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A COMPREHENSIVE REVIEW: LIQUISOLID TECHNIQUE

Vaibhav N. Patil[1]*, Yashpal M. More[2] and Ashish M. Sonawane[3]

[1,3]Student, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Kalwan.

[2]Professor, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Kalwan.

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***Corresponding Author**
Vaibhav N. Patil
Student, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Kalwan.

ABSTRACT

Most newly developed drug choices are lipophilic and have poor water solubility. One of the biggest challenges facing the pharmaceutical business is improving these medications' solubility and bioavailability. A new and improved method to address the problem is the liquidsolid technique, It involves transforming the medication from a liquid into a powder that seems dry, non-adherent, free-flowing, and compressible. The purpose of this study is to provide an overview of the liquisolid technique and to summarize the evolution of its pharmaceutics applications. This strategy's main advantages are its low cost, processing simplicity, and vast industrial manufacturing potential. This technique is a relatively new technology to both speed up the dissolution of poorly water-soluble medications and effectively delay their release. In order to improve drug photostability in solid dosage forms, the liquisolid method has also been investigated as a way to lessen the effect of pH variations on drug release and as a workable alternative to conventional coating. Overall, the liquisolid method is a newly developed and promising tool for enhancing drug dissolving and sustaining drug release, albeit its prospective applications in pharmaceutics are still being explored.

KEYWORDS: Liquisolid Technique, Microparticles, PB screening design, Drug enhancement.

INTRODUCTION

Bioavailability, which depends on the drug's capacity to dissolve in gastrointestinal fluid, is the primary factor that determines a drug's therapeutic viability. The key requirements for reaching the optimal centralization of medicine for pharmacological reaction in basic

dispersion is dissolvability. Because of their limited dissolvability within the GI material, drugs that are not sufficiently water-soluble will typically be administered at a moderate rate. The rate that determines progress in the dissimilation of drugs is often the disintegration rate. Enhancing the rate of disintegration is the test for drugs that are not sufficiently water-soluble. In this way, absorption and bioavailability are enhanced.[1] To Improve the dissolving qualities of drugs that are not particularly soluble in water, a variety of methods are employed, including

- **Surfactant-based solubilization:** By generating small particles that encapsulate the medicine, surfactants can improve the solubility of medications that are poorly soluble in water.
- **pH modulation:** Altering pH of the environmen to increase a drug's solubility, particularly for substances whose solubility varies with pH.
- **Use of Co-solvents:** Adding supplementary solvents to help dissolve medications that don't dissolve well in water to increase their solubility.
- **Microemulsion systems:** Creating stable, transparent mixtures of water, oil, and surfactants that can improve the solubility of hydrophobic drugs.
- **Self-Emulsifying systems:** Formulating drugs in a way that they spontaneously form emulsions when exposed to aqueous environments, enhancing drug absorption.
- **Polymeric alteration:** Modifying the drug with polymers to improve solubility, stability, or to control the release of the drug.
- **Drug complex formation:** Combining drugs with other molecules like cyclodextrins to enhance solubility, stability, or to modify the drug’s release behavior.
- **Reduction of particle size:** Decreasing the size of drug particles to increase their surface area, improving dissolution and absorption.
- **Pro-drug strategy:** Designing inactive compounds that are metabolized into the active drug form in the body, often used to improve solubility or absorption.
- **Solid drug solutions:** Creating homogeneous mixtures of drugs with carriers in solid form to improve their solubility and dissolution rate.

Liquisolid technique

When liquid medications, Suspensions or medication solutions can be transformed into dry, non-sticky, free-flowing, and compressible powder mixes by combining them with specific coating and carrier materials. The Liquisolid system is the name given to this transformation

process. It is a very successful strategy for improving medication solubility. By improving their dissolving rates, the Liquisolid technology enables the efficient delivery of solid medications that are poorly soluble in water, lipophilic liquid medications, or solid medications dissolved in non-volatile solvents. These liquid medications are converted into dry, compressible powders using suitable carriers and coating agents, resulting in either free-flowing or non-free-flowing formulations.

Due to the drug's presence in the liquid in a solubilized or molecularly dispersed state, the resulting formulation enhances drug wettability and increases surface area exposure, leading to improved disintegration and bioavailability. Liquisolid tablets prepared from poorly water-soluble drugs have demonstrated superior dissolution profiles compared to conventional formulations.

