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Open Access Journal of Pharmaceutical Research
ISSN: 2574-7797

A Review on Liquisolid: A Novel Technique for Enhancement of Solubility and Bioavailability of Poorly Water-Insoluble Drugs

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Review Article

Volume 7 Issue 3

Received Date: June 23, 2023

Published Date: August 23, 2023

DOI: 10.23880/oajpr-16000284

Abstract

Liquisolid technique is a novel approach that is used for the enhancement of bioavailability and solubility of poorly water insoluble drugs. According to Biopharmaceutical Classification System (BCS), drugs are classified based on their solubility and permeability. Class II and IV drugs have low solubility-high permeability, and low-solubility-low permeability respectively. This issue of solubility has been a major challenge over the years especially for water-insoluble drugs. Liquisolid system involves the formulation of drugs by conversion of liquid drugs, drug suspension or drug solution in non-volatile solvents, to form non-adherent, free flowing and compressible powder mixtures by blending the solution with appropriate carriers and coating materials. The method is most efficient and novel approach for solubility and bioavailability enhancement.

Keywords: Liquisolid Technique; Solubility; Bioavailability; Non-Volatile Solvents

Abbreviations: BCS: Biopharmaceutical Classification System; SEDDS: Self-emulsification Drug Delivery Systems; PVP: Polyvinylpyrrolidone; MCC: Microcrystalline Cellulose; PEG: Polyethylene Glycol; PG: Propylene Glycol.

Introduction

Over the years, the oral route has been the most preferred route for drug administration due to high patient compliance [1]. In systemic circulation, solubility is one of the major factors required to achieve the desired drug concentration [2]. Dissolution is the rate limiting step for poorly water soluble drugs. The major challenge for these drugs is to enhance the rate of dissolution and solubility, which in turn would subsequently improve absorption and bioavailability [3]. About 50 % of orally administered drugs suffer from formulation difficulties related to their water insolubility. A lot of research has been conducted into methods of improving drug solubility and dissolution rates in order to increase the oral absorption of hydrophobic drugs. Reduction of particle size is one major way of improving dissolution [4]. This reduction can be achieved by a common micronization process called milling. It is a well-established technique that is relatively cheap, fast and easy to scale up. Size enlargement of drug particles with different polymers and excipients is also another alternative to milling. The compaction of drug with hydroxypropyl methylcellulose (HPMC) and other hydrophilic polymers shows change in crystal form and habit which in turn may change the solubility, dissolution rate and other physicochemical properties [5]. Other methods that have been employed to improve the dissolution rate and bioavailability of water-soluble drugs include:

a. Solubilization in surfactants
b. Micro-emulsion
c. pH adjustment
d. Co-solvents

e. Self- emulsification
f. Polymeric modification
g. Drug complexation
h. Particle size reduction
i. Solid solutions.

Solubilization

This is the formation of a thermodynamically stable, isotropic solution by the addition of a surfactant. The micelles of the surfactant are responsible for the solubilization of the substrate [6]. Solubilization is applied in many industrial processes for the administration of insoluble chemicals such as in drug administration, dying and agrochemical applications [7]. Solubilization is also known to increase the solubility of poorly water-soluble substance using surfactants. The simple mechanism involves the entrapment of molecules in micelles and the tendency of surfactants to form colloidal aggregation at critical micelle concentration levels. Increase in the concentrations of micelles lead to increase in drug solubility. Some of the commonly approved surfactants include: Polysorbate 20, 40 and 80, deoxycholate [8].

Microemulsion

A microemulsion is a thermodynamically stable fluid that differs from kinetically stable emulsion which will separate into oil and water over time. The particle size ranges from 10-300 nm. Due to their small size, they appear as either clear or translucent solutions. Microemulsion may be broken by a variety of mechanisms including use of chemicals or by temperature change, but the simplest way is by dilution [9]. The particle size of microemulsion is measured by dynamic light scattering or neutron scattering. They have ultra-low interfacial tension between the water phase and the oil phase.

