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# The Most Recent Advances in Liquisolid Technology: Perspectives in the Pharmaceutical Industry

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**Abstract**

Hydrophobic drugs exhibit altered bioavailability and pose other challenges at an industrial level due to their poor solubility and dissolution rates. In addition, poor flowability, compressibility, complex dosing schedules, and light-sensitivity problems associated with hydrophobic drugs have led to poor patient compliance. To overcome these problems at an industrial level, the liquid-solid technique is a promising approach for tackling such challenges. This study outlines the prementioned challenges related to hydrophobic drug candidates and introduces the liquisolid technique as a potential alternative using non-volatile water-miscible solvents, carrier agents, coating substances, and their subsequent applications in the pharmaceutical industry. Furthermore, this study highlights the role of liquisolid technology in achieving sustained-release kinetics, emphasizing its benefits in minimizing pH changes in drug release and enhancing photostability. The study aimed to explore the liquisolid technique as an important tool for improving drug delivery, overcoming solubility issues, and optimizing therapeutic outcomes. In addition, this manuscript holds significant importance by highlighting the applications and recent advances in liquisolid technology, focusing on industrial-level applications. Moreover, it is impressive that such a technique offers improved formulation options to enhance the safety and efficacy of therapy. Overall, this study serves as a valuable resource for researchers to overcome formulation challenges and optimize drug delivery in the pharmaceutical industry.

**Keywords:** hydrophobic drugs; liquisolid technique; dissolution rate enhancement; sustain release; pH disparity

## 1. Introduction

Oral drug administration is an authentic route of delivery due to its high patient compliance, ease of administration, and cost-effectiveness. However, the main issue with the oral route is the lack of suitable plasma drug levels [1]. Furthermore, to provide the desired concentration of the drug in the systemic circulation, the drug must be present in solution at the gastrointestinal level. Thus, the dissolution rate is a limiting step in the bioavailability of hydrophobic drugs, and poorly water-soluble drugs have incomplete systemic availability [2]. The main challenge for hydrophobic drugs is enhancing their dissolution rates and bioavailability. In the past, different approaches have been employed to increase the dissolution rate of hydrophobic drugs, such as drug solubilization using surfactants [3], and the dissolution rate of ketoprofen has been enhanced using this technique [4]. Celecoxib is linked to a complexing agent that has a higher dissolution rate than its conventional form [5, 6]. Crystal engineering [7] and ball milling [8] are other techniques that improve dissolution rates. The dissolution rates of indomethacin and naproxen were enhanced using a ball milling technique [9]. Microprecipitation [10] and solid dispersion [11] are other approaches in this chain. Itraconazole is a hydrophobic drug that has been investigated for enhancing its dissolution rate using these techniques [12]. Cosolvency and salt-formation techniques have been applied to hydrophobic drugs. However, all of these techniques have challenges, and the results obtained are dissatisfactory because fine particles recombine to form agglomerates or clumps. Higher surface energies of the particles and van der Waals forces are the main factors involved in such a scenario [13]. In the case of solid dispersions, commercially available products are limited because the required conditions for the process are not easily obtained. Solid-dispersion techniques involve solvent evaporation and melting. Evaporating the solvent is at times difficult during the solvent evaporation process, which changes the overall product performance. Moreover, the melting process is unsuitable for heat-labile drugs [14]. Ball milling is an expensive technique, and drugs handled using salt-formation techniques are vulnerable to moisture scavenging (hygroscopicity). Furthermore, special adjustments are required for heat dissipation during the process. Dilution of the co-solvent results in drug precipitation [2, 15-17]. In microprecipitation, a risk of toxicity from the solvent used (non-aqueous) exists. Wide size distribution is a major issue concerning the microprecipitation technique [18].

Thus, in the context of the aforementioned drawbacks, powder-solution technology (the liquisolid technique) is a novel and problem-free approach. Powder-solution technology is based on the conversion of a liquid drug (liquid medication) into powder form. This technique involves the introduction of hydrophobic drugs, either dispersed or dissolved in a non-volatile water-miscible solvent, into a specified quantity of excipients (carrier/coating materials). Drying the solvent by absorption/adsorption produces a nonsticky, free-flowing, and readily compressible powder [19-21]. Liquid medication refers to a hydrophobic drug dissolved (solution) or dispersed (suspension) in a non-volatile water-miscible solvent. Occasionally, oily drugs are introduced directly into the carrier and coating material. The carrier materials are porous and have good absorption capabilities. When applied to liquid medication, they provide residence to solubilized drug particles. Commonly used carrier materials are microcrystalline cellulose (MCC) and amorphous cellulose. Drug particles that are unabsorbed by the carrier materials due to saturation are then adsorbed by the coating materials. Coating materials have a high adsorption capacity with a fine particle size and provide free flow to the powder. One such example is silica and its various kinds [22]. A recent study on liquisolid tadalafil tablets showed that when silica was used as a coating material, it provided an angle of slide 33°, which is an acceptable powder flow range. All the other parameters of the powder flow were within the required optimal range. Because good flow ensures the best compression, tablets will be efficiently compressed with accepted physical process parameters [23].

This review article highlights the potential of liquisolid technology to overcome challenges related to hydrophobic drugs, such as poor dissolution rate and solubility, which further create reduced and incomplete bioavailability. Although various approaches have been attempted, scaling up in the pharmaceutical industry has proven to be difficult. This article highlights a few important findings to improve hydrophobic drug bioavailability by improving solubility and dissolution rate. From a formulation perspective, it converts clustered hydrophobic drugs into free-flowing and nonadherent powders, facilitating easy compression. Additionally, patient compliance is crucial, as this technique helps formulate a sustained-release dosage form that overcomes complex and multidosing schedules. Therefore, the liquisolid technique is a promising tool for optimizing drug delivery in the pharmaceutical industry.

## 2. Theory/Calculation

### 2.1 Liquisolid Technique

The development of effective delivery systems for hydrophobic drugs is challenging for the industry. Poor solubility, dissolution rate, release kinetics, and photolability are prominent problems associated with most drugs. The liquisolid technique has emerged as an important approach for overcoming these challenges. The liquisolid technique is grounded in the Spirease theory.

#### 2.1.1 Spirease theory

Spirease described a basic mathematical model for motif formulation in a liquisolid system. According to this model, the powder excipients used in a liquisolid system can retain a specified quantity of liquid vehicle, by maintaining efficient flow and compressibility [24]. In addition, this model helps calculate the desired quantity of excipients. Additionally, it is based on flowable and compressible liquid retention potentials (Φ- and Ψ-values, respectively). These parameters are constant for a particular powder/liquid (P/L) admixture. Flowable liquid retention potential (Φ-value) is the maximum part of the liquid vehicle (non-volatile) preserved within the bulk (w/w) while retaining admissible flow. Whereas the compressible liquid retention potential (Ψ-value) is the maximum quantity of liquid vehicle entrapped within the bulk (w/w) while retaining acceptable compression in terms of efficient friability and hardness. This compactness can be explained in terms of a new model known as pactisity theory, which assesses the compaction behavior of powder. The “ratio of carrier and coating material is termed the excipient ratio” denoted by R. mathematically,

$$R = \frac{Q}{q}$$

Where R = ratio of carrier and coating materials

Q = quantity of carrier materials

q = quantity of coating materials

The mathematically flowable liquid retention potential (Φ-value) could be calculated as follows:

$$\Phi - \text{value} = \frac{weight\ of\ liquid\ medication}{weight\ of\ carrier\ material}$$

Acceptable flowability as an application of the liquisolid technique for powders is possible only when a suitable quantity of the liquid vehicle is retained. This property, according to Spirease theory is termed, the liquid load factor and can be defined as the ratio of the weight of liquid medication (drug and liquid vehicle) and the weight of carrier material.

$$Lf = \frac{W}{Q}$$

Where

Lf = load factor

W = weight of liquid medication

Q = weight of carrier material

To produce powder with acceptable flowability, the load factor is determined as follows:

$$^{\varphi}L_{f} = \emptyset + \frac{\varphi}{R}$$

Whereas Ø = flowable liquid retention potential of carrier material

φ = flowable liquid retention potential of coating material

R = excipients ratio

To produce powder with acceptable compressibility, it is determined as follows:

$$^{\Psi}L_{f} = \Psi + \frac{\Psi}{R}$$

Where Ψ is the compressible liquid retention potential for carrier and coating material and R is the excipient ratio.

