicam liquid tablets. Liquisolid formulations made from MCC PH 101 were observed to exhibit superior flowability, compressibility and dissolution profiles compared to those made from MCC PH102 and 200. Furthermore, aging does not significantly affect the hardness and dissolution profile of manufactured Liquisolid tablets.

Overall, MCC PH 101 is a suitable carrier for manufacturing Liquisolid systems in terms of flowability, compressibility, and dissolution profile. Apart from MCC, other common excipients such as lactose (SSA 0.35 m2/g), sorbitol (SSA 0.37 m2/g) and starch (SSA – 0)6 m2/g) is of relatively limited use due to their low SSA value. As a result of the low SSA value of the carrier, a large amount of carrier is required to convert the liquid drug into a dry, free-flowing compressible powder blend, further leading to increased tablet weight. In addition to these carriers, Eudragit RL and RS are also widely used in the preparation of sustained-release liquid-solid systems.[6]

1.3. Coating materials

Coating materials are very fine and highly absorbent materials such as Aerosil® 200, Neusilin, and powdered calcium silicate or magnesium aluminometasilicate. These materials play a major role in enveloping the wet carrier particles by adsorbing excess liquid to form a dry, non-dry, clump-adhesive, free-flowing powder. Replacing Aerosil 200 with Neusilin US2 as the coating material in the Liquisolid system has been demonstrated to significantly increase liquid adsorption capacity and reduce tablet weight. As Neusilincan be either a carrier or coating material, its use greatly simplifies the manufacturingprocess of Liquisolid formulations.

1.4. Additives

The disintegration of solid dosage forms affects the release of active ingredients. Therefore, Liquisolid tablets usually contain a disintegrant to allow rapid disintegration. Commonly used disintegrants in the Liquisolid system include sodium starch glycolate, croscarmellose sodium, and low-substituted hydroxypropyl cellulose. Polyvinylpyrrolidone (PVP) is another promising excipient that may incorporate high levels of the drug into the Liquisolid system, thereby reducing tablet weight. Furthermore, liquid tablets containing PVP show improved dissolution rates due to the crystal growth inhibitory effect of PVP. There is another additive

in the Liquisolid system. HPMC typically acts as a release retardant to prolong drug release. [7]

1.5 Drug candidate

BCS Class II and IV drugs are commonly selected as drug candidates for the Liquisolid system. This leads to the increased water solubility of such candidates. B. naproxen, digitoxin, prednisolone, hydrocortisone, ketoprofen. [8]