Co-Solvents

Co-solvents are substances that are added to a primary solvent in small amounts in order to increase the solubility of a poorly soluble compound [10]. Co-solvents improve solubility between non-miscible phases. A co-solvent miscible in both phases and able to dissolve the solute is added to form a homogeneous solution of water. Common co-solvents used are: ethanol, propylene glycol, glycerine and polyethylene glycols [10].

Self-Emulsification

Self-emulsification drug delivery systems (SEDDS) are used to increase the solubility and bioavailability of poorly soluble substances. SEDDS are composed of oil, surfactants and solvents [11]. Self-emulsification is influenced by the quality and nature of the concentration of surfactants, oil/surfactant ratio, pH and temperature. A wide variety of nanocarrier systems are prepared from SEDDS because their scaling and manufacture are very simple [12]. Factors affecting SEDDS include: dose and nature of drug, polarity of the lipophilic phase. SEDDS preparation is very simple and they are not affected by instabilities associated with emulsions [13].

Liquisolid Technique

Liquisolid technique is a novel concept used in the dissolution rate of water insoluble drugs. Also known as 'powdered solution technology' it is applied to prepare water-insoluble drugs into rapid release solid dosage forms. The liquid drug, drug solution or drug suspension is transformed into a free flowing, readily compressible and apparently dries powder by simple physical blending with selected carrier and coating materials [14]. The liquid drug in suitable non-volatile liquid vehicle is incorporated into the porous carrier material. A liquid layer is formed on the particle surface which is instantly adsorbed by the coating material. This leads to the formation of a dry, free flowing and compressible powder [15]. Coating material is required to cover the surface and maintain the powder flowability. It should be very fine and highly adsorptive silica powders [16] (Figure 1).

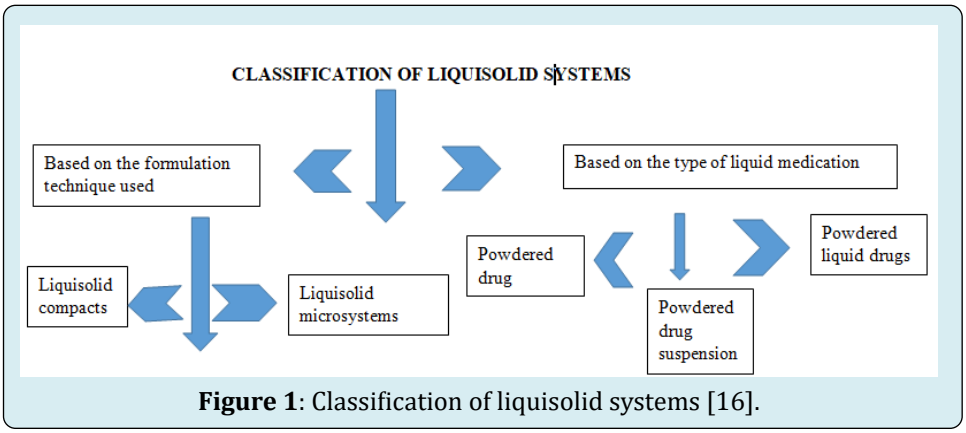

Figure 1: Classification of liquisolid systems [16].

Components of Liquisolid System

Liquid Vehicle

The liquid vehicle used in liquisolid systems should be orally safe, inert and less viscous. Examples of water-miscible, non-volatile solvents commonly used include: propylene glycol, glycerin, PEG-200 and 400 and polysorbate 20 and 80 [17]. The solubility of a drug in a liquid vehicle has a direct correlation with its dissolution rate.

The higher the drug solubility in the solvent the greater the fraction of molecularly dispersed drug [18]. Solvents commonly employed in LS system have high-boiling point, non-volatile in nature, water-miscible and not highly viscous solvents properties. Propylene glycol (PG) is used to solubilize and give homogenous dispersions of the active component in the formulation. The choice of any liquid vehicle depends on the aim of the study for dissolution enhancement of a particular drug, the liquid vehicle that has high ability to solubilize drug will be selected, while for prolong drug release, the liquid vehicle with the lowest capacity for solubilizing drug will be selected [19]. Some reports have documented that in low concentration, liquid vehicle can act as a binder [20].