### 2.1.2 Components, advantages, and disadvantages of the liquisolid technique

Drug candidates must be water-insoluble, slightly, or partially soluble and must be included in classes II and IV of the biopharmaceutical classification system (BCS). Examples include digoxin, clofibrate, loperamide, hydrophobic vitamins, and oils. Using low-dose hydrophobic drugs is beneficial because it requires a smaller quantity of excipients for drying the liquid medication, resulting in lower-weight tablets. This was overcome by the introduction of poly vinyl pyrrolidone (PVP) directly after the addition of the carrier material [25-27]. In addition to hydrophobic entities, in the case of sustained-release formulations, the drug must have a multidosing schedule with a short half-life. The solvents/vehicles used in a liquisolid system must be non-volatile, miscible in water, and inert. Therefore, these compounds must be both edible and biocompatible. Examples include polyethylene glycol (PEG), propylene glycol (PG), Tween-80, Tween-19, Span-80, Span-19, fixed oil, and glycerin [28].

Carrier materials should be porous, easily compressible, and have sufficient absorption capacity. Owing to their porous nature, they provide space for drug particles to be absorbed. Commonly used carrier materials include MCC, starch, lactose, dibasic calcium phosphate, etc. [29-32]. MCC has a specific surface area (SSA) value of 1.18 $m^2/g$ and has been used as a carrier material in immediate liquisolid formulations. According to Javadzadeh et al., when different grades of MCC were used as carriers in the formulation of piroxicam liquisolid tablets, MCC Ph-101 was efficient due to the optimum flowability, compression, and enhanced dissolution rate it provided [33]. The use of starch and lactose is limited due to lower SSA values of 0.6 and 0.37 $m^2/g$, respectively [34]. Compared to that in MCC, Neusilin-grade US2 has a seven-fold higher absorption capacity, thus making it a suitable carrier material for liquisolid systems. Mesoporous silicates are alternative carrier materials because of their high surface area of 1500 $m^2/g$ [35]. Carbamazepine was formulated using the liquid-solid technique with mesoporous silicate as the carrier material [36]. Coating materials have fine particle sizes of 10 nm–4560 mm, providing free-flowing powders by adsorbing drugs not absorbed by carrier materials. Silica is the most commonly used coating material for this purpose. Various types include Cab-o-sil M5 and Aerosil-200. Calcium silicate and neutralin have been used as coating materials [37]. Aerosil-200 has less adsorption capability than that in neusilin; thus, more liquid can be effectively adsorbed using the latter, leading to a reduced tablet weight [38]. Disintegrants are agents that break liquisolid compacts and release drug contents. They are used in rapid-release liquid compacts and are excluded from sustained-release compacts. For hydrophobic drugs, disintegration

significantly affects the dissolution rate. In liquisolid fast-releasing compact disintegrants used are sodium starch glycolate, croscarmellose sodium, starch (pre-gelatinized), and cross-povidone [39].

Liquisolid-based techniques have several advantages over other methods. First, they enhance the bioavailability of hydrophobic drugs by converting liquid medications (drug solutions/dispersions) into free-flowing powders with good compression. Such hydrophobic drugs lie within non-volatile solvents that diffuse well in contact with water. Therefore, the whole drug cargo is released with a small particle size compared to that in the conventional form; therefore, small-sized drug cargo and its high wettability offer a greater dissolution rate and consequently high bioavailability [40]. Drug release can be modified using this technique because the main components of this technique are the carrier and coating materials, as discussed in Section 2.2. Therefore, using materials with sustained-release kinetics, drug release can be easily controlled and sustained through the liquisolid technique. Furthermore, photo-unstable drugs can be protected from light using this technique. Moreover, it involves the use of photo-protective coating materials, such as titanium, that protect photosensitive drugs from the effects of light [41, 42]. Soft gelatin capsules are expensive; therefore, instead of putting oily drugs within soft gelatin capsule shells, oily drugs can be easily converted into free-flowing powder for compression purposes. This indicates that the liquisolid technique is cost-effective. Moreover, sophisticated machinery is not required and can be easily scaled up as an industrially applicable process. The liquisolid technique, in addition to its advantages, poses certain limitations. Additionally, it requires non-volatile water-miscible solvents, and reliance on such solvents poses toxicity, interactions, and stability issues. This technique is mostly applicable to low-dose hydrophobic drugs; high doses are a limitation because of their low drug-loading capacity. Furthermore, high-dose hydrophobic drugs require large quantities of carrier and coating materials, and sometimes the weight of the dosage form crosses the official limit.

## 2.2 Pharmaceutical applications of liquisolid technology

### 2.2.1 Enhancing drug dissolution rate

In liquisolid compacts, the drug is entrapped in liquid form within the powder, indicating a molecularly dispersed state of the drug. When the compacts are exposed to dissolution media, the

solvent present in the system is reduced, and the interfacial tension and reduced size of the drug particles (molecularly dispersed state) provide more wetting surface area. Both of these properties result in higher dissolution rates [43, 44]. In addition, the concentration of the liquid vehicle used in the liquid-solid system plays a crucial role in enhancing the dissolution rate. In this regard, the drug-to-vehicle ratio was evaluated for dissolution rate enhancement in a previous study. An increase in the concentration of the liquid vehicle versus the drug concentration significantly enhances drug release from the liquisolid system. In addition, the pH and volume of the dissolution medium significantly influence drug release from the liquisolid system [45]. The increase in the dissolution rate is shown in Fig. 1.

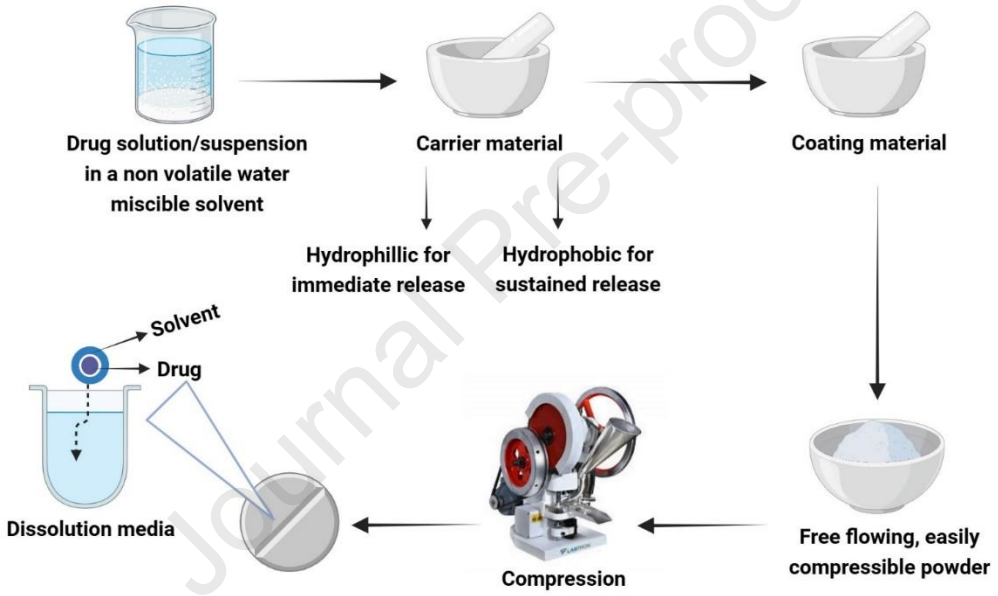


Fig. 1. Effect of the liquisolid system on dissolution rate enhancement and drug release from the liquisolid system

