



## A Comprehensive Review on Lquisolid Tablets

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### ABSTRACT

The Lquisolid process is a novel and effective approach to improving solubility. Bioavailability relies on drug solubility. With the evolution of modern pharmaceutical products, solubility is a big problem for the pharmaceutical industry. One of the most daunting aspects of drug production remains the enhancement of oral bioavailability of poorly water-soluble drugs. A newer methodology "powdered solution technology" or "Lquisolid technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. This method is efficient, economic, viable for industrial production, also useful in control drug delivery system. Hence due to above reasons Lquisolid technique is most efficient and novel approach for solubility enhancement. To prepare water-insoluble drugs into rapid-release solid dosage forms, 'powdered solution technology' or 'Lquisolid technology' has been applied. This approach is reliable, cost-effective, viable for industrial production, and also useful in the drug delivery control system. Therefore, Lquisolid technique is the most effective and novel method for enhancing solubility due to the above factors.

**Keywords:** Liquid solid, solubility, dissolution rate, bio availability.

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- (f) polymeric modification
- (g) drug complexation
- (h) particle size reduction
- (I) the pro-drug approach and
- (j) solid solutions.

### LIQUISOLID TECHNIQUE

A Lquisolid structure refers to information shaped by the conversion of fluid medicines, drug suspensions or medication arrangements into unpredictable solvents into dry, non-following, free streaming and compressible powder combinations by mixing the suspension or arrangement with selected transporters and materials covering.<sup>2</sup> The Lquisolid framework is the most encouraging strategy for advancing disintegration Rapid delivery rates are obtained in Lquisolid definitions and can be used effectively for strong water-insoluble drugs or lipophilic fluid drugs or strong water-insoluble drugs broke up in unstable dissolvable and this fluid drug can be converted into free streaming, non-free streaming. On, dry looking, and promptly compressible powders with utilization of transporter and covering materials. As the medication is as fluid medicine, it is either in solubilized or in microscopically scattered state. Because of expanded wetting and expanded surface territory for disintegration, Lquisolid tablets of water insoluble medications show improved disintegration profile and expansion in bioavailability.<sup>3</sup>

A Lquisolid framework alludes to details shaped by transformation of fluid medications, drug suspensions or medication arrangement in non-unpredictable solvents, into dry, non-follower, free streaming and compressible

### INTRODUCTION

The essential determinant of a drug's remedial viability is bioavailability, and therefore relies on the solvency of the drug in the gastrointestinal fluid. Dissolvability is one of the essential limits for achieving the ideal centralization of medicine for pharmacological reaction in basic dissemination. Inadequately water-dissolvable medications will be characteristically delivered at a moderate rate inferable from their restricted dissolvability inside the GI substance. The disintegration rate is regularly the rate deciding advance in the medication dissimulation. The test for inadequately water-solvent medications is to improve the pace of disintegration. This thusly along these lines improves assimilation and bioavailability.<sup>1</sup>

Different methods are employed to improve the dissolution characteristics of poorly water-soluble drugs, which include,

- (a) solubilization in surfactants
- (b) pH adjustment
- (c) co-solvents
- (d) micro emulsion
- (e) self-emulsification



powder combinations by mixing the suspension or arrangement with those transporters and covering materials.<sup>2</sup>

Rapid release rates are obtained in Liquisolid formulations and this can be used effectively for water-insoluble solid drugs or liquid lipophilic drugs or water-insoluble solid drugs dissolved in non-volatile solvent, and this liquid drug can be transformed into free-flowing, non-adherent, dry-looking, and readily compressed. As the drug is in the form of liquid medication, it is either in solubilized or in molecularly dispersed state. Due to increased wetting and increased surface area for dissolution, Liquisolid tablets of water insoluble drugs show improved dissolution profile and increase in bioavailability.

A Liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials.<sup>3</sup>

#### Need of Liquisolid technique:

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Therefore, low solubility is one of the main obstacles facing drug production today, as an estimated 40 percent of all newly formulated drugs are poorly soluble or insoluble in water. By reducing particle size, decreasing crystallinity, and/or increasing the area of the surface, the dissolution rate of these drugs can be increased. Several studies have been carried out to boost the rate of drug dissolution by rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles. However, the fine drug particles have high tendency to agglomerate due to Vander Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface area carrier.

