Review Article

Liquisolid Technique - A Newer Approach for Research in Pharmaceutical Sciences

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ABSTRACT

The low water solubility of many contemporary medications makes it challenging to create solid dosage forms with adequate bioavailability. An innovative method for enhancing the solubility, dissolution, and bioavailability of such medications is the creation of liquisolid system (LS). The fundamental idea behind LS preparation is to absorb the drug in a suitable excipient—porous carrier—and then coat it with a substance with a high absorption capacity. This process transforms the medication from a liquid into a free-flowing, compressible, dry powder. Compared to soft capsules, LS have lower production costs, require less processing, and provide improved drug release. The primary advantage is the liquid drug's increased bioavailability, which is brought on by a wide surface area for absorption. It is possible to optimize liquidsolid systems for the purpose of producing preparations with extended release by lowering the rate of medication disintegration. Instead of hydrophilic carriers, liquidsolid formulations with extended drug release may contain hydrophobic carriers. The current review discusses the liquidsolid methodology, including its benefits and drawbacks, theory behind it, classification of liquidsolid systems, components and preparation.

Keywords: Bioavailability, liquisolid system, dissolution, hydrophilic carriers.

INTRODUCTION

A scientific method for categorizing active pharmaceutical ingredients (APIs) according to their gastrointestinal permeability and aqueous solubility is called the Biopharmaceutical Classification System (BCS)[1]. A high solubility substance is defined by the BCS as one that is soluble in 250 mL of water over the pH range of 1–7.5 at 37°C and at the highest advertised dosage strength. When a medication's systemic absorption (parent drug + metabolites) in humans is found to be at least 90% of an administered dose, either by an intravenous reference dose comparison or a mass balance determination, the substance is deemed extremely permeable, according to the BCS.

A large number of potentially novel medications fall into either BCS class IV (low permeability) or class II (high permeability), and many of them show poor water solubility. For medications classified as BCS class II, which are extremely permeable and poorly soluble, the most crucial factors affecting bioavailability are the drug's solubility and dissolution behavior[2]. Poorly water-soluble medicines present numerous challenges in the formulation of pharmacological dosage forms for oral administration because of their low bioavailability[3]. One crucial factor in achieving the appropriate drug concentration in the systemic circulation[4] and demonstrating a pharmacological response is solubility.

Due to their limited solubility in the gastrointestinal tract, drugs that are poorly soluble in water will naturally release their contents slowly. The task at hand for these medications is to optimize their rate of solubility or dissolution. This ultimately enhances bioavailability and absorption. For many pharmaceutical formulations, dissolution is the rate-limiting step. The creation of LSs (LS) is the most creative and promising method for enhancing the dissolution and in vivo bioavailability of poorly soluble medications[5].

The technology of powdered solutions, which can be utilized to create "liquid medication," gave rise to the idea of liquisolid tablets. Solid medications dispensed in appropriate, non-volatile liquid vehicles are referred to as "liquid medication"[6]. By using a straightforward physical blending process with specific excipients known as the carrier and coating material, a liquid can be transformed into a free-flowing, easily compressible, and seemingly dry powder using the idea of "LSs," as described by Spireas et al.[7]. The drug's surface area available for disintegration and wetting qualities are greatly enhanced by the liquisolid compact. It is reasonable to anticipate that the liquisolid compacts of water-insoluble compounds will exhibit improved medication dissolution, leading to increased bioavailability.

LIQUISOLID TECHNIQUE

Spireas et al. initially presented this technology, which they used to combine medicines that are insoluble in water into solid dosage forms with quick release. The idea behind the construction of a LS is to use powdered liquid medications, such as drug solutions, suspensions, or liquid drugs, and to distribute the drug in a manner akin to soft gelatin capsules holding liquids. The phrase "liquidsolid technique" describes the process of combining liquid pharmaceuticals with appropriate excipients, also known as transporters and coating materials, to create powder combinations that appear dry, non-adherent, free-flowing, and compressible[8].

First, the liquid drug is absorbed into the carrier's internal structure.

A liquid layer forms on the surface of the carrier particles after the interior of the carrier is saturated with liquid medication. This layer is immediately absorbed by the fine coating materials. As a result, a powder mixture that seems dry, free-flowing, and compressible forms. Fig. 1 illustrates the mechanism of LS generation[9]. Typically, the liquid carriers are water-miscible organic solvents with a high boiling point that are safe to swallow, like propylene glycol and polyethylene glycol (PEG) 400. In order to absorb liquid medication, carriers refer to porous materials with a large specific surface area and a high liquid absorption capacity.

Different cellulose, starch, and lactose grades can be used as carriers. But the only excipients that can be utilized as coating materials are those that have extremely tiny particle sizes and highly adsorptive qualities, such silica powder[10]. The drug exists precisely in a fully or partially molecularly distributed state even though it is in a solid state within the LS[11]. Because of this, a LS may have a higher dissolving rate because of its superior wetting qualities, larger dissolution area or increased water solubility[12].

