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A Recent Advancement in Liquisolid Techniques: A Comprehensive Review

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Abstract:
Liquisolid technique has shown promise for improving the solubility and bioavailability of medications that are water insoluble. The thorough analysis examines the most current developments in liquisolid technology, emphasizing its guiding principles, approach to formulation, and techniques for characterization. The liquisolid method solves major formulation issues by transforming liquid drugs into dry, free-flowing, and compressible powder types. We look over the benefits, including higher rates of drug release and increased bioavailability, as well as the drawbacks, like formulation complexity and stability issues. Advances in technology and novel materials for coating and carriers have led to a greater range of uses for liquisolid systems in the pharmaceutical sector. The study also includes a number of pharmacokinetic studies that show how well liquisolid formulations work in comparison to traditional techniques. There is still lots of scope for growth and research in this area, despite current obstacles. With a focus on the necessity for ongoing research and development to fully realize the potential of liquisolid techniques in drug delivery systems, this study seeks to present a thorough grasp of the state of the art in this field.

1. Introduction

Oral drug delivery is widely favored due to its high patient compliance, ease of administration, and cost-effectiveness. However, the main challenge with this method is maintaining appropriate plasma drug levels [1]. Many active pharmaceutical ingredients (APIs) have been developed, but most of these drugs are highly lipophilic and poorly water-soluble, falling under the Biopharmaceutics Classification System (BCS) class II category [2]. The primary difficulty in formulating these drugs for oral use is their low dissolution rate. For APIs to be therapeutically effective, they need to be released and dissolved in gastrointestinal fluids. Improving the dissolution profile and bioavailability of these drugs can lead to a reduced dose requirement, which minimizes side effects and lowers costs. Therefore, enhancing solubility is crucial for achieving the desired pharmacological response [3].Solubility can be improved by a variety of techniques [4], as shown in figure 1.

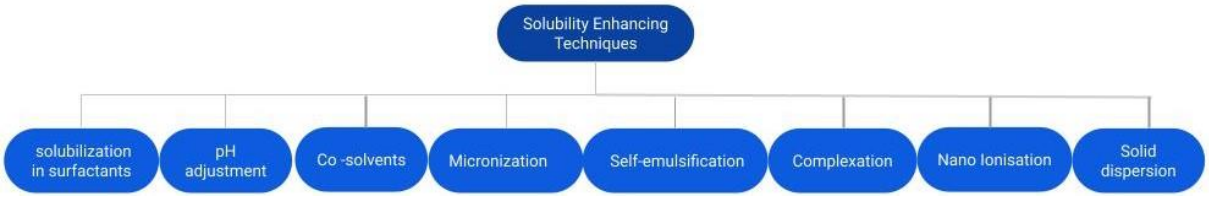

Figure 1: Solubility Enhancing Techniques

Among the various approaches to enhancing dissolution, powder solutions or liquisolid systems are particularly promising. The liquisolid technique involves converting liquid medication into a dry, free-flowing powder that can be easily encapsulated or compressed into tablets [5].

The present state of liquisolid techniques needs further improvements, so it is inevitable to done further research to optimize formulation strategies, improve process scalability, and guarantee the stability and uniformity of drug release profiles over an extended period of time in industrial applications. Furthermore, breaking through the present barriers will require advances in material science and creative methods for studying the interactions between drugs and excipients. To improve the bioavailability and therapeutic efficacy of hydrophobic pharmaceuticals, cooperation between academic researchers and the pharmaceutical sector will be necessary to translate these advancements into workable solutions [6, 7].

This review article investigates the potential of liquisolid technology to overcome the challenges associated with hydrophobic drugs, such as poor solubility and dissolution rates, which result in low bioavailability. We explore how this technology converts hydrophobic drugs into free-flowing, non-adherent powders, facilitating easier compression and enhancing patient compliance through sustained-release dosage forms. Additionally, we address current challenges in scaling up the process for industrial production and ensuring consistent drug release profiles. Future research directions are also discussed, focusing on optimizing formulation techniques, improving scalability, and investigating the long-term stability of liquisolid formulations.