The addition of liquid medicament (water-miscible solvent/non-volatile) to the carrier material results in wet mass production. The selection of carrier material is based on the desired drug release profile. The production of wet mass means the drug is not fully absorbed by the carrier; therefore, additional coating materials are added that adsorb the excess drug particles, resulting in free-flowing powder. When exposing such liquisolid system to dissolution media, the non-volatile solvent used reduces the interfacial tension between the drug surface and dissolution

media and abruptly releases the whole drug into the dissolution media, resulting in an enhanced dissolution rate.

In previous studies, drugs whose dissolution increased included hydrocortisone; the drug release rate and fraction of molecularly dispersed drugs were higher than those of conventional tablets [46]. Rofecoxib exhibited 90% cumulative drug release compared to 78% for conventional tablets [47] and the glyburide dissolution rate was 99.71% after 15 min as compared to 67.74% for conventional tablets [26], whereas carvedilol liquisolid tablets exhibit 21% greater drug release than in the marketed dosage form [48]. In contrast, the dissolution rate enhancement of the high-dose hydrophobic drug carbamazepine was discussed in a previous study [49]. When certain additives, such as polyvinyl pyrrolidone and hydroxypropyl methylcellulose, were used in the liquisolid system, owing to their higher absorption capacity, the tablet weight decreased significantly with an enhanced dissolution rate. Hentzschel et al. have used neusilin as an advanced carrier to overcome this problem. Recently, Felodipine liquisolid pellets were prepared at a higher dissolution rate [50].

According to the liquid-solid technique principles, a drug that is highly soluble in a liquid vehicle will exhibit a higher dissolution rate and vice versa, as discussed earlier. When the concentration of Tween-80 was increased from 1 to 4, the dissolution rate increased (LS10 and LS11). In other formulations, such as LS7 and LS9, a drop in the dissolution rate enhancement compared to LS11 was due to the lower solubility of the drug in the vehicle, justifying the associated effect. pH and volume of the dissolution medium affected the dissolution rate of the liquisolid system. Drugs with greater solubility at a higher pH will have a greater dissolution rate, and vice versa. At a higher pH (6.8), the associated drug exhibited higher solubility and, hence, a greater dissolution rate. However, in a few cases, variations in the volume of the liquid vehicle can cause fluctuations in the dissolution rate.

### 2.2.2 Improving bioavailability

The high drug dissolution rate associated with the liquisolid system ultimately leads to high bioavailability. For instance, hydrochlorothiazide liquid compacts in male beagle dogs showed 15% more bioavailability compared to their marketed conventional dosage form [51]. Better bioavailability results were obtained from the study conducted by Badaway et al. [52]. Male diabetic Swiss albino mice were exposed to pioglitazone liquid compacts. Blood glucose levels

were reduced due to the high bioavailability of pioglitazone formulated using the liquisolid technique [53]. The enhanced drug bioavailability of ritonavir was observed compared with that of its conventional dosage form [54].

### 2.2.3 Providing efficient flow ability and compressibility

Fickle, erratic, and giddy powder flows are the main problems at industrial levels. Liquid systems overcome this problem by producing a nonadherent, freely flowable, and readily compressible powder. This can be achieved by mixing the liquid medication with a biocompatible carrier and a coating material. Silica (a coating material) is responsible for efficient flow because of its fine particle size, whereas MCC (a carrier material) supports compression.

### 2.2.4 Liquisolid technique as a tool for photostability of light-sensitive drugs

Photodegradation of light-sensitive drugs produces toxic moieties, resulting in severe side effects. Therefore, photostability studies are an important part of pre-formulation trials. This liquid technique has the potential to protect photosensitive drugs from the destructive effects of light because it involves the incorporation of silicon dioxide and titanium dioxide as coating materials. Both the excipients can diffract light of various energies because of their high refractive indices. Amlodipine, a light-sensitive drug, was formulated using the liquisolid technique with Avicel Ph-101 as a carrier material and silicon dioxide and titanium dioxide (alone and in combination) as coating materials. The liquisolid formulation, conventional formulation, and active drug were irradiated with ultraviolet A (UVA) and UVB light. Results showed that the coating materials from the liquisolid formulation successfully protected the drug from light; the residual drug content was 97% after 8 h of irradiation compared to 74% of the active drug [26, 55]. This indicated that the liquisolid technique can be effectively used to protect light-sensitive drugs. Titanium dioxide's role as a photoprotective agent in the liquisolid system is shown in Fig. 2.

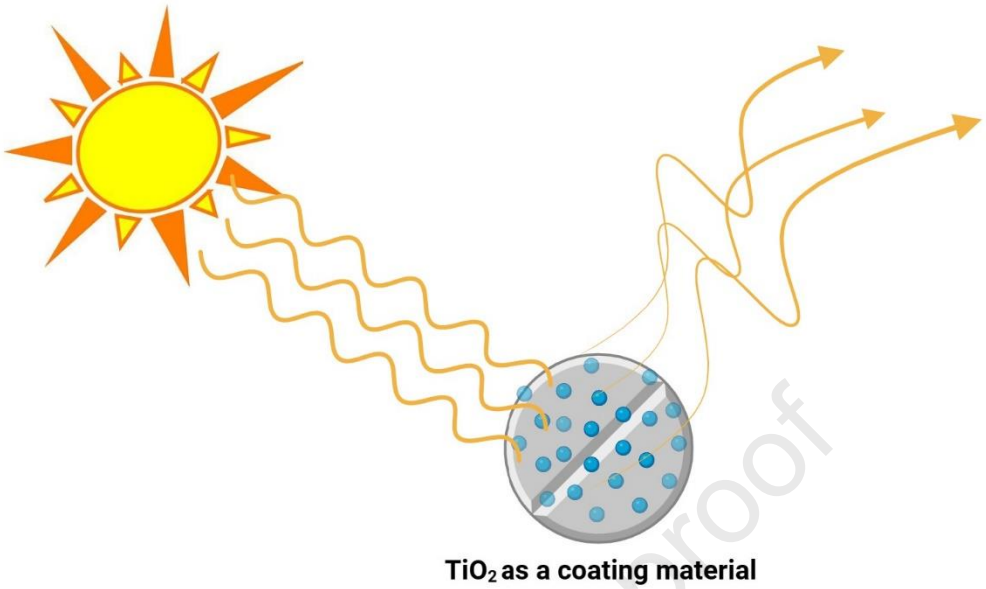


Fig. 2. Mechanism of photostability in solid dosage form provided by liquisolid technique

As illustrated in Fig. 2, $TiO_2$ deflects photo radiation from the surface of the dosage form when used as a coating material in liquisolid tablets/compacts due to its high refractive index, consequently protecting the photosensitive drug from degradation.