In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high surface area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents. To overcome the problem, the technique of 'Liquisolid compacts' is a new and promising approach towards dissolution enhancement.<sup>3</sup>

#### Historical Development

Historically, Liquisolid compacts are descendants of 'powdered solutions', an older technique focused on transforming a drug solution into a non-volatile solvent into a dry-looking, non-adherent powder by primarily

adsorbing the liquid on large specific surfaces of silica. However, these preparations were tested for their dissolution profiles while being in a powder dispersed in later studies on powdered solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems.<sup>3</sup>

#### Classification of Liquisolid systems:

A. Based on the type of liquid medication contained Therein, Liquisolid systems may be classified into three subgroups:

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or [e. g. prednisolone solution in propylene glycol] or drug suspensions [e. g. gemfibrozil suspension in Polysorbate 80], and the latter from the formulation of liquid drugs [e. g. clofibrate, liquid vitamins, etc.], into Liquisolid systems. Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn is dispersed throughout the final product.

Based on the formulation technique used, Liquisolid systems may be classified into two categories:

1. Liquisolid compacts
2. Liquisolid microsystems.

Liquisolid compacts are prepared for the development of tablets or capsules using the previously described process, while Liquisolid microsystems are based on a modern idea that uses similar technique combined with the addition of an additive, e.g., G., Polyvinylpyrrolidone [PVP], in the liquid drug incorporated in the carrier and coating materials to create an acceptably flowing admixture. The advantage stemming from this new technique is that the resulting unit size of Liquisolid microsystems may be as much as five times less than that of Liquisolid compacts.<sup>3</sup>

#### Main components of Liquisolid system

Coating Material and Carrier Material: Coating material forms a uniform film around carrier particles. This prevents particle aggregation and reduces inter-particulate friction. This phenomenon improves flowability and gives a dry-looking appearance to the Liquisolid by covering the wet carrier particles and absorbing any excess liquid. Usually, the coating materials are very fine. Example of coating material is colloidal silica of different grades similar to Aerosil 200. And the carrier material should have porous surface and closely matted fibres in its inertial. Carriers are involved in the liquid medication sorption process that improves the effective dissolution surface area. Example of coating material is colloidal silica of different grades similar to Aerosil 200. And the carrier material should have porous



surface and closely matted fibres in its inertial. Carriers are involved in the liquid medication sorption process that improves the effective dissolution surface area. These help the compression as well. Carriers have a sufficient adsorption property due to relatively large, preferably porous particles and matted fibres contribute to the interior. E.g., Lactose and cellulose.

**Non-Volatile Solvent:** The selected solvent should have the capability to dissolve the drug adequately. Appropriate vehicles are inert; firstly, they are miscible with water and having increased boiling point, like propylene glycol and fixed oils. The formulation kind and concentration will be based mostly on the observation's purpose while the use of disintegrant. Merging of super-disintegrant is positive for studies to improve solubility. Sodium starch glycolate is the most commonly used disintegrant.

### Mechanisms of increased drug release

The three main mechanisms proposed include increased surface area of drug available for release, increased drug aqueous solubility due to the presence of non - volatile vehicle and improved drug particle wettability due to the cosolvent effect of the used vehicle.<sup>4,5</sup>

**Enhanced effectual Surface Area:** In the liquid medium whenever the drug, be dissolved within the liquisolid system and it is in a molecularly dispersed condition.<sup>5</sup> Consequently, the drug's surface area accessible for release in directly compressed tablets is more than that of molecules of the drug. Consequently, by improving the solubility of the drug content and thus increasing the portion of the drug that is not dissolved in the liquid vehicle, the release rate decreases., the discharge rates in the liquid formulation may be exposed with many of drugs and to be directly proportional to the portion of the molecularly isolated drug (FM). According to spires FM as the fraction between the drug solubility, (Sd) the real concentration of the drug, (Cd) medium carried by all system.

**Lubricant:** Most commonly used lubricant is magnesium stearate.<sup>6</sup>

### Formulation of liquisolid:

It is mainly divided into two categories:

1. Pre formulation studies
2. Formulation of liquisolid compacts.

**Solubility of drug:** It is carried out by preparing saturated solution of drug in different solvents. This saturated solution is prepared by adding excess amount of drug in non-solvent. This solution is shaken with shaker for specific period of time than it is filtered and analysed under UV spectrophotometer.

**Determination of angle of slide:** Angle of slide is used as a measure of the flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placed at one end of a metal plate

with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. Angle of 33° is regarded as optimum.

**Determination of flowable liquid retention potential ( $\Phi$  value):** The term "flowable liquid-retention potential" ( $\Phi$ -value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The  $\Phi$ -value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.