In essence, a Liquisolid system uses the right carrier and coating materials to turn liquid drugs or drug solutions in non-volatile solvents into compressible, free-flowing powders.

Liquisolid technique requirement

Because it is convenient, affordable, and provides high patient compliance, the oral route is the most popular way to administer drugs. A medication must dissolve in gastrointestinal fluids before it can enter the systemic circulation following oral administration. However, a key challenge in pharmaceutical development is the poor water solubility of drugs—around 40% of newly developed compounds have low or virtually no solubility in water, which significantly hinders their bioavailability.

Techniques like decreasing the crystallinity of poorly soluble medications can be used to increase their rate of dissolution, decreasing particle size, or increasing the surface area. Techniques such as nanoparticle and microparticle formation have been extensively explored for this purpose. Nevertheless, these fine particles tend to aggregate due to hydrophobic interactions or Van der Waals forces, which ultimately reduces their effective surface area and hinders dissolution.

Adsorbing the medication onto carriers with a large surface area, such silica, is an alternate strategy, after dissolving it in a suitable organic solvent. This method helps prevent particle agglomeration by fixing the drug onto the carrier. However, the use of organic solvents can leave residual toxicity in the final product, which is a significant drawback.

To address these challenges, the Liquisolid compact technique has emerged as an innovative and promising solution. Without the use of hazardous solvents, this technique enhances the dissolving of medications that are not very soluble in water, offering a safer and more efficient approach in modern drug delivery systems.

Concept

When a medicine dissolved in a non-volatile liquid vehicle is combined with a porous carrier material, such as cellulose, which has a fibrous internal structure, both absorption and adsorption processes occur in liquidsolid systems. The liquid is first taken in by the carrier particles' internal pores. Any extra liquid is then adsorbed onto the carrier's internal and exterior surfaces after these pores are saturated. The flowability and compressibility of the resultant powder blend are enhanced by the addition of a coating material with a high specific surface area and strong adsorptive capacity in order to obtain desired flow parameters.

Powder excipients like microcrystalline cellulose and colloidal silica support the medicine in liquidsolid systems, which keep it soluble in a liquid medium. By enhancing wetting qualities and increasing the effective surface area available for dissolution, this method improves drug solubility and bioavailability, especially for water-insoluble substances. A drug's rate of dissolution is significantly increased when it is already in solution prior to delivery. The Liquisolid method successfully aids in overcoming this barrier because dissolution is frequently the rate-limiting stage for the absorption of poorly soluble, non-polar medications.

Increased wettability is one hypothesized cause for the better dissolving observed with Liquisolid compacts. The drug particles can moisten more quickly because the non-volatile solvent in the formulation lowers the interfacial tension between the tablet surface and the dissolving liquid. Because of this, liquidsolid compacts usually dissolve more quickly than traditional pills. As seen in Figure 1, liquidsolid compacts have a smaller contact angle, which suggests improved wettability and allows for more effective drug release.

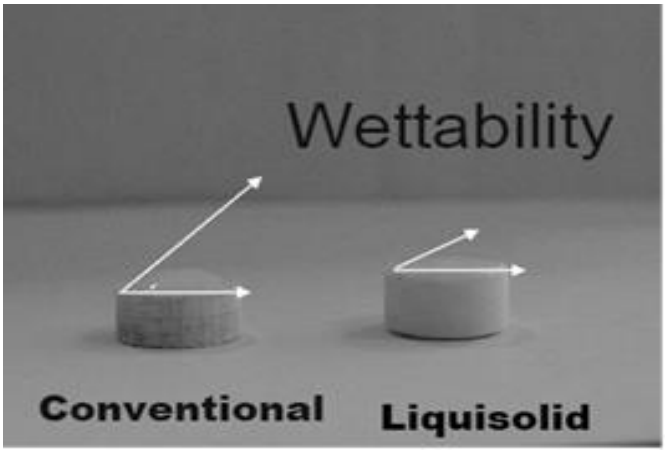

Fig. 1: Wetting Behavior Comparison between Liquisolid Compacts and Conventional Tablets.