### 2.2.5 Liquisolid technique as a tool for controlling pH-triggered variations in drug release

The ionization constant (pKa) of a compound and the pH of the local environment are two basic parameters that depend on the solubility of weak acids and bases. Therefore, gastrointestinal pH has a significant influence on the dissolution rate, hence the bioavailability of weak acids and bases. Disturbances in this scenario lead to fluctuations in drug bioavailability and ultimately therapeutic outcomes [56, 57]. The release of loratadine was first assessed by minimizing the effect of pH variation using a liquisolid technique. In the formulation of liquisolid tablets, loratadine was dispersed in propylene glycol (PG), absorbed by MCC, and coated with colloidal silica. The compressed tablets were subjected to dissolution in media with pH values of 1.2, 2.5, and 5. The results showed that the dissolution rate of the hydrophobic drug was higher than that of conventional commercial tablets, independent of pH variation [58]. This clearly shows that the liquisolid technique can be effectively used to reduce pH-triggered variations. The optimal formulation of telmisartan showed a higher dissolution rate than that in the conventional form,

irrespective of pH variation [59]. In a recent study, Badawy et al. fabricated mosapride liquisolid compacts and observed that their release was not influenced by pH variations [60].

### 2.2.6 Liquisolid technique as a tool for sustained release formulations

Sustained-release dosage forms release drugs at a predetermined rate compared to the burst release of conventional dosage forms. Therefore, an important benefit is patient compliance by reducing the multidosing schedule and avoiding unwanted side effects related to conventional dosage forms burst effect [61]. A plethora of methods for preparing sustained-release dosage forms exist, among which controlling the dissolution rate is of prime importance because of its cost-effectiveness and ease of preparation [62]. As the liquisolid technique is a dissolution-controlling process, it can be effectively used for sustained-release dosage form, resulting in zero-order release kinetics.

In addition to retarding the dissolution rate of hydrophobic drugs, the liquisolid technique retards the dissolution rate of hydrophilic drugs. As the main technique for hydrophobic drugs, hydrophilic drugs can benefit from it and can be formulated in a sustained release form, as carried out for propranolol HCl [43]. Trimetazidine 2-hydrochloride is another water-soluble drug formulated in sustained-release form using the liquisolid technique [63]. In our previous study on aceclofenac liquisolid sustained-release tablets, Eudragit (methacrylic acid) grade RL and RS were used as coating materials because they are hydrophobic and possess a lower surface area (lower wettability) than MCC, thus retarding drug release [64]. The entire mechanism is illustrated in **Fig. 3**.

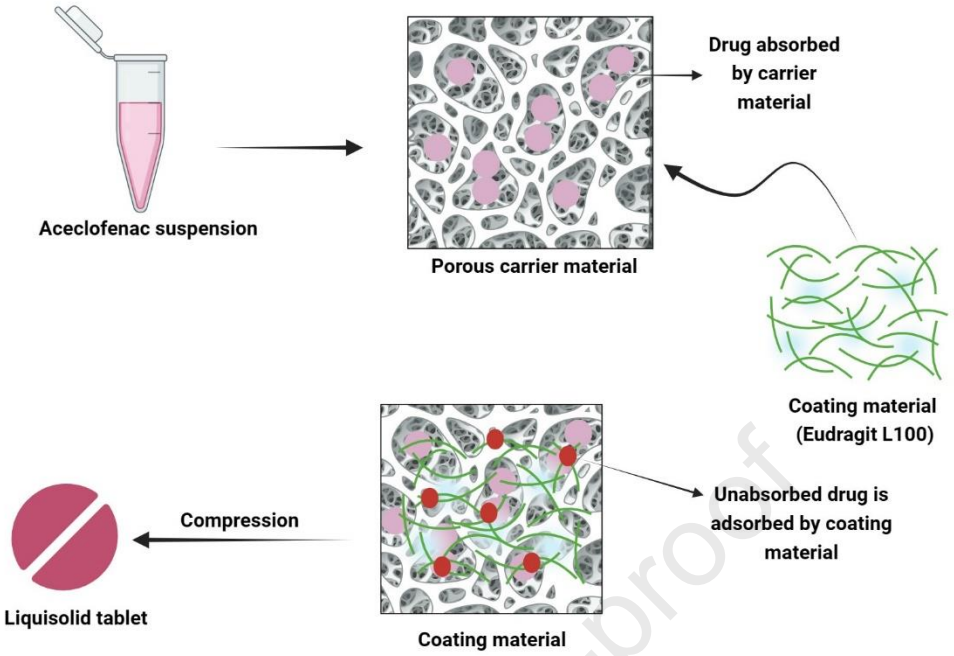


Fig. 3. The role of Eudragit (methacrylic acid) during a liquisolid sustained-release formulation

As illustrated in Fig. 3, the absorbed drug within the porous carrier material remains intact, whereas the unabsorbed drug is adsorbed by methacrylic acid (Eudragit L100). The drug is slowly released from the porous carrier and hydrophobic coating material, resulting in sustained release kinetics.

In contrast, hydrophilic carriers, such as hydroxypropyl methylcellulose (HPMC), form a swellable matrix system, and drug release is ensured through small channels in the carrier. The non-volatile solvent used in the preparation of liquid medication has a significant effect on drug release from the matrix. For example, PEG 600 showed the slowest release because of soft and lost compacts. Conversely, Tween-80 formed compacts with acceptable breakage and efficient powder flow [65, 66]. Liquid vehicles with higher drug solubility are used for dissolution enhancement, whereas solvents with lower solubility are used to sustain drug release [44]. Liquid vehicles maintain polymer porosity by reducing the glass transition temperature (Tg) of the polymers. If Tg increases, the porosity of the polymer decreases and tortuosity increases, hindering drug release. Using a high concentration and quantity of HPMC (greater R-value) could retard drug release. The R-value (carrier-to-coating material ratio) should not increase significantly as it increases the tablet weight, which cannot be swallowed. In a recent study, the

liquid vehicle most commonly used in sustained-release dosage form was Tween-80, and the mechanism behind its retarded release was the reduction in the glass transition temperature of the polymer. A few of the drugs formulated for sustained release are listed in **Table 1**.

Table 1. Preparation of sustained release formulations through the liquisolid technique

| Drug | Solvent | Carrier material | Coating material | References |
|---|---|---|---|---|
| Trandolapril | PEG-400 | HPMC | Colloidal silica | [67] |
| Trimetazidine 2HCl | Tween-80 | MCC | Eudragit L100 | [63] |
| Tramadol HCl | Propylene glycol | MCC | HPMC | [68] |
| Propranolol HCl | Tween-80 | Eudragit L100 | Colloidal silica | [69] |
| Griseofulvin | Synperonic PE/L61 | MCC | Cab- O –sil M5 | [70] |
| Venlafaxine HCl | Tween-80 | Eudragit L100 | Colloidal silica | [71] |
| Theophylline | Polysorbate-80 | Eudragit L100 | Colloidal silica | [72] |

## 3 Material and Methods

### 3.1 Preparation of tablets through the liquisolid technique

During the preparation of liquisolid tablets, the drug was dissolved or dispersed in a liquid vehicle to form a solution or suspension, respectively. The resulting solution or suspension was incorporated into an accurately weighed carrier material in a mortar and triturated. The resulting wet mass was spread on the sidewalls of the mortar and kept stable to completely absorb the liquid vehicle. Then, the crispy and moist layers were scratched using a spatula, and the coating materials were added and uniformly blended using a pestle. Other necessary excipients were added, mixed, and compressed into tablets using a tablet compression machine [73]. The type of solvent has a significant effect on the dissolution rate of hydrophobic drugs. Solvents with higher solubility resulted in higher dissolution rates, and vice versa. Similarly, higher dissolution was observed when MCC and colloidal silica were used as carrier and coating materials, respectively. These arguments can be justified by the dissolution profiles of various drugs available in the literature, as shown in **Table 2**.