The  $\Phi$  values are calculated according to equation

$$\Phi \text{ value} = \text{weight of liquid} / \text{weight of solid}$$

**Calculation of liquid load factor:** Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier coating material admixture and blended. Using equation drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

$$L f = \text{weight of liquid medication} / \text{weight of carrier material}$$

**Liquisolid compressibility test (LSC):** Liquisolid compressibility test is used to determine  $\Phi$  values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and  $\Phi$  value and LF.

### FORMULATION OF LIQUISOLID TABLETS

Drug was dispersed in non-volatile solvent to make 10–50% w/w solutions (denoted as LS-1 to LS-6). A carrier material was added to the liquid medication containing the drug and non-volatile solvent under continuous mixing in a mortar. Further addition of coating material it converted the damp mass into a free-flowing powder at a fixed carrier: coating ratio 20:1. Depending upon the type of vehicle in the formulation, different liquid load factors were employed in cliquishly preparations. Different carrier: coating ratio of carrier and coating materials were also used to prepare different cliquishly formulation.

liquisolid formulation is prepared using a carrier and a coating material. The high liquid loading capacity of this may be explained by its extremely high specific surface area of  $339 \pm 1 \text{ m}^2$  Determination of flow properties /g as well as its good flow and tableting properties. Finally, or sodium starch glycolate as a super disintegrant and 3% w/w PVP K-30 as a binder were added in the above powder blend. Then the powder blend is subjected to compression in single pinch press compressor

**Mechanisms of increased drug release:** The three main mechanisms proposed include increased surface area of



drug available for release, increased drug aqueous solubility due to the presence of non - volatile vehicle and improved drug particle wettability due to the cosolvent effect of the used vehicle.<sup>6</sup>

The three recommended mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles.<sup>7</sup>

**Enhanced effectual Surface Area:** In the liquid medium whenever the drug, be dissolved within the liquisolid system and it is in a molecularly dispersed condition. Consequently, the drug's surface area accessible for release in directly compressed tablets is more than that of molecules of the drug. Consequently, by improving the solubility of the drug content and thus increasing the portion of the drug that is not dissolved in the liquid vehicle, the release rate decreases., the discharge rates in the liquid formulation may be exposed with many of drugs and to be directly proportional to the portion of the molecularly isolated drug (FM). According to spire as FM as the fraction between the drug solubility, (Sd) the real concentration of the drug, (Cd) medium carried by all system.

#### Enhanced Aqueous Solubility:

For enhancing drug unharness to the primary methodology, the liquisolid systems are doubtless to boost the drug's solubility. In fact, in a very liquisolid compact, the comparatively bit of liquid vehicle isn't adequate to extend the drug's overall solubility within the liquid medium. Though, within the small - setting of the solid / liquid interface between a personal primary liquid particle and therefore the unharness medium, the quantity of liquid vehicle that spreads from one liquid particle along with the drug molecules could also be adequate to extend the drug's liquid solubility if the liquid vehicle will act as a cosolvent. In varied studies, the common raise in drug solubility and caused by liquisolid systems was established.

Therefore,

$$FM = Sd/Cd$$

Where, FM is 1

Furthermore, it is assumed that the adsorption and absorption of molecularly dispersed drugs on the surface and inside of the carrier molecule exerts an enhanced effective surface area usually available for mass movement during the method of drug dissolution.

**Better Wetting Properties:** Because the liquid medium may also perform as a surface-active agent or enclose stumpy tension on the surface, it boosts the various wetting properties of the molecules of main liquisolid. Contact angles and water rising times can demonstrate the wettability of these systems. The drug's adsorption on the carrier particles also increases the effective surface area, enhancing drug contact.<sup>6</sup>

#### Evaluation of Compressed Tablets:

**Friability Test:** The test was performed using Roche friabilator.

**Hardness:** The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm<sup>2</sup>. Six tablets from each formulation were tested for hardness.

**In-Vitro Disintegration Time:** The disintegration time of the tablets was measured in distilled water (37±2°C) using disintegration test apparatus with disk. Five tablets from each formulation were tested for the disintegration time calculations.

**Content Uniformity:** Five tablets were powdered, and 20 mg equivalent weight of Olmesartan was accurately weighed and transferred into a 100 mL volumetric flask. Initially, 10 mL of methanol was added and shaken for 10 min. Then, the volume was made up to 100 mL with phosphate buffer pH 6.8. The solution in the volumetric flask was filtered, diluted suitably, and analysed spectrophotometrically at 257 nm using UV-visible double-beam spectrophotometer.