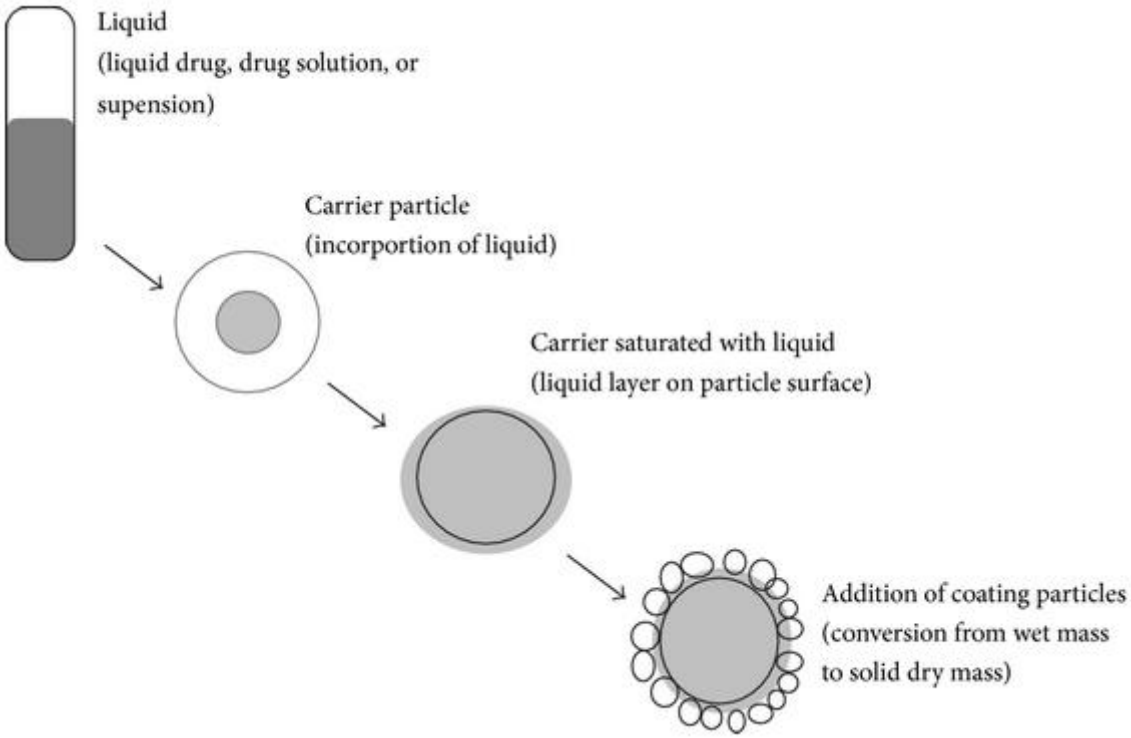

Figure 1: Schematic of the Liquisolid system.[8]

Methodology

Methodology

First Stage

The weighed ingredients are mixed at an estimated mixing speed of one rev/sec/min. This helps the liquid take its place in the powder.

Second Stage

The above mixture should be soaked on the surface of the mortar for about 5 minutes so that the liquid is completely absorbed into the voids of the powder particles.

Third Stage

Mix the above mixture with super disintegrant at mixing speed for 30 seconds to produce a final mixture ready for compression.[8],[3]

Preformulation studies

Preformulation studies were performed to confirm the physiochemical characterization and it includes the following studies.

Drug Solubility Studies in Solvents

• Slip Angle Measurements

• Retention Power of Flowing Liquids

• Liquid Load Factor (LLf)

• Liquid-Solid Compressibility Testing (LSC)

Drug Solubility in Non-Volatile Solvents

Saturated solutions of drugs are prepared and used for solubility studies. The excess drug is added to the vehicle to obtain a saturated solution by using a solution shaker for a given time with constant oscillation. The chemical filtrate is then analyzed spectrophotometrically.

Angle of slide

The sliding angle measures the flow behavior of powders. A metal plate with a smooth surface is used for the test, the test powder is placed on one end of the plate, and the plate is gradually lifted until the plate forms an angle with the horizontal surface on which the test powder slides. A powder angle of 33° ensures optimum flow properties.

Liquid flowable liquid retention potential (Φ)

It shows liquid retention potential of the powder with adequate flow behavior.

Liquid load factor (LLf)

It is the ratio of the weight of liquid medication (W) to the weight of carrier material (C). This is determined by taking adequate quantities of nonvolatile solvents in which the drug is dissolved, the resulting solution is converted to a free-flowing powder by the addition of carrier and coating materials.

Liquisolid compressibility test (LSC)

This test determines the Ψ values (compressible liquid retention value). It is done by preparation of carrier and coating material admixture, and converting the admixtures into tablets. The average rigidity is measured by the average liquid content of crushed tablets.

Evaluation of liquisolid system:

Flow behaviour

Differential Scanning Calorimetry (DSC)

X-ray diffraction (XRD)

Scanning Electron Microscopy (SEM)

Dissolution testing

In vitro drug release studies

Flow behavior

Bulk density

Weighed quantities of the powder blend is transferred into a graduated measuring cylinder. The bulk volume (Vb) of the weighted amount of the powder (W) is determined.

