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The Liquid Technique: A Novel Approach to Improve the Solubility and Bioavailability of Insoluble Drugs

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Abstract— *The purpose of this review is to elucidate how a liquisolid system may enhance the bioavailability as well as dissolving rate of less soluble medications. A variety of techniques, including complexation, solid dispersion, ball milling, crystal engineering, and Drug delivery systems that self-emulsify have been used. in recent research to improve drug solubility; nevertheless, liquisolid compacts have shown superior results in terms of increasing dissolution. These days, a lot of medications on the market have less solubility, which causes less dissolution and bioavailability. As a result, soluble is starting to slow down the development of new medications. There are other approaches to solving this issue; however, the most promising approach is the liquisolid technique, which is covered in this article. Spireas et al.'s novel mathematical model serves as the foundation for this technique. The majority of a liquid solid is made up of a drug, a non-volatile solvent, a carrier material, a coating material, and a disintegrant.*

Keywords— *Bioavailability, Dissolution, Liquisolid compacts, Solubility, Non-volatile solvent.*

I. INTRODUCTION

A drug's solubility plays a major role in determining its bioavailability Approximately 70% of novel drug candidates and 40% of newly introduced new pharmaceuticals are available in oral rapid release dosage form. have been shown to have low water solubility in recent years (1). For drug distribution, the oral route is usually advised because it is easy to administer, inexpensive, and patient-complies. A sufficient amount of the drug's dissolution in the stomach secretions is required for an oral medication to be adequately absorbed. The primary obstacle in the creation of innovative therapeutic substances is their Solubility is limited. Solid dispersions, inclusion complexes with -cyclodextrins, micronization, eutectic mixtures, and spray-drying are all possibilities. are some of the techniques that can resolve this problem; nonetheless, the liquisolid method is the most straightforward and economical approach. The liquisolid technique improves the drug. dissolving characteristics by preserving the drug within the powder substrate in solution or in a solubilized virtually molecularly dispersed form (2). With the advancement of combinatorial chemistry and creative high-throughput screening, we now have a better understanding of physicochemical properties (such as crystal structures and salt formation) as well as biological factors (such as drug metabolizing enzymes and transporters) (3). As a result, many active medicinal compounds have been developed. However, the majority of these drugs are highly lipophilic and have low water solubility. (4). Solubility issues have been reported to impact approximately 60% of chemically synthesised compounds and approximately 40% of newly developed pharmaceuticals (5, 6). Dissolution is still a necessary step in the drug absorption process, especially for water-insoluble medications. Consequently, increasing these weakly water-soluble drugs' solubility, dissolution, and bioavailability is of interest to a large number of pharmaceutical professionals. "Liquisolid systems" are pharmaceutical liquids (including liquid lipophilic drugs) that can be dissolved into suitable water-miscible, non-volatile solvent systems to produce acceptable powdered forms that flow and compress. This liquid drug can be made into a powder that appears dry, is non-adherent, flows freely, and easily compresses by combining it with a few carefully chosen powder excipients, also known as the carrier and coating ingredients. Liquisolid compact formulation consists of three main ingredients: a coating material, a carrier, and a liquid medication. Additional excipients, such as disintegrants and release retard polymers, are also used based on the requirements and objectives of the formulation.

II. THEORETICAL CONSIDERATION

It was believed that the powdered solution technique described above represented a more advanced version of the liquisolid technology (7). It offers mathematical formulas for preparing the actives and excipients so that formulations with the required flow and compression properties can be produced (8, 9). A list of theoretical concepts that formulators should be familiar with is provided below.

Liquid medication:

The term "liquid medication" describes drug suspensions, water-insoluble drug solutions, or liquid lipophilic medications in appropriate non-volatile solvent systems. In the formulation of liquisolid systems, a variety of non-volatile solvents such as propylene glycol, glycerin, polysorbate 80, and polyethylene glycol 200 and 400 are used. (10).

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Liquisolid systems:

These are powder versions of liquid medications made by combining selected carrier and coating materials with liquid lipophilic medications, drug suspensions, or solutions of water-insoluble solid drugs in appropriate non-volatile solvent systems to produce "dry" (i.e., dry-looking), non-adherent, free-flowing, and easily compressible powder admixtures. (11). When a suitable amount of a suitable non-volatile solvent is heated, the medication dissolves or disperses in the solvent. The liquisolid system is created by combining this liquid medication with the coating and carrier elements.

Liquisolid Compacts:

These are "liquisolid systems"—a method of making tablets or capsules with immediate or sustained release. Adjuvants for tableting or encapsulation are lubricants, while binders or disintegrants are used for rapid or sustained release action, respectively. Additionally, disintegrants like Primogel (sodium starch glycolate) are used. Adjuvants such as HPMC K4 M are employed in order to attain extended release. (12).