**In-Vitro Drug Release Study:** The in vitro drug release study of the tablets was performed using USP type II apparatus paddle (EDT-08L, Shimadzu, Japan) at 37° C ± 0.5° C using phosphate buffer pH 6.8 (900 mL) as a dissolution medium and 50 rpm. At the predetermined time intervals, 10 mL samples were withdrawn and replaced with fresh dissolution media. Withdrawn samples were filtered through a 0.45 µm membrane filter, diluted, and assayed at 257 nm using a Shimadzu UV-1800 double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

**Calculation of Dissolution Parameters:** Calculation of Dissolution Parameters. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time *t* (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Cumulative percent drug release was plotted as time required for 50% of drug release from dose was also a function of time, and percent drug release in 5 minutes (*Q*<sub>5</sub>) was calculated. time required for 50% of drug release from dose was also calculated.

**PB screening design:** In PB screening design, five factors that may affect the experimental responses and three dummy factors were selected as independent variables at two levels for the study. The outline and observed responses of PB formulation (PBF) on two levels were considered.<sup>8</sup>

Optimization of liquisolid formulation for enhanced drug release Optimizing the liquisolid method is mostly intended on improving the dissolution rate of drug formulation and flow properties. Since the releasing rates in formulation of liquid are directly proportional to the part



of drug dispersed molecules (FM), elevated drug dose needs more liquid entities for the preferred discharge profile. In addition, to get liquisolid systems with acceptable flowability and compatibility, high levels of carrier and coating materials are required. However, this eventually leads to an increase in tablet weight, difficulty in processing and swallowing development. Therefore, to solve these and numerous other liquisolid technology problems, many formulation parameters need to be optimized<sup>(4)</sup> These factors are mentioned in below table no:1

**Table 1:** Formulation parameter for liquisolid system with rapid drug release

Formulation parameters	Optimization	Effects
Liquid vehicle	High solubility of drug in the vehicle	Increased fraction of the molecularity dispersed drug (Fm)
Addition of excipients	Polyvinyl pyrrolidone	Increased viscosity of liquid vehicle inhibition of precipitation
Excipient ratio (R)	High R-value	Fast disintegration inhibition of precipitation

#### Advantages and Disadvantages of Liquisolid technique:

Advantages Numerous advantages of liquisolid technique have been reported.

- i. Huge number of slightly water-soluble, very slightly water-soluble and practically water-insoluble drugs can be formulated into liquisolid systems with enhanced dissolution and bioavailability.
- ii. Sustained release formulations with zero order release pattern can be achieved provided that hydrophobic carriers, such as Eudragit® RL and RS, or retarding agents such as hydroxypropyl methylcellulose (HPMC) are used in the liquisolid systems.
- iii. This technique has the potential to produce liquisolid tablets or capsules with pH-independent drug release profiles.
- iv. It is a promising alternative to conventional coating approach for the improvement of drug photostability in solid dosage forms.
- v. The applied excipients are easily available and cost-effective. Besides, the preparation process is simple, which is similar to conventional solid dosage forms (i.e., tablets and capsules). Moreover, the good flowability and compressibility of liquisolid powder make the technique feasible for largescale production.
- vi. The active ingredient is considered as highly soluble when their highest dose is solubilized in a

solvent of 250 ml at the entire pH range (1-7), reported by FDA and BCS. Moreover, the active ingredient is categorized as permeable when its absorption across the intestine will be 90 percent.<sup>8</sup>

#### Disadvantages:

There are also disadvantages associated with liquisolid technique.

a. The technique is successfully applied for low dose water-insoluble drugs, whereas the incorporation of high dose water-insoluble drugs into liquisolid systems is its main limitation. As these drugs require large quantity of liquid vehicle, therefore, in order to obtain liquisolid powder with good flow and compressible properties, large amounts of carrier and coating material are required.<sup>(9)(10)</sup> This may increase tablet weight over the limit, which is difficult for patients to swallow. Several strategies have been reported to address the above obstacle. For example, adding some additives (i.e., PVP and PEG 35000) into the liquid medications to increase the viscosity can reduce the quantities of carrier and coating material. Additionally, application of modern carrier and coating materials with large specific surface area (SSA) and high absorption capacity is another efficient way to load high dose water-insoluble drugs.<sup>11</sup>

b. A high solubility of drug in liquid vehicle is required to prepare liquid solid systems.<sup>12</sup>