Carriers

The carriers used in liquisolid systems should possess porous surface and have high liquid absorption capacity [21]. In designing the formulation of liquisolid system, the properties of carriers such as the liquid absorption capacity are of great importance. Examples of carriers include: microcrystalline cellulose (MCC), Neusilin lactose, sorbitol and starch, Fujicalin Avicel pH 102 and 200, Eudragit RL and RS. Large amounts of carriers are required for the conversion of liquid medication into dry, free flowing and compressible powder mixture [22]. The choice of a carrier depends on its liquid, binding size, flowability of powders and compressibility. Based on their chemical structure, they are classified into four classes (Table 1).

Carrier category	Carrier	Surface area (m^2/g)
Cellulose and cellulose derivatives	Microcrystalline cellulose, hypromellose	~ 1.18
Saccharides	Lactose,	~ 0.35
	Sorbitol	~ 0.37
Silicates	Magnesium aluminometasilicate	110-300
	Kaolin	~ 24
	diosmectite	
Others	Anhydrous dibasic calcium phosphate	30
	Polymethacrylates	
	Starch	~ 0.60
	Magnesium carbonates	10

Table 1: Classification of carrier materials into four categories and their surface area [22].

Coating materials

They possess fine and highly adsorptive properties. Examples include Aerosil® 200, Neusilin®, calcium silicate. They play a major role in covering the wet carrier particles to form a dry non-adherent and free flowing powder by adsorbing any excess liquid. Neusilin® US2 can be used as a coating and carrier material.

Additives

The most common additive used in liquisolid technique is the disintegrant. They play a major role in the influence of drug release (fast disintegration). Examples are sodium starch glycolate, croscarmellose sodium, hydroprophyl cellulose and polyvinylpyrrolidone (PVP), sodium starch glycolate, hypromellose. Additives are known to incorporate high amount of drug into liquisolid systems and thus reduce the tablet weight [23].

Theory of Liquisolid Systems

A powder of known quantity can only retain limited amount of liquid medication, while maintaining acceptable flowability and compressibility. A mathematical model has been introduced for liquisolid system that desires to have an acceptable flowable and compressible properties. This model was validated by Spireas and is used to calculate the appropriate quantities of carrier and coating materials [24-26]. Two fundamental properties characterize this

model. They are the flowable liquid retention potential and compressible liquid retention potential (ω value). These two potential values represent the maximum quantity of liquid vehicle that can be retained in the powder bulk without compromising flowability and compressibility [26]. The angle of slide is used to determine the Ø value, while plasticity (the maximum strength of a tablet with a tablet weight of one gram) when compressed at sufficient compression force is used to determine the ω value. The excipients ratio (R) is the ratio between the weights of carrier (Q) and coating material (q). R = Q/q. An increase in excipient ratio leads to decrease in the quantity of the coating material and vice versa. Loading factor (Lf) is another term associated with liquisolid technique. It is the weight ratio of the liquid medication (W) and the carrier material (Q) in the liquisolid system. Lf = W/Q [26].

Mechanisms Involved in Liquisolid Systems

Liquisolid technique and its application

With the advent of combinatorial chemistry and innovative high-throughput screening, knowledge concerning physiochemical properties and biological factors of drug candidates have been accumulated [27]. It has been reported that about 40 % of the newly developed drugs and nearly 60 % of the synthesized chemical entities suffer from solubility issues [28]. A matter of concern for many pharmaceutical scientists is to enhance the solubility and dissolution of these poorly water-soluble drugs and improve their bioavailability. The bioavailability of these Biopharmaceutical Classification System class II (BCS II) drugs is often limited by their solubility and dissolution rate [29].