Table 2. Drug candidates formulated through the liquisolid technique with immediate release kinetics

| Drugs | Solvent | Carrier material | Coating material | Reference |
|---|---|---|---|---|
| Famotidine | Propylene glycol | MCC | Colloidal silica | [74] |
| Loperamide | Propylene glycol | MCC | Colloidal silica | [66] |
| Carvedilol | Polyethylene glycol | MCC | Colloidal silica | [48] |
| Curcumin | Polyethylene glycol | MCC | Colloidal silica | [75] |
| Telmisartan | Polyethylene glycol | MCC | Colloidal silica | [46] |
| Spironolactone | Polyethylene glycol | MCC | Colloidal silica | [76] |
| Nimesulide | Polyethylene glycol | MCC | Silica gel | [77] |
| Furosemide | (9Z)-9 octadecenoate | MCC | Fumed silica | [78] |
| Risperidone | Tween-80 | MCC | Colloidal silica | [79] |
| Prednisolone | Propylene glycol | MCC | Amorphous silicon dioxide | [80] |
| Carbamazepine | Polyethylene glycol-200 | Neusilin /MCC | Colloidal silica | [81] |
| Baclofen | Propylene glycol | MCC | Colloidal silica | [82] |
| Itraconazole | PEG-600 | MCC | Colloidal silica | [83] |
| Olmesartan | Tween-20 | Neusilin | Colloidal silica | [84] |
| Domperidone | Tween-80 | Fujicalin | Cabosil M-5 | [85] |
| Naproxen | Cremophor EL | MCC | Cabosil M-5 | [86] |
| Bromhexine HCl | Propylene Glycol | MCC | Colloidal silica | [87] |
| Valsartan | Propylene Glycol | MCC | Colloidal silica | [88] |
| Amlodipine | Propylene Glycol | MCC | Colloidal silica | [89] |
| Piroxicam | Tween-80 | MCC | Colloidal silica | [90] |

| Drugs | Solvent | Carrier material | Coating material | Reference |
|---|---|---|---|---|
| Ketoconazole | PEG-400 | MCC | Amorphous silica | [91] |
| Embelin | Caproyl | Neusilin | Colloidal silica | [92] |

The mechanistic approach behind the higher drug release is attributed to the following reasons:

3.1.1 Increasing surface area

In the liquisolid system, the drug is dissolved or dispersed in a non-volatile solvent; therefore, the drug is entrapped in a molecularly dispersed state. The reduced particle size of the drug provides a greater surface area for the dissolution process. Therefore, the dissolution rate was higher than that of micronized drug particles in the conventional dosage form. Similarly, when the solubility limit increases, the percentage of undissolved drugs increases, leading to decreased drug release [93]. Regarding drug dissolution, the spirease theory focuses on a portion of molecularly dispersed drugs ($F_M$). The release rate of hydrophobic drugs is directly proportional to the concentration of molecularly dispersed drugs. Mathematically, $F_M$ is the ratio of the solubility of a drug ($S_d$) to the actual drug concentration ($C_d$) in a nonvolatile solvent [94].

$$FM = \frac{Sd}{Cd}$$

When drug solubility is greater than or equal to the actual concentration of the drug in a non-volatile solvent, $F_M$ tends to unity.

$F_M = 1$, when $S_d \geq C$

3.1.2 Increasing aqueous solubility

The quantity of non-volatile solvents used in liquisolid systems is minimal. This minute quantity is responsible for the overall drug solubility. However, at the solid–liquid interface between the dissolution media and drug particles, this lower amount of liquid vehicle carries the whole drug and is thus effective in enhancing aqueous solubility as a co-solvent [95].

3.1.3 Enhancing wetting properties

The liquid vehicle used in the liquisolid system acts as a surfactant to reduce the interfacial tension between the tablet surface and the dissolution media. This was further confirmed by determining contact angles. A drop of water of approximately 2 µL was poured on a tablet surface, and the image was clicked. Subsequently, the angle of the drop on the tablet surface was determined [74]. Contact angles of less than 90° indicate high wettability [96]. Liquisolid tablets usually have lower contact angles (<90°) than that in conventional tablets. The comparative contact angles are shown in **Fig. 4**.

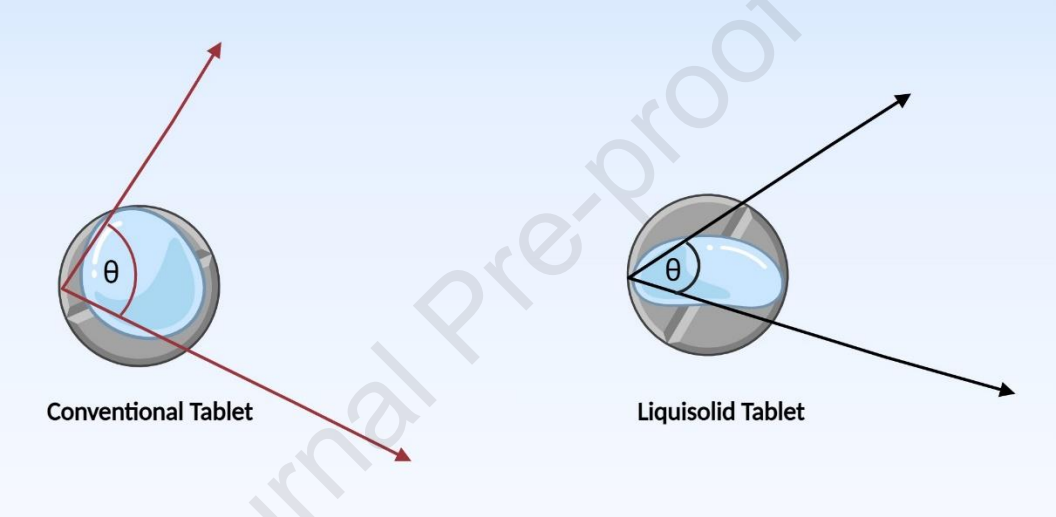


**Fig. 4.** Comparative contact angle of conventional and liquisolid tablets

As illustrated in Fig. 4, liquisolid compacts reduce the interfacial tension between liquid media and the contact surface due to the presence of a non-volatile water-miscible solvent. Consequently, the media "spread over" and results in a lower contact angle. On the contrary, conventional tablets, due to unfavorable interactions, show low adhesion on the contact surface with a "bead up" phenomenon and a higher contact angle.

## 4 Results

### 4.1 Pre-compression evaluation

Pre-compression evaluation of liquisolid systems is crucial because flowability and wettability are two basic parameters at the industrial level. If this evaluation is not performed, problems may arise during compression and physical processes at the process level.