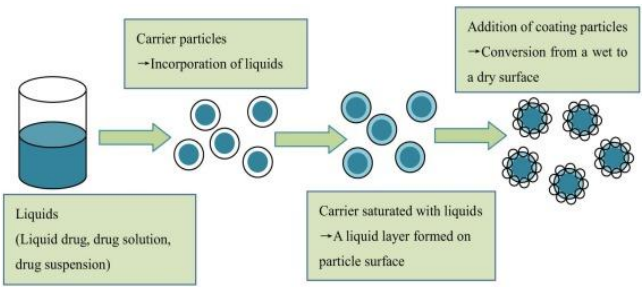

Figure 1: Mechanism of LS formation. Figure adapted from Reference[9].

ADVANTAGES OF LS[13,14,15]

1. LSs can be created from a variety of liquid and solid medications that are almost water insoluble and just very slightly soluble in water.

2. The medication is retained in a solubilized liquid condition even if it is in tablet or capsule form, which increases drug wetting qualities and improves drug dissolving.

3. It can be used to create liquid prescriptions, including greasy liquid pharmaceuticals.

4. A medicine that is water insoluble when taken orally is more readily available.

5. Compared to tablets and capsules, production costs are lower.

DISADVANTAGES OF LS[16,17]

1. It cannot be used to create insoluble large dosage medications.

2. The pill becomes difficult to swallow when extra carrier is added to create free-flowing powder, increasing the weight to more than one gram.

3. Because liquid medication may be forced out of the liquisolid tablet during compression, resulting in tablets with an inadequate hardness, acceptable compression qualities might not be reached.

4. It might not be possible to introduce this technology on an industrial scale and find a solution to the issue of combining small volumes of viscous liquid solutions onto huge amounts of carrier material.

THEORY OF LS

Only a certain amount of liquid medication can be retained in a powder while still allowing for proper flow and compressibility. Therefore, it is advised to use a mathematical model developed and verified by Spireas to determine the proper amounts of carrier and coating material in order to achieve a LS with acceptable flowable and compressible qualities[18]. Two essential characteristics of a powder—its flowable liquid retention potential (Ø value) and compressible liquid retention potential (ϕ value)—form the basis of the concept. The highest amount of liquid vehicle that may be kept in the powder bulk without sacrificing flowability and compressibility is represented by a powder excipient's Ø and ϕ values[19]. Preferably, the created liquid-powder admixture's angle of slide should be measured in order to determine the Ø value. And the φ value can be measured by an experiment called pactisity, which is defined as the maximum crushing strength of a tablet with a tablet weight of one gram when compressed at sufficient compression force[20].

The excipients ratio (R), which is also known as the carrier/coating ratio, is defined as follows:

$$R = Q/q$$

As a result, R is the ratio of the coating material (q) to the carrier (Q) weights. Higher carrier and lower coating material quantities are the results of increasing the R value. An ideal value of R is suggested to be 20 because it is connected to the LS's flowability, compressibility, disintegration, and dissolution rate[21]. The weight ratio of the liquid medication (W) to the carrier material (Q) in the LS is known as the liquid loading factor (Lf), and it is another crucial LS parameter.

$$Lf = W/Q$$

The liquid loading factor for the production of a LS with acceptable flowability can be determined by:

$$Ø\ Lf = Ø_c + Ø\ co/R$$

Where $Ø_c$ and Ø co values correspond to the flowable liquid retention potential of the carrier and coating material, respectively.

Correspondingly, the liquid loading factor to ensure acceptable compressibility of a LS can be determined by:

$$\varphi\ Lf = \varphi c + \varphi co/R$$

Where φc and φco values correspond to the compressible liquid retention potential of the carrier and coating

material, respectively. Therefore, the optimum liquid loading factor (L0) that produces a LS with acceptable flowability and compressibility is equal to either Ø Lf or φ Lf, whichever has the lower value.

COMPONENTS AND PREPARATION OF LS

Formulation design of LS

1. Liquid vehicle

Propylene glycol, glycerin, PEG 200 and 400, polysorbate 20 and 80, and other water-miscible, nonvolatile organic solvents are examples of liquid vehicles that are suitable for use in LSs and should be safe to swallow, inert, and not excessively viscous[22]. Tablet weight and dissolution profile are significantly impacted by the drug's solubility in nonvolatile solvent. Lower amounts of carrier and coating material are required when the medicine is more soluble in the solvent, which allows for the production of tablets with reduced weights. However, a larger FM value (the percentage of the medication that is molecularly distributed) results from a higher drug solubility in the solvent, which increases the rate of dissolution[23].