Over the years, many suitable formulation approaches have been developed to increase the solubility of poorly water soluble drugs. The most commonly used approach that is deployed to improving the drug solubility is the micronization technique [30]. The aggregation tendency of micronized hydrophobic drugs makes it less effective to circumvent the solubility problem especially for drugs formulated as tablets [31]. Another approach used to improve the solubility of drugs is the solid dispersion, although its commercial application is very limited due to its poor stability during storage and lack of understanding of its solid-state structure [32]. Soft gelatin capsule formulation is another technique employed to increase drug solubility, but it is costly and requires sophisticated technologies [33]. Other approaches include: inclusion complexation, microencapsulation, preparation of nanosuspensions, self-nanoemulsions and solid lipid nanoparticles [34-37].

Liquisolid technique was first introduced by Spireas, et al. and applied to incorporate water-insoluble drugs into rapid release solid dosage forms. The liquisolid technique is designed in such a way as to contain liquid medications (liquid drugs, drug solutions or suspensions) in powdered form and delivery drug in a similar way to soft gelatin capsule containing liquids. Liquisolid technique is defined as the process that converts liquid medications into dry, non-adherent free flowing and compressible powder mixtures by blending the liquid medications with suitable excipients such as carriers and coating materials [38]. The liquid medication is first absorbed into the interior framework of the carrier. Once the interior of the carrier is saturated with liquid medication, a liquid layer is formed on the surface of carrier particles, which is adsorbed by the fine coating materials. This leads to the formation of a free flowing and compressible powder mixture [39]. (Figure 2) illustrates the mechanism of liquisolid system formation.

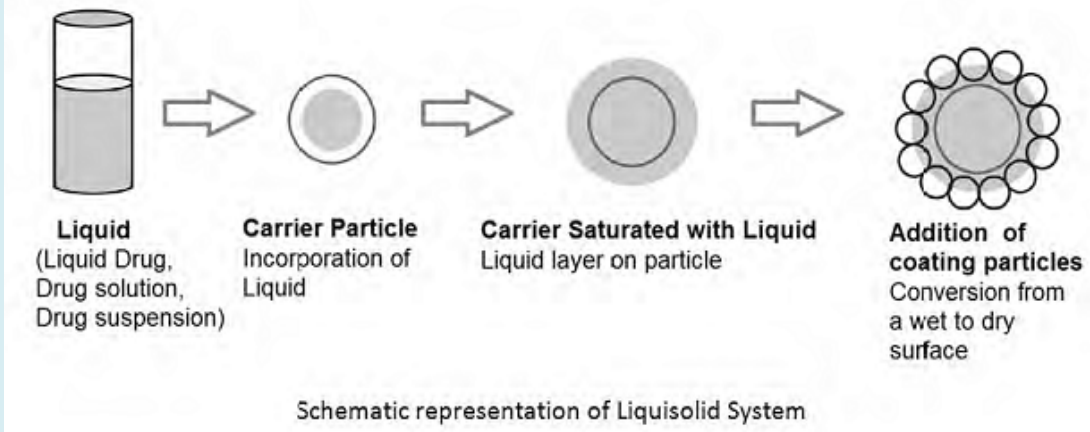

Figure 2: Mechanism of liquisolid system formation [39].

In the formulation of liquisolid tablets, orally safe and water-miscible organic solvents with high boiling point such as propylene glycol and polyethylene glycol (PEG) 400 are used as the liquid vehicle [40]. Porous materials that have large surface area and high liquid absorption capacity to absorb liquid medication are referred to as carriers [40]. Examples of coating materials used in formulation are silica powder, cellulose starch, lactose and Neusilin®. Although the drug within liquisolid system is in a solid state, it exists in a completely or partly molecularly dispersed state [41]. A liquisolid system may exhibit enhanced aqueous solubility, increased dissolution rate, improved wetting properties and retard drug release [41]. Solubility enhancement and improvement of bioavailability is one of the major challenges associated with pharmaceutical dosage forms. Table 2 shows the descriptive terms for solubility according to Indian pharmacopoeia.