Advantages

- Liquisolid compacts offer remarkable versatility, particularly for formulating drugs with poor water solubility.
- By improving the solubility and absorption of weakly water-soluble medications, they significantly increase their oral bioavailability.
- Compared to formulations like soft gelatin capsules, Liquisolid systems are more cost-effective to produce.
- These systems enable the drug to be presented in a solubilized form through various formulation strategies, thereby improving both the drug release profile and wetting properties.
- Liquisolid compacts offer versatility in dosage form design, as the selection of carrier materials allows them to be tailored for either immediate release or sustained (controlled) drug release.
- The use of hydrophobic carriers combined with surface-active agents can further improve the drug's dissolution rate and enhance its wettability.
- Overall, this technique contributes to improved manufacturing efficiency and better control over formulation parameters, making it a promising approach in pharmaceutical development.

Limitations

- This method is not appropriate for creating high-dose water-insoluble pharmaceuticals because it is often restricted to low-dose, poorly water-soluble compounds.

- The total weight of the tablet increases due to the requirement for coating and carrier ingredients, which could affect dosage design or patient compliance.
- For the formulation process to provide the best flow and compressibility, the right amounts of liquid vehicle, carrier, and coating ingredients must be determined mathematically.[6,7]
- While the addition of substances that enhance absorption can improve drug release, they may also reduce the tablet's compact size, potentially affecting its structural integrity or dosing accuracy.
- If proper compression forces are not applied during manufacturing, the resulting tablets may lack sufficient hardness, leading to mechanical instability.
- The drug's solubility in the selected non-volatile liquid vehicle is crucial in determining how quickly it dissolves and how bioavailable it is, limiting the technique's applicability for drugs with low solubility in such vehicles.

Formulation of liquisolid tablets

In order to create the Liquisolid systems, the medication was dissolved in a chosen non-volatile solvent to create drug solutions that ranged from 10% to 50% w/w. This drug solution was completely mixed with a carrier material using mortar and pesticide to create the final liquid medication.

A 20:1 fixed carrier-to-coating substance ratio was used to turn the wet a mixture into a powder that flowed freely. This was achieved by gradually incorporating the coating material, which facilitated proper absorption and adsorption of the liquid onto the solid matrix.

The formulations were optimized by adjusting liquid load factors, which varied depending on the specific type of non-volatile vehicle used. Additionally, various carrier-to-coating ratios were explored to develop different Liquisolid formulations with suitable flow and compressibility characteristics.

The Liquisolid system relies on the use of both carrier and coating materials. The coating material used in the study possessed an exceptionally high specific surface area of approximately 339 ± 1 m^2/g, which significantly enhances the liquid absorption capacity while supporting good flow and tablet-forming properties.

In the final powder blend, sodium starch glycolate was added as a superdisintegrant to encourage quick disintegration, and 3% w/w of PVP K-30 was added as a binder to increase the mechanical strength of the tablets. Following preparation, a single-punch tablet press was used to compress the powder combination into tablets.

Designing and Preparing liquisolid formulations

Liquisolid system formulation design

Liquid vehicle

Liquid vehicle choosing in liquisolid systems

The appropriate liquid carrier for Liquisolid formulations should be low to moderately viscous, non-toxic, inert, and safe to take orally. To guarantee compatibility with the medication and the formulation procedure, the vehicle must be non-volatile and water-miscible. Propylene glycol, glycerin, polyethylene glycol (PEG) 200 and 400, and surfactants like polysorbate 20 and 80 are examples of frequently used solvents.[9]

The weight of the tablet and its dissolution characteristics are both heavily influenced by the drug's solubility in the chosen non-volatile solvent. Lighter tablets are produced when a drug that is highly soluble in the solvent requires less coating and carrier material to absorb the liquid medication. Higher solubility also results in a faster rate of dissolution by improving the FM value, which is the percentage of the medicine that is molecularly disseminated within the liquid vehicle.[10,11]

Carriers

In Liquisolid formulations, the carrier material must possess a high liquid absorption capacity and a porous surface structure to effectively incorporate the liquid drug.[12] These properties are essential, as they allow the liquid transformation of medications into drying, compressible, and free-flowing powders.

Among the key characteristics of carrier materials, specific surface area (SSA) plays a pivotal role. A higher SSA directly correlates with a greater ability to adsorb liquid medication, making it a critical factor in the design of efficient Liquisolid systems.