Rest of the paper organize in following sections. Section 2 outlines the background study of liquisolid system, Section 3 presents formulation and design process of liquisolid tablets. Section 4 presents Merits and Demerits of Liquisolid Technique. Section 5 presentsat a glance: Drug candidate incorporated via liquisolid technique. At last section 6 in finally concludes the paper. It include conclusion and future perspective.

2. Background of Liquisolid Technique

Liquisolid compacts have their roots in the earlier technique known as "powdered solutions." This method involved the adsorption of a liquid drug solution onto silica with a large specific surface area, converting the drug in a non-volatile solvent into a dry, powder-like form. However, these powdered solutions could not be effectively compressed into tablets and were primarily analyzed for their dissolution properties as powders rather than as compacted forms. In later research aimed at improving the compressibility of such systems, compression enhancers like microcrystalline cellulose were incorporated into similar dispersions. [6].

Liquisolid compacts, on the other hand, are powdered formulations of liquid medications that flow and compress adequately for industrial use. The term "liquid medication" encompasses drug suspensions, emulsions, and liquid oily medications, as well as drug solutions, such as powdered solutions [7]. These compacts possess acceptable compressibility and flow properties. Their preparation involves a simple mixing process using specific powdered excipients known as coating ingredients and carriers. While finely powdered silica is

commonly used as a coating material, different grades of cellulose, starch, and lactose can serve as carriers [8].

Liquisolid systems can be categorized into two types:

*(*A)Based on the type of liquid medication used, three types of liquisolid systems can be created:

1. **Powdered Medication Solutions**: These are formed by converting drug solutions, such as prednisolone in propylene glycol, into liquisolid systems.
2. **Drug Suspension in Powder**: These involve converting drug suspensions, like gemfibrozil in Polysorbate 80, into liquisolid systems.
3. **Powdered Medicines in Liquid Form**: This type includes formulating liquid drugs, succlofibrate liquid vitamins, into liquisolid systems [9].

(B)Based on the formulation technique used, liquisolid systems can be categorized as follows:

1. **Liquisolid Compacts**: These are prepared using the traditional method, producing tablets or capsules.
2. **Liquisolid Microsystems**: These are based on a novel concept that employs a similar methodology as liquisolid compacts but with an added component, such as Polyvinylpyrrolidone (PVP), in the liquid medication. This additive is incorporated into the carrier and coating materials to create an acceptable flowing admixture suitable for encapsulation [10].

The liquisolid approach is an incredibly effective method for increasing the dissolution rate of medications with low water solubility. This method transforms the drug's liquid form into a powder that is directly compressible, non-adherent, dry-looking, and free-flowing. The liquid portion of a liquisolid system can consist of a drug suspension, liquid drug, or drug solution prepared in suitable non-volatile liquid carriers. Following this transformation, liquisolid tablets are prepared as shown in Figure 2 [11].

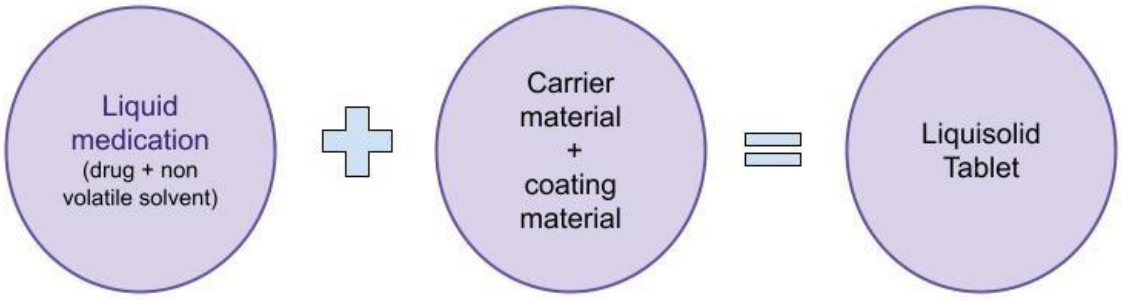

Figure 2. Formation of liquisolid tablets.