S/N	Descriptive terms	Parts of solvent required to dissolve one part of solute
1	Very soluble	< 1
2	Freely soluble	>1 but <10
3	Soluble	>10 but <30
4	Sparingly soluble	>30 but < 100
5	Slightly soluble	>100 but < 1000
6	Very slightly soluble	>1000 but < 10,000
7	Insoluble	> 10,000

Table 2: Descriptive terms for solubility according to Indian Pharmacopoeia [42]

Advantages of Liquisolid Systems

1. It is suitable for the formulation of slightly water-soluble, very slightly water-soluble and practically water-insoluble drugs [43-45].
2. It is suitable for the formulation of sustained release drugs that exhibit zero order release pattern.
3. It is suitable for the formulation of liquisolid tablets with pH independent drug release profiles.
4. It is suitable for improving the drug photo stability in solid dosage forms.
5. The excipients commonly used are available and cost-effective.
6. It is a simple technique similar to conventional solid dosage forms.
7. It is suitable for large scale production of tablets and capsules.
8. Improvement of bioavailability of an orally administered water insoluble drug is achieved.
9. Production coast is low compared to soft gelatin capsules.
10. Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug, wetting properties thereby improving drug dissolution profiles.
11. Greater drug surface is exposed to the dissolution medium
12. The liquisolid system could be formulated into immediate release or sustained release dosage forms.
13. Drugs can be molecularly dispersed in the formulation.
14. Capability of industrial production is possible.
15. They omit process approaches like nanonization and micronization techniques.

Disadvantages of liquisolid technique

1. It is not suitable for high dose water insoluble drugs.
2. A high solubility of drug in liquid vehicle is required to prepare liquid solid systems.
3. If more amount of carrier is added to produce free flowing powder, it will increase the weight of the tablet, thus making it difficult to swallow.
4. During compression, liquid drug may be squeezed out of the liquisolid tablet, making it difficult to achieve an acceptable compression properties.
5. Difficulty associated in mixing small quantities of viscous liquid solutions onto large amount of carrier materials [43-45].

Preparation Procedure of Liquisolid System

The actual amount of drug and liquid vehicle are mixed together and heated or sonicated for complete solubilization. According to Spireas and Bolton [46], there are three steps involved in the mixing process of the resulted liquid medication with other excipients used in the liquisolid formulation.

1. The calculated liquid medication is poured onto a given quantity of carrier material and blended at an approximate mixing rate of one rotation/sec for 1 min for homogenous distribution.
2. The prepared powder mixture is spread as a uniform layer on the surface of a mortar and left standing for 5 min for complete absorption of the drug medication into the carrier and coating materials.
3. Addition of disintegrant to the above mixtures which forms the final liquisolid system. The liquisolid system formed is subsequently compressed as a tablet or encapsulated in a capsule (Figure 3).

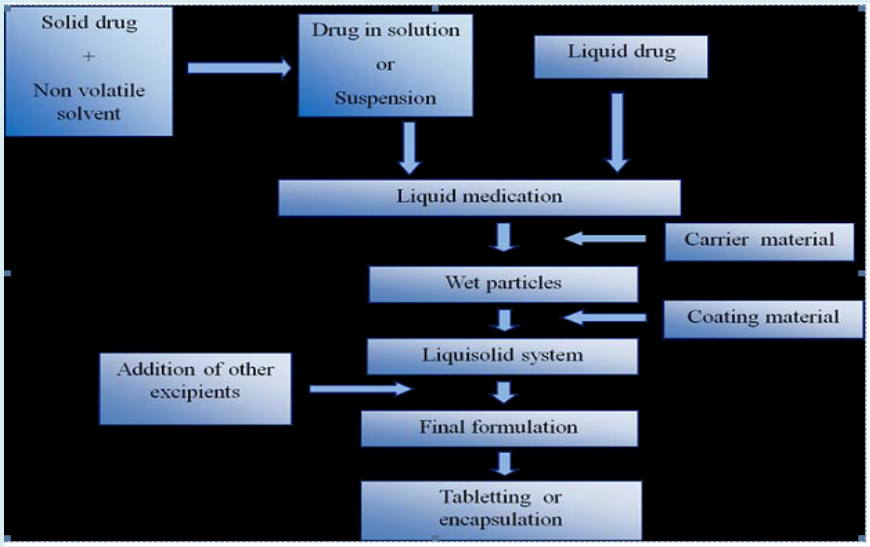

Figure 3: Preparation procedures of liquisolid system [47].