In addition to the carrier's attributes, the formulation's performance is also greatly influenced by the coating material selection and the liquid vehicle's physicochemical parameters, including its polarity, viscosity, and chemical structure. The total amount of liquid

medication that can be contained within the solid matrix without compromising flow and compressibility is determined by these criteria.

Film-forming materials

Function of coating materials in liquisolid systems

Coating materials in Liquisolid systems are ultrafine, highly adsorptive substances that play a crucial role in converting liquid-loaded carriers into dry, free-flowing powders. Common examples include powdered calcium silicate, magnesium aluminometasilicates, colloidal silicon dioxide (Aerosil® 200), and Neusilin®.[14]

These materials function by adsorbing excess liquid from the wet carrier particles, effectively encapsulating them and forming a powder that appears dry and is non-adherent. Their high surface area and excellent adsorption properties are key to ensuring the final blend maintains suitable flowability and compressibility, which are essential for successful tablet manufacturing.

Additives

Role of disintegrants in liquisolid compacts

The disintegration process of solid dosage forms plays a critical role in enabling the drug's release and absorption. To ensure rapid tablet breakup and enhance drug release, disintegrants are commonly incorporated into Liquisolid formulations.

Among the often utilized disintegrants in liquidsolid systems are These excipients—croscarmellose sodium, sodium starch glycolate, and low-substituted hydroxypropyl cellulose (L-HPC)—help tablets dissolve well in the digestive system, thereby accelerating the onset of drug dissolution.

An additional excipient of interest is polyvinylpyrrolidone (PVP), which has shown potential not only as a binder but also as a means to reduce overall tablet weight. This is due to its ability to facilitate the incorporation of higher drug loads into the Liquisolid matrix.[16]

Mechanisms of increased drug release

Three main mechanisms account for the improved medication release seen in liquidsolid formulations:

1. Improved wettability of drug particles: The drug and dissolution medium interact better thanks to the liquid vehicle's cosolvent effect.

2. Improved aqueous solubility: When a non-volatile solvent is present, it aids in the dissolution of poorly soluble medications, making them more soluble in water.
3. Greater surface area for dissolution: Improving the drug's rate of release and bioavailability requires a larger surface area for dissolution.[17]

Enhanced effectual surface area

Drug release mechanism in liquisolid systems

Because the medicine is molecularly distributed throughout the liquid vehicle in a liquisolid system, the surface area accessible for disintegration is significantly increased. Consequently, when tablets are compressed, the drug's surface area that can be released is greater than in its native solid form.

The fraction of the drug that is molecularly distributed (FM) in these systems is directly correlated with the release rates. Accordingly, faster drug release is typically associated with higher FM values, which indicate greater molecular dispersion. On the other hand, when the medication becomes more soluble, a larger percentage of the drug stays undissolved in the liquid medium, which could slow down the rate of releasing.

According to Spire, FM is the ratio of the drug's solubility (Sd), real concentration in the system, and formulation-specific medium concentration (Cd). This connection aids in comprehending how the degree of molecule dispersion in the liquid-solid system affects medication release and dissolution.

Enhanced aqueous solubility

Effect of Liquisolid Systems on Drug Solubility and Release

Liqisolid systems are designed to enhance the solubility of medications, thereby improving drug release through the primary mechanism of dissolution. However, In a highly compressed liquisolid compact, the small amount of liquid vehicle is not enough to significantly increase the drug's total solubility in the liquid medium. Alternatively, the little amount of liquid vehicle may interact with drug molecules at the solid/liquid boundary if it functions as a cosolvent, preserving and potentially extending the drug's solubility in that specific area. This results in better dissolving properties by allowing the liquid vehicle to promote the drug's solubility even in the solid matrix.

Numerous studies have confirmed that Liquisolid systems significantly enhance drug solubility, supporting their role in improving the drug release profile.

The fractional molecularly dispersed state (FM) is defined by the equation:

FM=Cd/Sd

Where, FM denotes the fraction of the drug that is dispersed at the molecular level. S_d refers to the solubility of the drug. C_d represents the concentration of the drug in the dissolution medium. An FM value of 1 indicates that the drug is optimally dispersed molecularly within the system.

Additionally, it is thought that the effective surface area accessible for dissolution is increased by the molecularly dispersed drug's adsorption and absorption on the carrier's surface as well as inside its internal structure. The mass transfer mechanism during drug breakdown is facilitated by this increased surface area, which improves drug release.