Before the preparation of the liquisolid system, drug solubility was determined in various water-miscible non-volatile solvents. Saturated solutions were prepared, centrifuged, sonicated, and analyzed. The solubility was determined from the results of a specific analysis tool [57]. Solvents with greater drug solubility are used for dissolution rate enhancement, while solvents with lower solubility are used for sustained-release formulations [97]. The angle of the slide shows the flowability of the carrier material and hence represents the overall flowability of the powder. To determine this angle, an accurately weighed quantity of the carrier material is transferred onto the surface of a polished and smooth metal piece. Moreover, it is raised and tilted slowly until the powder starts to flow downward. At this stage, the angle formed between the metal piece and the horizontal surface is termed the angle of the slide. An acceptable powder flow is $33^{\circ}$ [98]. Flowable liquid retention potential determination (Φ-value) investigates the quantity of liquid vehicle required for the carrier and coating material to produce powder with acceptable flowability and compression. According to Naik et al., the incorporation of liquid medication into the carrier material changes the behavior of the powder and provides a smooth flow [46]. Liquisolid compressibility is performed to investigate compressible retention potential. During the liquisolid compressibility test (LCT), different co-mixtures of carrier and coating materials and liquid-powder co-mixtures were prepared. These were subjected to different physical tests, such as sponge index and hardness tests, to ensure efficient compression. This will ultimately help in the determination of the Ψ-number [46].

The load factor plays an important role in the liquisolid system because if the quantity of non-volatile solvent exceeds the desired range, then the liquisolid system cannot be compressed into tablets owing to the squeezing-out phenomenon. The factor is calculated by dividing the weight of the liquid medication by the weight of the carrier coating material admixture [99]. The angle of repose is determined using the fixed funnel method for liquisolid powders. The powder is dropped from a fixed height to form a heap on the surface. The angle of the heap concerning the horizontal surface was determined. The determination process is repeated three times and the average angle of repose was determined.

$$Tan\ \theta = \frac{h}{r}$$

where h is the height from which the powder is dropped, and r is the radius of the heap [100].

An accurately weighed quantity of liquisolid powder was poured into a graduated cylinder, and the volume occupied was observed visually. This bulk density (usually in g/mL) is termed the initial bulk density ($D_{Bi}$). Simultaneously, the graduated cylinder was tapped several times, and the volume occupied after tapping was observed. This is the tapped density, known as the final bulk density ($D_{Bf}$) [101].

Carr's compressibility index and Hausner's ratio were calculated from the bulk and tapped densities using the following equations:

$$carr's\ compressiability\ index\ (\%) = \frac{bulk\ density - tapped\ density}{bulk\ density} \times 100$$

$$Husner's\ ratio = \frac{bulk\ density}{tapped\ density}$$

The active drug, excipients, physical mixture of drug excipients, and liquisolid system were subjected to X-ray diffraction (XRD). A drug in its amorphous or molecularly dispersed state has a higher dissolution rate and solubility than its crystalline or micronized forms. The amorphous form of the drug was confirmed by the absence of characteristic peaks in the liquisolid system. Differential scanning calorimetry (DSC) studies were performed on the drug, excipients, and liquisolid system to identify possible drug-excipient interactions. In addition, we investigated whether the drug in the liquisolid system exists in solution form (a molecularly dispersed state). This was confirmed using the DSC thermogram, in which the drug characteristic peak did not exist [66], and Fourier-transform infrared spectroscopy (FTIR) studies indicated drug-excipient chemical interactions. The presence of characteristic drug peaks in the liquisolid system and the absence of additional peaks confirmed the lack of chemical drug interactions. FTIR studies showed the functional groups of drugs used in liquisolid systems and bond stretching and vibrations [102]. Scanning electron microscopy (SEM) is a tool that shows the presence or absence of crystals in a drug (morphological characteristics). If drug crystals were observed, they

were not solubilized. The absence of drug crystals indicated that the drug was in a molecularly dispersed state within the bulk powder, resulting in a greater dissolution rate [103].

### 4.2 Post-compression evaluation

Resistance to external mechanical shock is mandatory for tablet dosage forms. Hardness and friability tests have shown that liquisolid tablets are capable of shipping, blistering, and resisting breakage during the process [2]. Similarly, disintegration time is directly related to drug dissolution. If a drug disintegrates quickly, it is expected to have greater dissolution, and vice versa. Sustained-release liquisolid tablets are not exposed to disintegration time but to the dissolution process. A content uniformity test showed that each core unit had the desired drug strength. This ensured that the drug was uniformly distributed within the liquid tablets. The applied limit should be within the official range [6, 104]. Dissolution studies were performed for both the fast and sustained release of the liquisolid tablets. The method adopted should be based on an official specification or should be self-validated. A recent study using the liquisolid technique revealed that when the concentration of the drug in the liquisolid system was low, it exhibited a rapid dissolution rate [46]. Higher drug concentrations of carbamazepine were observed to have less pharmacological activity against convulsions because the drug precipitates in the solvent, leading to a low comparable dissolution rate and systemic availability [105]. Stability studies of various drugs formulated using the liquisolid technique showed that the liquisolid system was stable under harsh humidity and temperature conditions. These conditions did not affect the release profile or physical process parameters of the dosage form.

Therefore, many drugs whose dissolution rates have been enhanced using the liquisolid technique are available in the literature. A few drugs have been formulated using the liquisolid technique to enhance the dissolution rate.

Itraconazole is an antifungal agent used to treat fungal infections because of its hydrophobicity. According to research work on itraconazole, the liquisolid formulation of the model drug showed a higher dissolution rate (90.73%) as compared to that in conventional tablets. Famotidine is a poor water-soluble H-2 receptor blocker used to treat gastric and intestinal ulcers. The optimized liquisolid formulations of Famotidine showed a greater dissolution rate (78.36%) during the

initial 10 min, which was 39% higher than in the conventional form. *In vivo* studies showed no significant variation compared to that in the marketed conventional form. Norfloxacin is controversial in the literature regarding liquisolid techniques. Norfloxacin is a biopharmaceutical classification system (BCS) class IV (low solubility and low permeability) fluoroquinolone antibacterial drug. As expected, its dissolution was not enhanced by the liquisolid technique. This was attributed to the interaction of the liquid vehicle with the drug, which resulted in the formation of interacting layers. Moreover, the zwitterionic structure of the model drug was mainly responsible for its lower release [106]. The liquisolid technique has been successfully employed in traditional Chinese medicine. Tanshinone II-A is a traditional Chinese medicine with low water solubility used to treat cancer and cardiovascular diseases. The liquisolid technique was used for dissolution enhancement, which provided improved results compared to that in the conventional form. The dissolution rate was directly proportional to the dissolution of the liquid-phase solvent [107]. Atorvastatin calcium is a BCS class II antihyperlipidemic drug with low solubility and permeability. Moreover, its poor systemic availability was assumed based on *in vitro* dissolution studies using the liquisolid technique. The dissolution rate was 47.47% higher than that of conventional tablets [108]. Rofecoxib is a poorly soluble nonsteroidal anti-inflammatory drug. The liquisolid formulations showed 25% more drug release than that in commercial tablets *in vitro*, which was directly proportional to the excipient ratio. Increasing the quantity of the carrier material improved the dissolution rate. The Rofecoxib flowability issue was overcome by the addition of 10% cab-o-sil [109]. Candesartan cilexetil is a hydrophobic anti-hypertensive agent. XRD and SEM studies of the liquisolid formulations showed that the drug was in a molecularly dispersed state due to its higher dissolution rate (90%) than that of conventional tablets (35%) after 30 min [110]. The dissolution profile of the hydrophobic ketoprofen was enhanced using the liquisolid technique. The formulation was optimized using a Box–Behnken design. The optimized formulation showed a 100% dissolution rate [111]. Spironolactone, a hydrophobic drug, was formulated using the liquisolid technique with three different solvents as liquid vehicles. The dissolution rate of the liquisolid compacts was significantly ($P<0.05$) higher than that of the commercially available dosage form and pure drug. They observed that using a combination of liquid vehicles resulted in a higher dissolution rate [112]. The liquid technique successfully improved the furosemide dissolution rate. The optimal formulation with a 50% loaded drug concentration exhibited a 90% dissolution rate as compared