Application of liquisolid Technique

As a tool to enhance drug dissolution

The dissolution rate of low dose insoluble drugs have been improved using the liquisolid technique. Examples of such drugs include: prednisolone, famotidine, valsartan, ketoprofen, raloxifene hydrochloride, clonazepam and clofibrate [48-52]. According to Pezzini et al, they prepared liquisolid pellets for disoolution enhancement of felodipine [53]. The results they obtained showed clearly that it is possible to obtain liquisolid pellets as novel drug delivery systems to improve the dissolution rate of poorly water soluble drugs. According to Khan et al, they developed the liquisolid system to enhance the dissolution rate of hydrochlorothiazide in comparison to the solid dispersion technique. The results obtained indicated that the liquisolid system enhanced the drug dissolution rate to 95 %, while the solid dispersion enhanced it to 88 %. Thus they concluded that the liquisolid technique was more effective in improving the rate and extent of drug release than the solid dispersion technique. The dissolution of tadalafil a water soluble drug was improved by employing the liquisolid technique [54]. The result obtained showed that there was a reduction in the particle size and crystallinity, and an enhancement of the wettability.

As a tool to sustain drug release

Liquisolid technique is one of the techniques used to enhance the dissolution rate of poorly-water-soluble drugs. It is also used in the preparation of sustained release formulations of different drugs [55,56]. This is to achieve a zero order release kinetics [56]. Many attempts have been made to optimize the sustained release liquisolid formulations. Propranolol hydrochloride was investigated by Javadzadeh et al in order to improve its feasibility. Polysorbate 80 was used as one of the excipients and it played a major role in sustaining drug release. Also the effect of non-volatile co-solvent played a major role in prolonging drug release. The type of liquid vehicle was observed to affect drug release significantly Khan far, et al. [57] reported that venlafaxine hydrochloride liquisolid tablets exhibited greater retardation effect compared with the directly compressed tablets.

As a tool to minimize the influence of pH variation on drug release

Ionization constant (pka) and pH have a role to play in the solubility of weak acids and bases. The pH of the gastrointestinal fluid affects the dissolution and bioavailability of these drugs. El-Hammadi, et al. [58] studied the effect of liquisolid technique on laratidine and the effect of pH variation on the drug. They prepared several liquisolid formulations using propylene glycol, MCC and silica as a liquid vehicle carrier and coating tablets were significantly higher and less affected by pH variation in comparison with the directly compressed and marketed tablets. Badawy, et al. [59] studied mosapride citrate, a poorly weak base. They discovered that it minimized the effect of pH variation on drug release on the gastrointestinal tract.

As a tool to improve drug photostability in solid dosage forms

The principle behind photo protective action of liquisolid technique is based on the photo protective property of silicon dioxide (a common coating material used in formulation)

due to its high refractive index and the ability to diffract light waves of different energies. Khames, et al. [60] studied the effect of drug photostability on amlodipine (a photosensitive drug) using liquisolid technique as against the conventional coating technique. Different amlodipine formulations were prepared and the carrier material that was used was Avicel pH 102. Amorphous silicon and titanium dioxide were used in combination as coating material. The drug formulations were irradiated with visible light for eight hours in comparison with the conventional film coating tablets and drug alone. They observed that the liquisolid formulations showed significant photo protective effect with a residual drug percentage of 97.3 % compared to 73.8 % for the drug alone after 8 hours of irradiation. This conclusion was drawn from the fact that liquisolid technique was proven to be a promising alternative to conventional coating for improving drug photo stability in solid dosage forms.

Conclusion

The liquisolid technology has shown to be the most promising approach for improvement in solubility and bioavailability of water insoluble drugs. It is a simple manufacturing process with low production cost and the possibility of industrial manufacture due to the good flow and compaction properties.

Conflict of interest

The authors declare no conflict of interest.

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