Better wetting properties

- **Improved wetting properties:** By lowering surface tension or functioning as a surface-active agent, the liquid medium enhances the wetting properties of the main liquisolid components.
- **Wettability measurement:** Contact angles and water rising times can be used to evaluate the system's wettability.
- **Improved drug interaction:** The drug's interaction is enhanced as it adsorbs onto the carrier particles, which increases the available surface area for interaction.[17]

Evaluation of compressed tablets

Friability test

The friability of the tablets was determined using a Roche friabilator, which gauges their mechanical durability by measuring weight loss after subjecting them to controlled abrasion.

Hardness test

Tablet hardness was evaluated using a hardness tester. Hardness is quantified in kg/cm². For each formulation, six tablets were assessed to determine the average hardness value.

Time for In-Vitro disintegration

Using a disintegration instrument with a disk, the tablets' disintegration time was measured in distilled water at 37 ± 2°C. Each formulation was tested with five tablets, and the amount of time it took for each pill to dissolve was noted.

Content uniformity

Five tablets were ground into a fine powder in order to evaluate the homogeneity of the content. Twenty milligrams of Olmesartan (equal weight) were carefully weighed and transferred to Ten milliliters of methanol were added to a 100 milliliter volumetric flask, and the mixture was swirled for ten minutes. The capacity was then filled to 100 mL with phosphate buffer (pH 6.8). After filtering and properly diluting the solution, a double-beam UV-visible spectrophotometer set to 257 nm was used for analysis.

In-Vitro dissolution study

A USP Type II dissolve equipment (paddle technique, EDT-08L, Shimadzu, Japan) was used to evaluate tablet drug release in vitro. Phosphate buffer (pH 6.8) was used as the dissolution media (900 mL), and the test was conducted at 37 ± 0.5°C with a stirring speed of 50 rpm.

At regular intervals, 10 mL samples were removed from the dissolution medium and replaced with new buffer to preserve volume. After passing through a 0.45 µm membrane filter, the samples were examined at 257 nm using a Shimadzu UV-1800 double-beam spectrophotometer.

The spectrophotometer's absorbance data were entered into an algorithm generated from the calibration curve to determine the cumulative drug release percentage.

Dissolution parameter calculation

Dissolution parameter determination

To get the area under the dissolution curve at a given time point (t), the dissolution efficiency (DE) was computed using the trapezoidal rule. After that, the DE was shown as a percentage of the area of a rectangle that, at the time, indicated 100% dissolution. The percentage of drug released in five minutes (Q5) was also determined, and a graph was created to show cumulative drug release over time. The time it took for 50% of the drug to be released was also calculated, providing key insights into the formulation's release profile.

PB Screening Design

A PB (Plackett-Burman) screening design was implemented in this study to analyze the effect of several factors on the experimental responses. This design included three dummy factors and five primary factors, each tested at two levels. The observed responses guided the next steps in optimizing the formulation. This design helps identify the most significant factors affecting drug release in the liquisolid system.[19]

Liquisolid formulation optimization for improved medication release

The optimization process of liquisolid formulations is centered on improving drug flowability and dissolution rate. The liquisolid technique significantly enhances drug release, with the release rate being directly influenced by the fraction of the drug in molecular dispersion. (FM). For higher medication doses, a greater quantity of liquid components is required to achieve the desired release profile, ensuring that the drug molecules are more effectively dispersed within the formulation.

To produce liquisolid systems with proper flow characteristics and compatibility, significant quantities of coating and carrier ingredients must be used. Eventually, nevertheless, this results in swallowing development, processing difficulties, and an increase in tablet weight. Consequently, various formulation parameters must be improved in order to address These and many other technical challenges associated with liquisolid systems (4). Table No. 1 below lists these factors.

Table 1: Formulation characteristic for a rapid-release liquisolid drug system.

Formulation factors	Enhancement	Outcomes
Fluid medium	igh drug loading capacity due to vehicle solubility	Greater percentage of drug present in molecularly dispersed form (Fm)
Addition of excipients	Polyvinyl pyrrolidone	Thicker liquid medium helps suppress precipitation
Proportion of excipients (R)	High insulating capability	apid dispersion of the dosage form inhibits precipitation

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