To achieve optimal compressibility and flow characteristics in liquisolid systems, Spireas et al. developed a mathematical model for designing liquisolid tablets. This model asserts that powder excipients in a liquisolid system can retain a specific amount of liquid vehicle while maintaining optimal flow and compressibility. It also helps in determining the appropriate quantity of excipients needed. The model relies on the compressible and flowable liquid retention potentials, represented by X- and Ψ-values, respectively.

These variables don't change for a specific powder/liquid (P/L) mixture. The maximum portion of the liquid vehicle (non-volatile) retained within the bulk (w/w) while maintaining acceptable flow is known as the flow able liquid retention potential (T-value). On the other hand, the maximum amount of liquid vehicle trapped in the bulk (w/w) while sustaining an acceptable compression in terms of effective friability and hardness is known as the compressible liquid retention potential (Ψ-value).

The excipient ratio, represented mathematically by R, is the "ratio of carrier and coating material."

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

Where R is the carrier to coating material ratio. Q is the number of carrier materials. q is the number of coating components.

The value of flowable liquid retention potential (ϕ-value):

$$\phi \text{ - Value} = \frac{weight\ of\ liquid\ medication}{weight\ of\ carrier\ material} \quad (2)$$

The following formula can be used to find the liquid loading factor needed to produce a liquisolid system with an acceptable flowability:

$$L_F = \phi + \psi/R \quad (3)$$

Where ϕ and ψ represent the carrier's and coating material's respective flowable liquid retention potentials.

Accordingly, the following formula can be used to find the liquid loading factor needed to guarantee a liquisolid system's appropriate compressibility:

$$L_f = \Psi + \psi / R \quad (4)$$

Where Ψ and ψ represent the carrier's and coating material's respective compressible liquid retention potentials. Consequently, or, whichever has the lowest value, is the ideal liquid loading factor (L_f) that creates a liquisolid system with appropriate flowability and compressibility.

One of the suggested mechanisms for the increased dissolving rate from the liquisolid compacts is the wettability of the compacts in the dissolution media. The non-volatile solvent in the liquisolid system lowers the interfacial tension between the tablet surface and the dissolution media, aiding drug particle wetting. Therefore, it is reasonable to assume that liquisolid compacts will exhibit improved release profiles of water-insoluble medications due to their significant increases in wettability and effective surface area for breakdown [13].

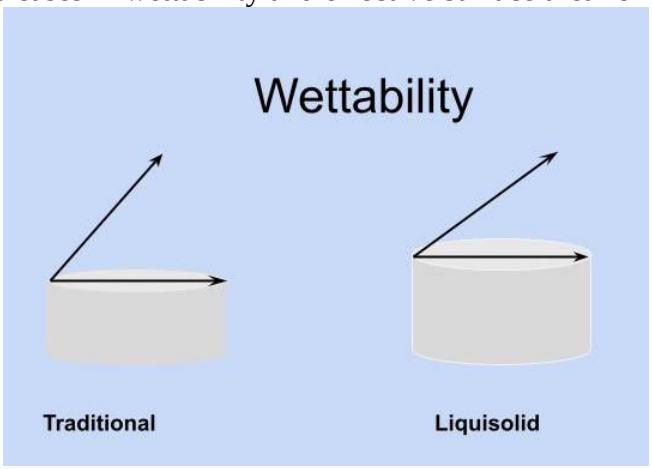

Figure 3.Comparison between Traditional and Liquisolid Tablets

Although the drug in a liquisolid system is in solid state, it exists either completely or partially in a molecularly dispersed form. This molecular dispersion can enhance the dissolution rate of the drug by increasing the dissolution area, improving aqueous solubility, or enhancing wetting properties. Beyond improving dissolution, the liquisolid technique has recently been explored as a means to delay drug release reduce the impact of pH variations on the dissolution profile and increase drug photostability. Importantly, liquisolid systems do not pose stability issues. This article provides an overview of the liquisolid technique and its advancements in pharmaceutical applications [14, 15, 16].