to 65% of its conventional form [113]. The optimal liquisolid formulation of simvastatin sustained-release showed 89% drug release at the end of 24 h. The optimal formulations were fitted using various kinetic models. The best-fit model was the Korsmeyer–Peppas model, which showed the mechanism of mass transfer (n>0.5) [114]. In their study, Korsmeyer–Peppas reported that glycerol and Eudragit efficiently improved the dissolution rate of hydrophobic drugs. Trandolapril is an antihypertensive drug with 4–9% bioavailability due to its poor water solubility. Trandolapril liquisolid plane and sustained-release formulations were subjected to *in vitro* dissolution experiments. The planar liquisolid tablets showed a 94% dissolution rate after 2 h processing, while the sustained-release formulation sustained the drug release up to 97% within 14 h, following the Peppas model of drug release kinetics (n = 0.9) [115]. Thus, the liquisolid technique has the potential to sustain the release of hydrophilic drugs. Trimetazidine is a hydrophilic drug processed using the liquisolid technique. The drug release was sustained using different polymers as carrier materials. Drug release was best sustained using Eudragit L100. The author investigated whether using Eudragit L100 as a carrier along with polysorbate-80 as a liquid vehicle effectively retarded drug release [63]. Tramadol is a water-soluble compound, and its drug release was retarded using propylene glycol as a liquid vehicle and HPMC as a coating material. The Peppas model was the best fit for drug release from tramadol HCl. Propranolol hydrochloride was dispersed in polysorbate-80 and incorporated into a binary mixture of Eudragit L100 and RS-100 as carrier polymers. A reduction in the glass transition temperature of the polymer by the liquid vehicle (polysorbate-80) was the main reason for drug retardation in the liquisolid compact. Griseofulvin was formulated using the liquisolid technique with three liquid vehicles. The performance of the liquid vehicle, drug concentration, and excipient ratio were the primary parameters evaluated. The selection of the solvent was based on drug solubility in that particular solvent. Cremophor EL was used as a liquid vehicle to enhance the dissolution rate and overcome the intestinal efflux transportation problem (a P-glycoprotein inhibitor). The drug release was affected when the excipient ratio was altered. In contrast, Kollicoat SR 30D was used as a liquid vehicle for sustained-release formulations with a high drug concentration, oozing out through a diffusion mechanism from the matrix. In this study, the griseofulvin dose could not be reduced after dissolution rate enhancement; however, it could be retarded, resulting in a liquisolid sustained-release formulation of griseofulvin. Therefore, all the above model drugs were formulated using the liquisolid technique, and their *in vitro* dissolution studies showed that

hydrophobic drugs efficiently benefit from the technique; thus, the liquisolid technique can be employed to enhance their dissolution rate.

### 4.3 *In vivo* studies

Liquisolid compacts were evaluated in animal models to determine the bioavailability of hydrophobic drugs. The pharmacokinetic parameters obtained from *in vivo* studies were compared with that of conventional marketed dosage forms, which showed a significant improvement in bioavailability [116]. In this context, itraconazole is an antifungal class II BCS drug that exhibits poor solubility and bioavailability. Itraconazole tablets were prepared using PEG 600 as the vehicle, HPMC as the carrier, and Aerosil 200 as the coating agent. The resultant formulation showed a significantly higher dissolution rate in 90 min, with a higher $C_{max}$ and $AUC_{0\text{-}24}$, showing its enhanced bioavailability after oral administration [83]. Conventional hydrochlorothiazides have poor systemic availability. To overcome this problem, hydrochlorothiazide was formulated as a model drug using a liquid technique. The *in vivo* evaluation of the model drug was conducted in beagle dogs (n = 6) using a two-way crossover design. Results showed that drug-liquisolid compacts exhibited 15% greater bioavailability than hydrochlorothiazide conventional counterparts [117].

Furthermore, liquisolid tablets, mosapride citrate, were formulated through factorial design experiments. Based on drug solubility studies, propylene glycol was selected as the vehicle, whereas MCC and colloidal silicon dioxide were used as the carrier and coating materials, respectively. The results showed enhanced oral bioavailability and pharmacokinetic parameters of the liquisolid technique. The $C_{max}$ values were 45.86 ± 3 ng/mL and 35.38 ± 4.52 ng/mL, the $T_{max}$ values were 0.5 ± 0 h and 0.71 ± 0.1 h, $AUC_{0-12}$ were 162.12 ± 9.62 and 133.77 ± 22.79 ngh/mL for liquisolid and commercial tablets, respectively. The oral *in vivo* bioavailability of model drug liquisolid tablets in human volunteers was 121.20% compared to that in commercial products [60]. Fexofenadine liquid tablets were prepared using propylene glycol or Cremophor EL as the drug vehicle, MCC as the carrier, and silicon dioxide as the coating material. The drug concentration used was 30–40% w/w, and the prepared formulations were evaluated for pharmacokinetic parameters in 18 healthy volunteers relative to Allegra tablets. The *in vivo* results showed $C_{max}$ values of 221.95 ± 34 ng/mL and 179.083 ± 27 ng/mL, $T_{max}$ values were 2.16 ± 0.4 h and 2.66 ± 0.5 h, and $AUC_{0\text{-}\infty}$ were 2640.19 ± 1830 and 1628 ± 928.47 ngh/mL for

liquisolid and commercial tablets, respectively. Overall, fexofenadine liquisolid tablets showed an increased bioavailability of 62% by reducing $T_{max}$ 2.16 h as compared to that by Allegra marketed tablets [118].

Meloxicam is a cyclooxygenase (COX) inhibitor and non-steroidal anti-inflammatory drug (NSAID) with poor solubility and dissolution rate challenges. Moreover, its solubility was evaluated in multiple solvents, including propylene glycol, glycerin, and polyethylene glycol 400. Based on the solubility results, polyethylene glycol 400 was selected as the non-volatile water-miscible vehicle, MCC as the carrier, and silicon dioxide as the coating material for the fabrication of liquisolid tablets. The *in vivo* activity and pharmacokinetic parameters of meloxicam liquisolid tablets were evaluated in male albino rats. The $C_{max}$ and $AUC_{0-\infty}$ were 1.09- and 1.2-fold higher than the marketed product, respectively. $T_{max}$ was less than that of the marketed product and higher than that of the pure drug. This indicated that the liquisolid technique can be efficiently used to enhance the bioavailability of hydrophobic meloxicam [119]. In the context of bioavailability enhancement to improve dissolution performance, pioglitazone was formulated as liquisolid tablets using the QbD approach with polyethylene glycol 400 as the liquid vehicle, MCC as the carrier, and silicon dioxide as the coating material. To evaluate the antidiabetic and *in vivo* pharmacodynamic activities, an optimal formulation was administered to diabetic and normal male Swiss albino mice. Compared with that in marketed alloxan tablets and plain pioglitazone, the liquisolid tablets of pioglitazone showed a significant ($p<0.001$) reduction in blood glucose levels. These results suggest that liquisolid tablets reduce blood glucose levels more than that in conventional tablets and pure drugs, thus enhancing their antidiabetic activity [120].