The bulk density is given below:

$$\text{Bulk density} = W/Vb$$

Tapped density [9]

The weighed amount of powder (W) mass is poured to a graduated measuring cylinder and tapped for a fixed number of times and the volume is determined (Vt).

Tapped density can be given by

$$\text{Tapped density} = W/Vt$$

Compressibility index [10]

The compressibility index is given by the following equation:

$$\text{Compressibility Index} = (\text{Tapped Density} - \text{Bulk Density}/\text{Tapped Density}) \times 100$$

Compressibility index values lower than 15 % shows good flow characteristics of powders and values higher than 25 % indicate poor flow nature.

Hausner's ratio

The indirect measurement of flow pattern of powders is given by

$$\text{Hausner ratio} = \text{Tapped density}/\text{bulk density}$$

A value below<1.25 indicates good flow behavior, whereas>1.5 signify poor flowability. Hausner's ratio can vary depending on the method used for the determination, so it is not taken as a critical parameter in flow behavior. Flow property of powders are represented in the table.

Angle of repose [9]

The powder blend is passed through a funnel that is made to ascend vertically till the funnel tip touches the pile of powder. The height of pile (h) and radius of the base of powder pile (r) is measured. The angle of repose is calculated as follows:

$$\Phi = \tan^{-1} h/r$$

Table 1: **Flow behavior of the powder**

Compressibility index	**Haussner's ratio**	**Flowability**
5-15%	1.05-1.18	Excellent
12-16%	1.14-1.19	Good
18-21%	1.22-1.27	Fair-passable
23-35%	1.30-1.54	Poor
33-38%	1.49-1.69	Very poor
>40%	>1.67	Very very poor

Differential Scanning Calorimetry (DSC)

The thermal behavior of pure components and liquid compacts can be evaluated by DSC investigations. Approximately 3–5 mg of sample is vacuum-packed in aluminum pans and heated at a fixed rate of 10 °C/min over a temperature range of 30–300 °C. An aluminum pan is used as a reference and purged with nitrogen to study the overall thermal behavior. The absence of a characteristic drug peak in the presence of an excipient indicates that the drug is incompatible with the excipient and that the crystal pattern of the drug has changed. at the molecular level [11].

X-ray diffraction (XRD) Studies

XRD studies determine the crystalline properties of liquid compact mixtures by X-ray diffractometry. This study uses a copper target with a current of 30 mA and a voltage of 40 kV. The device operates with scan angles from 5 to 70 degrees and a count rate of 0.4 sec/step. The change in the peak pattern from a well-defined sharp pattern to a random pattern indicates that the drug crystallinity changed to an amorphous drug form [12].

Scanning electron microscopy

This technique helps in determining the surface behavior of the drug, which gives an idea whether the drug is crystallized from the liquisolid system. The solubilized nature of the drug in a liquisolid system results in the disappearance of these molecular forms [13].

In Vitro Dissolution Testing

In vitro dissolution testing ofLiquisolid tablets is performed using a USP Type II Dissolution Apparatus. The test is performed in 900 ml of 0.1 N HCl at a constant temperature of 37° C.±2° C. with a stirring speed of 50-200 rpm. After adding a known amount of drug formulation to the medium, the percentage of dissolved drug is determined by collecting samples at regular intervals and maintaining sink conditions by replacing them with fresh buffer. Drug concentration can be determined spectrophotometrically [8][10].

Advantages

1. Liquisolid technology has many reported advantages.

2. Many poorly water-soluble, very poorly water-soluble, and virtually water-insoluble drugs can be formulated into liquid systems with improved solubility and bioavailability.

3. Hydrophobic carriers such as Eudragit® RL or RS or controlled release agents such as hydroxypropyl methylcellulose (HPMC) can be used with the Liquisolid system to achieve sustained release formulations with a zero-order release pattern. gain.

4. This technology has the potential to produce liquid tablets or capsules with pH-independent drug release profiles.

5. This is a promising alternative to traditional coating methods for improving the photostability of drugs in solid dosage forms.