2. Carriers

Carriers should have a high capacity for absorbing liquids and a porous surface. The properties of carriers, such as their liquid absorption capacity and specific surface area (SSA), are crucial in the formulation of a LS because they enable the incorporation of large amounts of liquid medication into the liquisolid structure. The SSA value is a major determinant of the liquid adsorption capacity. It is also affected by the kind of coating material and the liquid vehicle's physicochemical characteristics, including its viscosity, polarity, and chemical composition[24]. Classification of carriers is shown in Table 1.

Table 1: Classification of carrier material into four categories and their SSA

Carrier category	Carrier category	SSA [m²/g]
Cellulose and cellulose derivatives	microcrystalline cellulose	~1.18
	hydroxypropyl methylcellulose[$]	-----
Saccharides	lactose	~0.35
	sorbitol	~0.37
Silicates	magnesium aluminometasilicate	110–300
	kaolin	~24
	diosmectite	
	ordered mesoporous silicates	up to 1500
Others	anhydrous dibasic calcium phosphate	30
	Polymethacrylates[$]	-
	starch	~0.60
	magnesium carbonate	~10

[$]Carrier material for LS with controlled drug delivery

3. Coating materials

Coating materials include powdered calcium silicate or magnesium aluminometa silicates, Aerosil® 200, Neusilin®, and other extremely fine and highly adsorptive compounds. By adsorbing any extra liquid, these compounds help to cover the wet carrier particles to form an ostensibly dry, non-adherent, and free-flowing powder[25]. It was demonstrated that the liquid adsorption capacity and tablet weight were significantly enhanced when Neusilin® US2 was used in place of Aerosil® 200 as the coating material in a LS[26]. Neusilin® can be used as a coating material or a carrier, which makes it much easier to prepare liquisolid formulations.

4. Additives

Liquisolid pills typically contain disintegrants to facilitate a quick disintegration. Low substituted hydroxypropyl cellulose, sodium starch glycolate, and croscarmellose sodium are a few disintegrants that are frequently utilized in LSs[27]. Another intriguing addition that may be able to reduce the weight of tablets by incorporating a large amount of medication into LSs is polyvinylpyrrolidone (PVP). Furthermore, PVP-containing liquisolid tablets have an improved dissolving rate because of its inhibitory effect on crystal development. HPMC is an additional component used in LSs that often serves as a release retarder to prolong the release of the medicine.

4.2. General preparation procedures of LS

The medicine and liquid carrier are combined in calculated amounts, and the mixture is heated or sonicated to completely dissolve the drug or blend it uniformly. According to Spireas and Bolton, there are three processes involved in combining the liquid drug that is obtained with the other excipients utilized in the liquisolid formulation. In order to enable a uniform dispersion of the liquid medication throughout the carrier powder, the first step involves pouring the liquid medication result over a calculated amount of carrier material and blending at a pace of about one revolution per second for a duration of one minute. The coating material is next added and thoroughly mixed in the calculated amount. In order to allow the drug medication to fully absorb into the interior structure of the carrier and coating materials, the prepared powder combination is spread in a uniform layer on the surface of a mortar and let to stand for five minutes. In the third step, a final LS is produced by adding disintegrant and completely combining it with the powder mixture mentioned before. There are two ways to compress or encapsulate the prepared LS. It should be noted that the standing time, mixing time, and speed can all be adjusted based on the circumstances. Fig. 2 illustrates the LS preparatory steps.

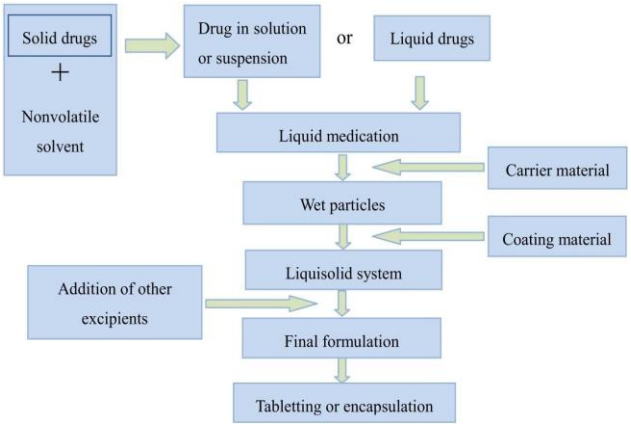

Figure 2: The LS preparatory steps

CONCLUSION

Compared to other dosage forms, the Liquisolid technique is a simple and cost-effective method of increasing the solubility and rate of dissolution of water-insoluble drugs. This increases the extent of absorption and bioavailability. By utilizing hydrophobic and hydrophilic carriers, it is also utilized in the formulation of immediate release and sustained release pharmaceuticals. Adding disintegrant to liquisolid compacts along with carriers and coating agents improves the drug release even more. As a result, choosing the right excipients—such as carriers, coatings, and detergents—is crucial. Additionally, this technology has proven to be very beneficial since it has improved the solubility, bioavailability, and dissolution of the majority of water-insoluble medications, particularly BCS class II and class IV medications.

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