3. Design and Development of Liquisolid Tablets

The selection of excipients is crucial in the development of all dosage forms. In the context of the liquisolid technique, the combination of the carrier and coating material significantly affects the final formulation's size, mechanical properties, and processability.

3.1. Formulation Strategy for Liquisolid Tablets

The formulation strategy for liquisolid tablets aims to optimize the delivery of poorly soluble drugs by converting liquid formulations into solid dosage forms. This method improves drug dissolution rates by integrating the liquid medication into a carrier and coating material, producing a dry, free-flowing, and compressible powder.

3.1.1. Drug Material

Drug candidates that work well with the liquisolid approach typically have low dosage requirements, poor water solubility, and solubility in non-volatile solvents like PEG or glycerine. For the finished product to be stable and effective, compatibility with excipients is also essential [18].

3.1.2. Liquid vehicles

The liquid vehicle should have high wetting properties and good solubilizing capacity for the drug. They should also be safe to ingest, inert, and not too viscous [19]. The drug's solubility in non-volatile solvent has a substantial impact on tablet weight and dissolving profile. When the medication is more soluble in the solvent, less carrier and coating material are needed, enabling the creation of tablets with lower weight Liquid vehicles that are appropriate for use in liquisolid systems include propylene glycol, glycerine, PEG 200 and 400, Polysorbate 20 and 80, and other water-miscible, non-volatile organic solvents [20].

3.1.3. Carrier

While LSS are an innovation over powdered solutions, one of the most important steps in the formulation process is still choosing the carrier and coating material. As previously mentioned by Spireas and Bolton (1999), materials possessing high porosity and considerable absorption capacity could be employed as carriers[21].

3.1.4. Coating Material

A uniform layer of coating material surrounds carrier particles. This reduces inter-particulate friction and stops particle aggregation. Coating materials adsorb drugs not absorbed by carrier materials. This phenomenon covers the wet carrier particles and absorbs any extra liquid, improving flowability and giving the Liquisolid a dry appearance,resulting in free flowing powders . Their tiny particle sizes range from 10 nm to 4560 mm. For this purpose, silica is the most commonly used coating material.[22, 23]

3.1.5. Disintigrants

Superdisintegrants expedite the release of drugs, enhance water solubility, and elevate the wettability of liquid-solid granules. Among these, crosspovidone and sodium starch glycolate are the most frequently employed [24].

3.2. Pre Formulations Studies

Preformulation studies are a critical phase in the development of liquisolid tablets, aimed at understanding the physicochemical properties of the drug and excipients. These studies involve evaluating the solubility, compatibility, and stability of the drug in various solvents and carrier-coating material systems to ensure optimal formulation performance.

3.2.1. Angle of repose -The angle of repose for the given sample will be determined using the fixed funnel method. In this method, a funnel is positioned so that its top is 2 cm above the surface. A measured amount of powder is poured through the funnel, forming a conical pile. The height (h) and radius (r) of this pile are then measured. The angle of repose is calculated using the following equation:

$$\theta = \tan^{-1}(h/r) \qquad (4)$$

Where r is radius of the base of pile, h is its height, and θ is its angle of repose[25].

3.2.2. Bulk density - Understanding the true and bulk densities of a drug substance is crucial for estimating the size of the final dosage form. This parameter is especially important for low-potency drugs, which may make up the majority of the final granulation or tablet. Density influences powder flow properties and impacts the size of high-dose capsule products or the homogeneity of low-dose formulations, particularly when there are significant differences in the densities of the drug and excipients. The volume measured was called as the bulk volume and the bulk density is calculated by following formula[25-26].

Bulk density = Weight of powder / Bulk volume

3.2.3. Tapped density -The same measuring cylinder was used to calculate the tap density. The tap density device ran for 500 taps at a rate of 300 taps per minute. After being tapped 750 times, the volume was recorded as [Vb] after first being recorded as [Va]. When there is a 2% or less discrepancy between Va and Vb, Vb is regarded as the final tapped volume. Here is the formula to compute the tapped density: [26]

Tapped density = Weight of powder / Tapped Volume.