Liquisolid microsystem:

When an additive is used to create capsules, the unit size of a "liquisolid system" can be up to five times smaller than that of a liquisolid compact.

Non-volatile solvent:

Depending on the kind of formulation (sustained release, immediate release, etc.), a non-volatile solvent may be lipophilic or hydrophilic in nature. Non-solvents have a high boiling point, are inert, and miscible in water (13).

Carrier material:

A "carrier material" is an ideal porous material that has sufficient absorption capacity, like microcrystalline cellulose. It facilitates the absorption of liquids.

Coating material:

The term "coating material" refers to a substance with tiny, extremely adsorptive particles that serves to cover the wet carrier particles and give them a dry appearance by adsorbing any surplus moisture. Several varieties of amorphous silicon dioxide (silica) are examples of such materials.

Need of liquisolid techniques:

Due to its low cost of drug production, good patient compliance, and ease of use, the oral route is still the most often used mode of medicine delivery. A drug must dissolve in the stomach's contents in order for it to enter the bloodstream after being taken orally. Solubility affects an estimated 40% of all newly found drugs, which is a significant obstacle to current drug research. These medications dissolve more quickly when their crystallinity is reduced, surface area is increased, or particle size is decreased. Several investigations have been carried out to produce nanoparticles and microparticles, which reduce the particle size, to speed up the dissolving of medications Due to hydrophobicity and Vander Waals attraction, which both reduce surface area over time, the small drug particles have a high tendency to clump together. Another method for accelerating the solubility of medication is adsorption of the drug onto a high-surface-area carrier. This method involves dissolving the drug in an organic solvent and then adding the combination to a high surface area carrier, like silica. In this instance, drug particle aggregation is inhibited due to the drug's binding to the carrier. Nevertheless, since residual solvent is present in the formulation of pharmaceuticals, there are drawbacks to the use of hazardous solvents. Liquisolid compacts are a novel and exciting approach to improving dissolving.

III. Basics of Liquisolid Systems

A mathematical process for formulating a liquisolid compact was proposed by Spireas et al. The primary goal of this technique is to ascertain the amount of carrier and coating material needed for the liquisolid process. This technique is based on the flowable (T -value) and compressible (Ψ -number) liquid retention potential since a powder can only hold a specific amount of liquid while maintaining acceptable flow and compression properties (14).

Flowable liquid retention potential (Φ-value):

"Flowable liquid retention potential (Value)" is the amount of liquid that a powder material can hold while still having appropriate flow properties. The "Φ value" denotes the highest liquid weight that may be sustained per unit weight of the powder material to create a properly flowing liquid/powder combination.

Compressible retention potential (ψ-value):

The "Compressible liquid retention potential (ψ -value)" of a powder material is the volume of liquid it can hold onto while still having adequate compression capabilities. To create an appropriate liquid/powder combination, the "ψ -value" indicates the maximum weight of liquid that can be kept per unit weight of the powder material.

Even with adequate flow and compression capacities, the carrier and coating powder materials can only contain a limited amount of liquid. Predicted on the employed powder system's excipients ratio (R),

$$R = Q/q \quad (1)$$

Where, Q = Amount of Carrier & q = Amount of coating material

Calculation of liquid load factor (L_f):

Various amounts of non-volatile solvent are added, and then the drug is dissolved. This liquid medicament is blended well with the carrier coating material mixture. Equation can be used to calculate drug loading factors, which in turn determine the amounts of carrier and coating ingredients in each formulation.

$$L_f = W / Q \quad (2)$$

Where W= weight of non-volatile solvent

Q= weight of powder admixture

To determine the necessary ingredient quantities, Spireas et al. calculated the powder excipients' flowable liquid retention potentials (T value). The following formula can be used to determine the liquid loading factor in order to produce a liquisolid system with the proper flowability:

$$L_f = \Phi CA + \Phi CO\ (1/R) \quad (3)$$

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IV. MECHANISN OF SOLUBILITY ENHANCEMENT: (15)

One of the proposed explanations for the higher rate of dissolution from the liquisolid compacts is the wettability of the compacts in the dissolution media. By lowering the interfacial tension between the tablet surface and the dissolve liquid, the non-volatile solvent in the liquisolid system makes it easier for the drug particles to be moistened. Liquisolid compacts can therefore be expected to exhibit enhanced release profiles of drugs that are insoluble in water due to their significant increase in wettability and effective surface area for disintegration. Since the rate-limiting stage in gastrointestinal absorption is frequently the dissolution of a non-polar drug, oral administration of water-insoluble medicines has a higher bioavailability when already in solution, resulting in faster rates of dissolution. The profile of medication release is however, greatly impacted by the properties of the medication, transporter, and mode of transportation. Therefore, the release of a medicine can be improved or delayed using the liquid solid technique by varying this parameters.