6. The secondary materials used are simple and inexpensive. In addition, the manufacturing process is as simple as that of conventional solid formulations (tablets and capsules).

7. Formulations are generally well tolerated unless strong surfactants are required for stabilization.

Disadvantages:

There are also drawbacks associated with Liquisolid technology.

1. Although this technique has been successfully applied to low-dose water-insoluble drugs, the main limitation is the incorporation of high-dose water-insoluble drugs into liquid-solid systems. Because these drugs require large amounts of liquid carriers, large amounts of carriers and coating materials are required to obtain liquid-solid powders with good flowability and compaction properties. This can increase the weight of the tablet beyond its limits and make it difficult for the patient to swallow. Several strategies have been reported to address the above barriers. For example, adding additives (such as PVP or PEG 35000) to the liquid to increase viscosity can reduce the amount of carrier or coating material. Furthermore, the application of modern carrier and coating materials with large specific surface area (SSA) and high absorption capacity is another efficient method for loading large amounts of water-insoluble drugs.

2. The preparation of liquid-solid systems requires high solubility of the drug in the liquid carrier. [2][15]

Application:

- Solubility and Dissolution Improvement This technique has been successfully applied to low-dose water-insoluble drugs. However, formulating high doses of insoluble drugs such as Liquisolid tablets is one of the limitations of Liquisolid technology. Indeed, when the therapeutic dose of drug exceeds 50 mg, the dissolution improvement is not significant in the presence of small amounts of hydrophilic carrier and coating material. However, by adding some materials such as polyvinylpyrrolidone (PVP) to liquid drugs (microsystems), it becomes possible to produce dry powder formulations containing liquids with high drug concentrations. The addition of such substances to liquid formulations results in free-flowing, well-tolerated dry powders requiring a small amount of carrier.

- Flowability and Compressibility:

The flowability and compressibility of Liquisolid Compact are acceptable. They are made by simply mixing selected powdered additives, so-called carriers, and coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, and very fine particle-size silica can be used as a coating material. Large amounts of carrier and coating materials must be added to liquid powder formulations to obtain acceptable flowability and compressibility. This makes them very difficult to swallow, weighing more than 1g per tablet. Therefore, it is virtually impossible to convert high-dose drugs into liquid tablets with a tablet weight of less than 1 g using conventional methods. In such systems, the drug was in a state of molecular compartmentalization and the system was a free-flowing, sticky, dry-appearing powder. Further studies added these compression enhancers, resulting in a significant in 'liquid squeeze' phenomenon.

- Enhanced Bioavailability

Enhanced Bioavailability In liquid and powder solution systems, the drug is either in solid dosage form, maintained in solution in a powder matrix, or solubilized into a nearly molecularly dispersed state. I have. Therefore, with greatly improved wetting properties and drug surface area available for dissolution, liquid compacts of water-insoluble materials can be expected to have improved drug release properties and consequently improved bioavailability [2], [16].

CONCLUSION:

Improving the solubility and solubility of poorly water-soluble drugs remains a concern for pharmaceutical scientists. A review of the extensive literature shows that the development of Liquisolid technology has progressed very rapidly in recent years. Liquisolid technology is not only a useful tool for improving the dissolution rate of poorly water-soluble drugs, but also an innovative and superior process for manufacturing sustained-release tablets with a zero-order release pattern.

Moreover, this technology shows great potential to reduce the effect of fluctuations on drug release and improve the photostability of drugs in solid dosage forms. Further potential applications of this technology in pharmacy will be investigated in the future. Further research into the development of superior solvents and modern carrier and coating materials for high-dose drug loading is still underway. Much of the current research work is still focused on formulation development and investigating in vitro drug release profiles of the Liquisolid system. Future work on high-dose water Insoluble Drugloading Measurements and in vivo evaluation of liquid systems should be investigated and strengthened.

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