3.2.4. Compressibility Index - The following formula used for calculating the compressibility index:

Compressibility index (%) = ρt – ρo* 100 / ρt (5)

In this case, ρo = Bulk density gram/ml and ρt = Tapped density gram/ml [27].

3.2.5. Hausner's Ratio The following formula was used to determine the powder's hausner's ratio[28].

Hausner Ratio= TBD / LBD (6)

3.2.6. Drug Excipient Compatibility Studies:

Drug - excipient incompatibility is a common phenomenon that affects not only the therapeutic efficacy of the medicine but also its stability due to chemical or physical interactions. API and excipients found in dosage forms are designed to produce the best possible formulation for Products, so allowing for a safer and more efficient management.

Certain excipients have the ability to alter the pharmacokinetics of a medicine, which can impact its efficacy.

FTIR spectrophotometer was used to obtain the FTIR spectra of drugs, polymers, and formulated formulations. The diamond ATR was immediately filled with samples (2–5 mg), which were then scanned throughout a 4,500–500 cm-1 scanning range[29].

3.3. Preparation of liquisolid tablets[30]

Initially, the drug was dispersed within non-volatile solvent systems, referred to as liquid vehicles, with varying ratios of drug to vehicle. While continuously mixing the liquid medication in a mortar, a combination of excipients and carriers, or various polymers, were added. Sufficient quantities of the carrier and excipients were maintained to ensure proper flow and compression characteristics [30].

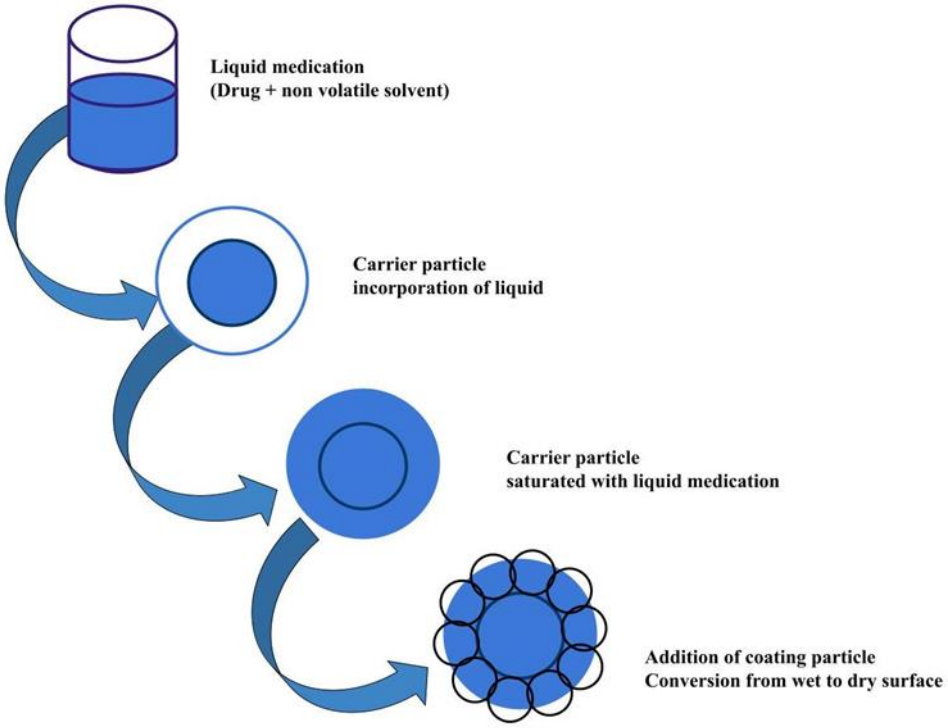

Figure 3: Mechanism of Liquisolid Techniques.

Other remaining additives were incorporated into the binary mixture according to their specific applications, such as disintegrants like sodium starch glycolate, and mixed in a mortar for ten to twenty minutes. To achieve the desired tablet hardness, the final mixture was compressed using a manual tableting machine. The mechanism involved in this process is illustrated in Figure 3.