V. PREPARATION METHOD OF LIQUISOLID SYSTEM

The process outlined by Spireas and Bolton was used to create the liquisolid compacts. weighing out the prescribed 5 milligrams of the drug, moving it to a mortar, and combining it with a colourless liquid. The dispersion was then blended using a porcelain mortar along with the proper amounts of coating material and carrier. Subsequently, the powder blend is enhanced with additional excipients and blended completely. A multi-station rotary punching machine that needed manual work was used to compress the final mixture into tablets. The weight of the tablet and the excipients used in the formulation were taken into consideration while adjusting

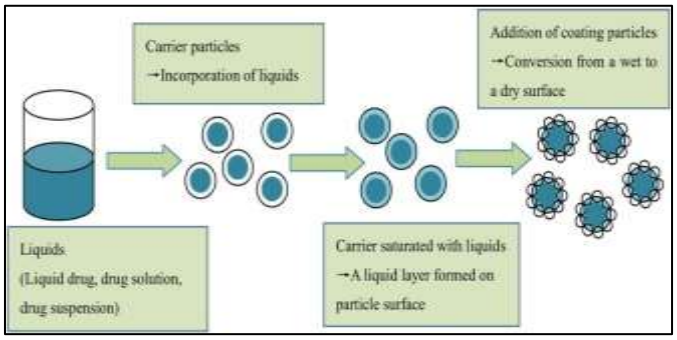

Fig. 1: Mechanism of liquisolid technique

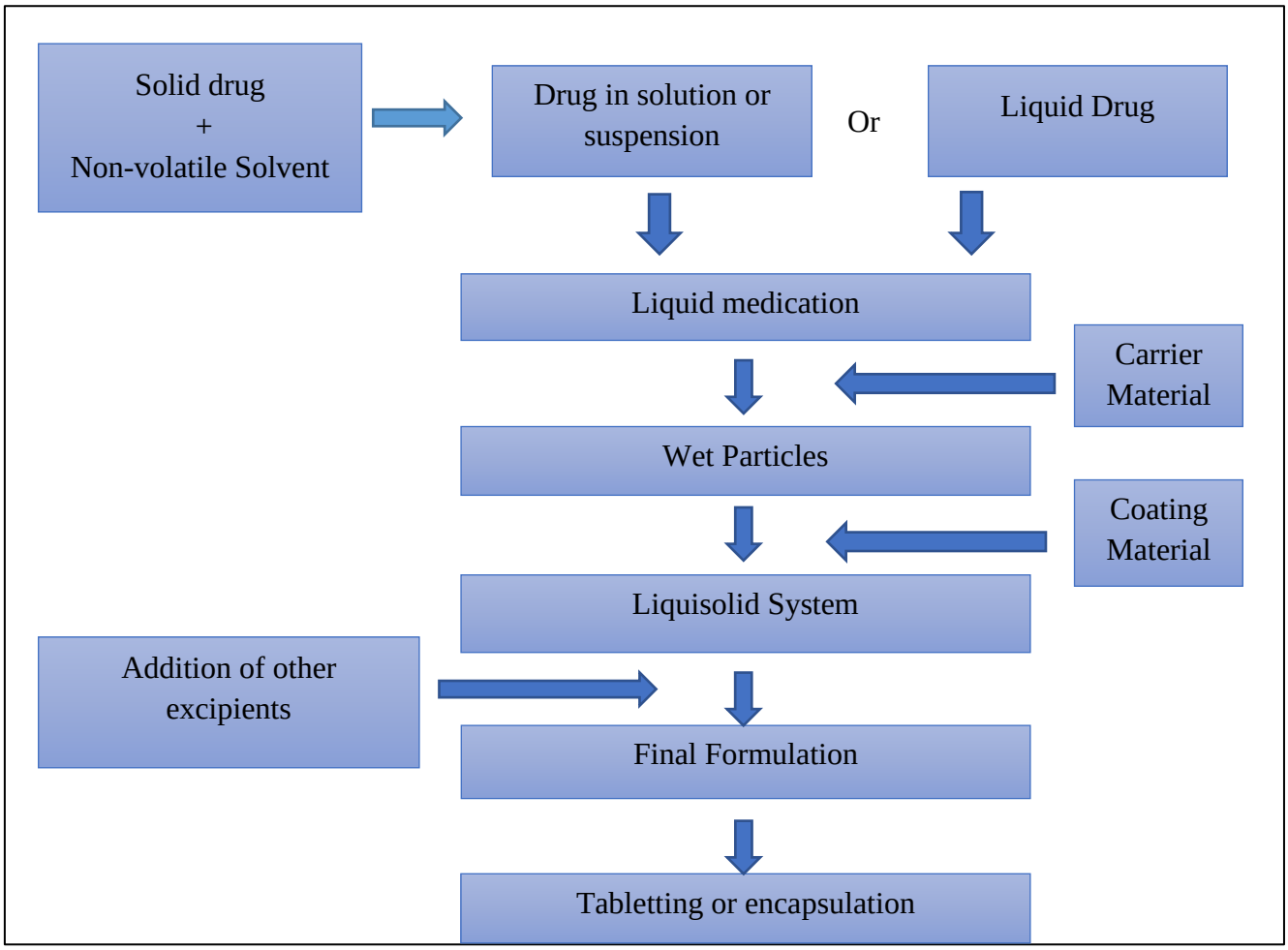

Fig. 2: Preparation method of Liquisolid compacts

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Advantages of Liquisolid System: (16, 17, 18, 19, 20)

1. Liquisolid systems are composed of a range of solid medications that are insoluble in water.
2. Improved accessibility to a medicine that is water insoluble when taken orally.
3. Liquisolid systems are produced in a manner akin to that of traditional tablets.
4. Less expensive to produce than soft gelatin capsules.
5. Suitable for controlled drug administration.
6. This technique can be used to create liquid solid tablets or capsules with medication release patterns that are independent of pH
7. It is an effective way to improve drug photostability in solid dosage forms as an alternative to the conventional coating procedure.
8. The correct formulation ingredients allow for the modification of drug release.
9. The rate of drug release or dissolution is higher for a medication that is molecularly distributed.
10. When compared to commercial counterparts, such as soft gelatine capsule formulations, demonstrates enhanced drug release both in vitro and in vivo.

Disadvantages of Liquisolid System: (17, 20, 21)

1. Synthesis of lipophilic drugs at high dosages One drawback of this method is the liquisolid tablet.
2. High amounts of carrier material and coating materials should be added to the liquisolid powder formulation in order to achieve acceptable flowability and compact ability. This will cause the tablets to weigh more than one gram, making them challenging to swallow.
3. The drug must have a high solubility in non-volatile liquid carriers.
4. Excipients with high specific surface area and adsorption capabilities are needed.