In addition to chemical drugs, nutraceuticals have been fabricated into liquisolid tablets and evaluated for their *in vivo* activity. Chronic renal failure (CRF) is a life-threatening condition with a wide spectrum of mortality and morbidity. The walnut extract is a suitable alternative, exhibiting renoprotective and antioxidant properties. However, it has poor bioavailability. To overcome this issue, walnut extract liquisolid compacts were fabricated using PEG 400 and Tween 80 as liquid vehicles, MCC as the carrier, and silicon dioxide as a coating material. The prepared system was evaluated using the CRF rat model. At doses of 50 and 100 mg/kg, the tablets significantly increased appetite and weight gain. In addition, renal function, antioxidant

activity, and oxidative stress were significantly improved [121]. Curcuma comosa is a Thai medicinal herb that exhibits estrogen-like effects and various pharmacological activities. However, its hydrophobic nature hinders efficient bioavailability. The optimized formulation was obtained at a ratio of 10 between the carrier and coating materials by adding PVP to slow its immediate release. *In vivo* pharmacokinetic evaluation performed in rabbits showed higher bioavailability compared to its administration in the conventional form [122].

Boswellia carterii is an ancient Egyptian medicine with anti-inflammatory activities. Liquisolid compacts were formulated using polyethylene glycol 400, MCC, and silicon dioxide as a vehicle, carrier, and coating material, respectively. The drug concentration (20 and 40%) was administered to a rat model, and the biological activity was compared to that in marketed indomethacin. Anti-inflammatory and anti-ulcerogenic effects were investigated in the rat model. A liquisolid formulation of the biologically active fraction was prepared and used in rats, and anti-gastrointestinal ulcerative and anti-inflammatory effects were investigated in the rats. Proposed drug-loaded liquid tablets showed greater efficacy, safety, and a longer duration of action than those in indomethacin [123]. In summary, all the results obtained from the *in vivo* evaluation of liquisolid compacts showed promising potential for bioavailability enhancement.

## 5 Discussion

### 5.1 Orodispersible liquisolid formulation

Recently, the liquisolid technique was combined with an osteodispersible drug delivery system. The benefit of a mixed-up strategy is that it improves patient compliance and boosts the bioavailability of hydrophobic drugs [124]. Felodipine was the first hydrophobic drug to be explored for this purpose. The formulation was optimized using a factorial design after evaluating various variables. The *in vivo* pharmacodynamic study of liquisolid orodispersible tablets showed a higher absorption rate than that in soft gelatin capsules filled with a felodipine solution under the same conditions and was investigated in human volunteers [125]. Chlorzoxazone is a sedative muscle relaxant that undergoes first-pass hepatic metabolism, which leads to poor bioavailability. Orodispersible liquid tablets were prepared and compared with formulations produced using co-processed excipients. The *in vitro* D-time was 25.42 s, whereas the *in vivo* D-time was 18.10 s in six volunteers [126]. This shows that the liquisolid technique can be effectively used by special groups (pediatrics and geriatrics) as a new-generation dosage

form. However, the liquisolid technique does not support palatability compared to the technique using co-processed excipients. Zolmitriptan is used to treat emergency pain associated with migraines. Orodispersible liquid tablets were prepared, and cross-povidone was observed to be the best super-disintegrant. D-time for optimal liquisolid formulation was 24 s, while 95.2% of the drug was released within 2 min, with satisfactory physicochemical properties and stability studies [127]. The liquisolid technique could be successfully used for the oral delivery of zolmitriptan in an orodispersible dosage form. Shah et al. formulated atorvastatin liquisolid orodisperable tablets to manage hypertensive crises using a factorial design. A higher drug release was observed (97.86%) within 54 s and an *in vitro* D-time of 5 s. The aqueous solubility of atorvastatin improved by 4 mg/mL. This suggests that formulating hydrophobic drugs in an orodispersible form using the liquisolid technique would be an effective approach for next-generation dosage forms because of its economical nature compared to other orodispersible formulation techniques [128].

**5.2 Liquisolid technique and computer aid**

Traditional methods of drug development and formulation are difficult due to their extensive time and cost. Thus, alternative approaches are needed to address these issues. In recent advancements in the domain of pharmaceutics, in silico modeling, algorithms, and artificial neural networks have been explored to accelerate the process and promote design and development. In this regard, computer aid programs collaborate with the liquisolid technique, and this combination significantly reduces costs and time. Apripitant was the first drug explored for this purpose. The dissolution rate was enhanced using the liquisolid technique with the aid of neural networks and genetic programming. Different formulation variables were correlated with dissolution profile parameters using neural networks and genetic programming. The results showed enhanced correlation efficacy [129].

The liquisolid technique is yet to be adopted by industries for commercial purposes because of limited clinical trials for liquisolid-technology-based dosage forms. Scaling up liquisolid techniques is a major challenge for pharmaceutical scientists. Moreover, the existing literature and research showed the formulation of the liquisolid dosage form at the extemporaneous level; therefore, there is a need for trials at the industrial level to formulate industrial-level liquisolid

batches and evaluate dosage forms for various physical in-process and formulation parameters. This will help scale up the liquisolid technique and dosage forms from benchtop to the market.

## 6 Conclusion and future perspectives

The hydrophobicity of drugs is a major challenge for pharmaceutical scientists and industry. Poor dissolution rates, flowability, and compressibility of hydrophobic drugs are major challenges at the industrial level. To cope with the pre-mentioned problems, the liquisolid technique is a novel and sophisticated tool to improve the dissolution rate of such drugs. In addition to enhancing the dissolution rate, this technique is used to sustain drug release, resulting in zero-order release kinetics. The liquisolid technique is an efficient technique for reducing the effect of pH variations on drug release and protecting photosensitive drugs in solid dosage form. Free-flowing and non-adherent powders, which can be easily compressed, can be produced using the liquisolid technique. Thus far, the liquisolid technique has proven to be a reliable and cost-effective approach. Orodispersible formulations were prepared using the liquisolid technique, resulting in better absorption, enhanced efficacy, and dose and frequency reduction, consequently maximizing patient compliance. The liquisolid technique is an efficient tool for improving the dissolution rate of hydrophobic drugs, developing sustained-release formulations for multidosing schedule drugs, and protecting light-sensitive drugs. However, no commercial product is available yet; therefore, there is a need for clinical trials of liquisolid formulations. This technique considers pH-triggered releases; therefore, further research is required to formulate enteric-coated formulations using this technique. By passing an additional enteric coating step, the main benefit is achieved. Administration of high-dose drugs is an issue with the liquisolid technique because a high dose requires high quantities of excipient and liquid vehicle, leading to an overweight tablet that is impossible to swallow. Therefore, in the future, high-dose drug loading will be the main target and challenge for pharmaceutical scientists. A review of novel polymers (carrier/coating materials) and liquid vehicles are required to check their abilities compared with existing materials. This is a productive approach toward next-generation dosage forms. Orodispersible liquid formulations are not palatable. Therefore, attention should be paid to taste masking. In addition, no research work is available on sustained-release formulations of an orodispersible liquisolid system.

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**Highlights**

- 40% of the newly formulated drugs are hydrophobic having low a dissolution rate and bioavailability.
- Their dissolution rate as well as flowability and compressibility are major challenges at the industrial level.
- Liquisolid technique convert liquid medication to dry, free flowing, non-adherent and readily compressible powder.
- It is more advantageous to controlled release dosage form by achieving zero order release kinetics easily.
- The use of liquisolid technique in photo-stability perfection, minimize the pH triggered variation in the release of dosage forms
- It has the great potential to be the next generation dosage forms.

## Conflict of Interest

*The authors have declared no conflict of interest*

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