3.4. Post compression evaluation -In this evaluation following steps are performed.[30, 31]

3.4.1. Weight variation test

Twenty tablets were weighed individually as well as collectively. The average weight was calculated from the total weight of all the tablets. Each individual weight was then compared to the average weight. The percentage difference in weight variation was checked to ensure it fell within the permissible limits. The % weight variation is calculated using following formula.

$$\text{Percentage weight variation} = \frac{Weight\ of\ each\ tablets - Average\ weight\ of\ tablets}{Average\ weight\ of\ tablets} \times 100$$

3.4.2. Hardness

Hardness of tablet is the force applied across the diameter of the tablet to break the tablet. Randomly Selected 6 tablets from each batch. Place a single tablet diametrically between the 2 probes of hardness tester.one probe is fixed and other one is movable. The pressure was applied on movable probe and the breaking force was recorded in terms of Kg/cm^2.

3.4.3. Tablet thickness and Diameter

Thickness and diameter are significant parameter for the uniform size of tablets.10 tablets from each batch were chosen and measured using a vernier calliper.

3.4.4. *Friability*

Friabilator is used to perform this test. Tablet equal to 6.5 gm randomly chosen from each batch and initial weight was noted. Then tablets were placed in plastic chamber of friabilator for the combine consequences of abrasion and shock, revolve the friabilator at a speed of 25 rpm for 4 min. then remove the tablets, dusted of the fine particles and weight. Percentage friability was calculated by the formula:

$$Percentag\ Friability = \frac{Inital\ weight\ of\ Tablet - Final\ Weight\ of\ Tablet}{Initial\ weight\ of\ Tablet} * 100$$

3.4.5. *Disintegration time*

The disintegration time for liquisolid tablets refers to the duration it takes for the tablet to break down into smaller particles in an aqueous environment. Use a USP disintegration apparatus, maintained at 37 ± 2°C. Place one tablet in each of the six tubes of the basket and add a disk to each tube. Lower the basket into the immersion fluid and start the apparatus. Observe the tablets at regular intervals until they completely disintegrate, ensuring that all particles pass through the mesh.

3.4.6. Drug content uniformity

The drug content uniformity test is essential to ensure that each tablet contains the correct amount of active pharmaceutical ingredient (API), guaranteeing consistent therapeutic effects. Follow these steps:

1. Randomly select 10 tablets from the batch.
2. Weigh each tablet individually and record the weights.
3. Crush each tablet into a fine powder using a mortar and pestle.
4. Accurately weigh a portion of the powder that equals 10 mg of the drug.
5. Transfer the weighed powder into a 10 ml volumetric flask.
6. Add phosphate buffer pH 6.8 to dissolve the drug and dilute to the mark to achieve a uniform concentration.
7. Filter the solution to remove any undissolved excipients.
8. Analyze the solution using a UV-Visible Spectrophotometer at 263 nm.

Amount of drug in each tablet was determined by following formula:

Drug Content (%) = $\frac{Absorbance\ of\ Test}{Absorbance\ of\ standrd\ at\ the\ same\ dilution} \times 100$

3.4.8. *In-vitro dissolution studies*

In vitro dissolution studies will be performed using a USP II (paddle type) dissolution test apparatus set to 50 rpm. The dissolution medium will be 900 ml of 6.8 pH phosphate buffer, maintained at a temperature of 37 ± 0.5 °C. At specified intervals, 5 ml of the dissolution medium will be withdrawn, and an equal amount of fresh medium will be added to maintain a constant volume. The samples taken will be diluted with phosphate buffer, filtered, and then analyzed at 263.5 nm using a UV-visible spectrophotometer. The cumulative percentage of the drug released will be calculated.