5. A liquid medication may occasionally be forced out of the tablet during compression, causing an incorrect hardness.

Application of Liquisolid System:

1. Hydrophobic carriers are used to simulate sustain release tablets, such as those containing theophylline, tramadol hydrochloride, and propranolol hydrochloride (21)
2. In order to accelerate the rate of dissolution of many medications, it is used to make them more soluble.
3. Several class II and class IV drugs have higher bioavailability when the liquisolid approach is used.
4. A liquisolid technique is used to improve the release rates of some drugs that are poorly soluble in water.
5. According to published research, the liquisolid technique has been extensively employed to quicken the dissolution of low dose insoluble drugs such clonazepam (25), valsartan (26), ketoprofen (27), clofibrate (28), and prednisolone (22).
6. Probiotics can be used with it.
7. Formulations for controlled release are also made using various carriers; these formulations may exhibit zero order release similarly to osmotic pumps.
8. Using the liquisolid approach to lessen the impact of pH shift on medicine release.
9. The liquisolid technique is a useful tool for enhancing drug photostability in solid dosage forms.

VI. CONCLUSION

Liquisolid technology is one of the most promising strategies being researched to enhance medication release and water solubility. By merely physically blending with specific excipients known as the carrier and the coating material, this approach transforms liquids, such as solutions or suspensions of poorly soluble medicines in a non-volatile liquid vehicle, into acceptably flowing and compressible powders. Liquid-solid technology works well because of its inexpensive formulation, similar tablet production capacity, and improved or sustained dissolve rate. In terms of cheap formulation costs and production capacity, this method is efficient. Thus, there is a chance that this technology will be developed in big quantities. The excipients needed for the liquisolid method are easily and widely accessible on the market. Since liquisolid procedures result in the highest drug release rates, liquisolid compacts can be made as effective as possible by choosing the right non-volatile solvent, carrier, and coating materials. It is expected that the liquisolid system will be a prominent player in modern solid dosage forms due to its advantages. Clinical studies have indicated that molecular dose distribution can improve drug absorption.

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