#### Applications of Liquisolid technique in pharmaceuticals:

Liquisolid technique as a tool to enhance drug dissolution Based on the literatures, liquisolid technique has been widely used to improve the dissolution rate of low dose insoluble drugs, such as prednisolone, famotidine, valsartan, ketoprofen, raloxifene hydrochloride, clonazepam, clofibrate, etc. In the case of high dose water insoluble drugs (i.e., carbamazepine), the feasibility of liquisolid technique has also been discussed. Jafarzadeh et al. suggested that it is possible to involve liquisolid technique in the incorporation of high dose water-insoluble drugs into liquisolid systems by adding some additives (such as PVP, HPMC and polyethylene glycol 35000), because these additives have the capability to increase the liquid absorption capacity of carrier and coating materials. have shown another potential approach to load high dose of poorly water-soluble drugs into liquisolid systems, namely by using modern carriers with larger SSA value and higher absorption capacity.<sup>12</sup>

Recently, explored that possibility of using this technique to prepare liquisolid pellets for dissolution enhancement of felodipine. It was observed that a liquisolid microenvironment with soft structures and high porosity was formed, which favoured the disintegration and dissolution process of felodipine liquisolid pellets. The results indicated that it is feasible to adopt liquisolid pellets as novel drug delivery systems to improve the dissolution rate of poorly water-soluble drugs.<sup>(13)</sup> A comparative study

to corroborate the feasibility of liquisolid technique is performed by Khan, in which the liquisolid technique was applied to enhance the dissolution rate of hydrochlorothiazide in comparison with solid dispersion technique. The obtained results showed liquisolid systems enhanced the drug dissolution rate to 95% while it only increased to 88% for solid dispersions. Thus, a conclusion could be drawn that the liquisolid technique was more effective than solid dispersion technique in improving the rate and extent of drug release.<sup>13</sup>

Furthermore, the in vivo profiles of liquisolid tablets have been studied by several researchers. For example, Khaled et al. Evaluated the in vivo performance of hydrochlorothiazide liquisolid tablets in six male Beagle dogs using two-way crossover design.<sup>15</sup> It was shown that hydrochlorothiazide liquisolid tablets exhibited 15% greater bioavailability than the commercial oral dosage form. Recently, in another study, the clinical evaluation of mosapride citrate liquisolid tablets was performed by Badawi et al. in six healthy male volunteers aged from twenty to forty years. A randomized, single dose, two-way crossover open-label design was used for the study.<sup>14</sup> The authors concluded that mosapride citrate liquisolid tablets could increase the oral bioavailability when compared with the commercial counterparts, with significantly improved pharmacokinetic parameters, C max, T max, and AUC.<sup>9</sup>

Three possible mechanisms of dissolution enhancement for liquisolid systems have been proposed in the literature, namely increased drug surface area, increased drug solubility, and increased wetting properties.<sup>15</sup> Even though the drug is held in a solid dosage form, it is presented either in a solubilized or dispersed state.<sup>16</sup> Therefore, the drug surface area available for dissolution is markedly increased. In addition to the preceding mechanism, the drug solubility could be increased in the aqueous diffusion layer. It is recognized that the relatively small amount of liquid vehicle existed in the liquisolid system may be insufficient to increase the overall drug solubility in the dissolution medium.<sup>17</sup> However, in the microenvironment of diffusion layer between the individual liquisolid primary particle and the dissolution medium, liquid vehicle may act as a co-solvent and diffuses out of the primary particle together with the drug, which might be adequate to increase drug solubility.<sup>18</sup> Moreover, due to the surface activity of liquid vehicles, the interfacial tension between tablet surface and dissolution media can be reduced, which leads to an improved wettability of the hydrophobic drug.<sup>19</sup> Recently, we have improved the dissolution of tadalafil, a poorly water-soluble drug, by employing the liquisolid technique. Meanwhile, the mechanism of enhanced dissolution was also investigated. The results suggested a reduction of the particle size and crystallinity as well as an enhancement of the wettability were the main mechanisms for the enhanced dissolution rate of tadalafil.<sup>20</sup>

## CONCLUSION

Liquisolid technique is an approaching method for increasing the solubility and rate of dissolution thereby increasing the bioavailability and the extent of absorption of water-insoluble drugs compared to other conventional tablets using less production costs and simple manufacturing process. It is also used to formulate sustained release drugs and immediate release drugs by using hydrophobic and hydrophilic carriers. The drug release from liquisolid compacts is further enhanced by the use of disintegrant along with carriers and coating agents. Furthermore, this technology has been truly favourable as the dissolution, bioavailability, solubility of most of the water-insoluble drugs has been enhanced to a noticeable value, especially to BCS class II and class IV drugs.

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