4. Liquisolid Technique Merits and Demerits

4.1. Merits [32, 33]

a. A variety of water-insoluble solid drugs can be formulated into liquisolid systems.

b. These systems can also be applied to formulate liquid medications, such as oily liquid drugs.

c. They offer simplicity and better availability for orally administered water-insoluble drugs.

d. Production costs are lower than those of soft gelatine capsules.

e. production process is similar to that of conventional tablets, making industrial production viable. f. liquisolid systems enhance in-vitro drug release compared to commercialcounterparts and

can be used for controlled drug delivery.

g. Optimized sustained-release liquisolid tablets or capsules of water-insoluble drugs demonstrate constant dissolution rates, following zero-order release kinetics.

4.2 Demerits [34, 35]

a. The fundamental disadvantage of this technique is its inability to incorporate high dose water-insoluble medications into liquisolid systems. Since these medications need a lot of liquid vehicle, a lot of carrier and coating material are needed to create a liquid-solid powder with good flow and compressible qualities. This might make tablets heavier than necessary, making it harder for patients to take them.
b. It involves non-volatile, water-miscible solvents but their reliance introduces challenges such as toxicity, adverse interactions, and stability issues.
c. It requires more efficient excipients with higher adsorption capacities, enabling faster drug release and a smaller tablet size to enhance liquisolid formulations.
d. Conducting more detailed investigations into the compaction behavior of Liquisolid system and the factors influencing it would enhance the industrial application of LS technology.

5. AT A GLANCE Key Drugs: A summary of key drug candidate incorporated via liquisolid technique is outlined in Table 1.

Table 1: Summery of Drug candidate based on Liquisolid Technique

S.No.	Drugs	Non- volatile solvents	Carrier material	Coating material	Ref
1.	Olanzapine	PEG 200 Tween80	Avicel PH 102	Aerosil 200	[36]
2.	Celecoxib	PEG 200	Microcrystalline Cellulose	Silica	[37]
3.	Pyroxicam	PG PEG400		Aerosil 200	[38]
4.	Rivaroxaben	Tween80	Avicel PH 102 Microcrystalline cellulose	Aerosil 200	[39]
5.	Acetazolamide	PEG400 Tween80	HPMC	HPMC, Colloidal silicon Dioxide	[40]
6.	Resperidone	PG	Microcrystalline cellulose	Aerosil 200	[41]
7.	Bilastine	PEG400	Avicel PH 102	Aerosil 200	[42]
8.	Ondansetron	PG	Avicel PH 102	Aerosil 200	[43]
9.	Lornoxicam	PEG400 Polysorbate80	Avicel PH 200	Aerosil 200	[44]
10.	Etoricoxib	PEG400	Microcrystalline Cellulose	Aerosil 200	[45]
11.	Mirtazepine	PG	Avicel PH 102	Aerosil	[46]

6. Conclusion and Future Perspectives

Liquisolid technique is a unique and advanced method that speed up the dissolution rate of hydrophobic drugs. This method produces zero-order release kinetics by sustain drug release and boosting the rate of dissolution. The liquisolid technique is a highly effective way to protect photosensitive pharmaceuticals in solid dosage form and minimize the impact of pH fluctuations on drug release. The liquisolid technique can be used to create powders that are

easily compressed, free-flowing, and non-adherent. So the liquisolid technology has proved to be a dependable and economical method.

The liquisolid approach is a useful tool for keeping light-sensitive pharmaceuticals, producing sustained-release formulations for multidosing schedule drugs, and increasing the rate at which hydrophobic drugs dissolve. However, as there is currently no commercial product on the market, liquisolid formulation clinical trials are necessary. Since this method takes into account pH-triggered releases, more investigation is needed to create enteric-coated formulations with this method. The principal benefit can be achieved by passing an extra enteric coating stage. The liquisolid approach creates a problem for administering high-dosage medications because a high dose necessitates large amounts of liquid vehicle and excipient which results in an overweight tablet that is difficult to swallow. Therefore, high-dose medication loading will be primary focus and challenge for pharmaceutical scientists. Liquisolid techniques have a promising future and have the potential to change oral medication administration. More advancements and research in this area should result in pharmaceuticals that are both more patient-friendly and effective

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