A review on solubility enhancement by liquisolid technique as a novel approach

Neha Kumari*, Saurabh Mishra
M. J. P. Rohilkhand University, Bareilly, India
Corresponding author: **Neha Kumari**

Abstract:
Problem: The pharmaceutical industry has significant hurdles today in creating innovative formulations with adequate solubility and bioavailability. Nowadays, 40% of all newly discovered pharmaceuticals are poorly soluble in water, making drug development a huge difficulty due to low solubility. As a result, developing new pharmaceutical formulations for the pharmaceutical industry has significant solubility and bioavailability challenges. **Approach:** The solubility of poorly water-soluble drugs has been improved over the past few years using a variety of techniques, including micronization, solid dispersion, complexation, hydrotrophy, cosolvency, surfactant use, particle size reduction, microemulsion, nano suspension, cryogenic techniques, and liquisolid. The different in-vitro evaluation parameters used to assess liquid-solids and their drug release are also discussed in this paper. These evaluation parameters include Fourier Transform Infrared Spectroscopy (FTIR), Terahertz Time-Domain Spectroscopy, Solid-State NMR (Nuclear Magnetic Resonance), Dissolution Study, and Stability Study. **Conclusion:** Liquisolid technique are increasingly recognised as having a critical role in medicine or scientific study. The countless reviews and research articles that have been published in various periodicals over the preceding 10 years are enough proof of this. In recent years, some pharmaceutical companies have begun worldwide asserting patents. These companies are growing fast as a result of the regulations and relation to intellectual property. This technique is an essential and efficient way to raise a drug's melting point, stability, and bioavailability.

Key words: Liquisolid compact, drug release, solubility, dissolution.

1. Introduction

A qualitative definition of solubility is the spontaneous interaction of two or more substances to generate a homogenous molecular dispersion[1]. A quantitative definition of solubility is the concentration of solute in a saturated solution at a specific temperature. The only way to change the solubility of a substance is by chemical modification of the molecule[2]. Contrarily, dissolution is an extrinsic material property that is susceptible to a variety of chemical, physical, or crystallographic influences, including complexation, particle size, surface characteristics, solid-state modification, or formulation techniques that increase solubilization[3].
Dissolution properties and release profile of a drug from dosage form of a drug affects the bioavailability of a drug[4]. Dissolution depends on the intrinsic solubility of a drug and particle size. Noyes-Whitney equation states that rate of dissolution is directly proportional to its solubility due to this reason solubility of a drug is an important factor that defines the dissolution as well as its absorption leads to bioavailability of a drug[5]. The oral route of administration is the most prefer and widely acceptable route of delivery due to ease of ingestion for many drugs. Drugs with slow dissolution rate show the incomplete absorption leading to low bioavailability when orally administered [6,7].

Liquisolid technology, which was recently developed and is also known as "powder solution technology," is based on a cutting-edge idea[8,9]. Liquisolid compacts are powder versions of liquid pharmaceuticals that flow well and can be compressed[10,11]. The medications that are carried in liquid form but are not volatile are those that are not soluble in water[12]. By adding proper excipients, this liquid drug is transformed into a free-flowing

powder. The key benefits of this strategy are its low cost, straightforward processing, and excellent industrial production potential. One of the finest ways to boost a drug's solubility, dissolution, and bioavailability is by this procedure [13-15].

This method of absorption and adsorption efficiency uses liquid medications, drug suspensions blended with appropriate carriers, coating materials, and powder forms that are free flowing, dry appearing, non-adherent, and decomposable[16]. These pre-flowing powder stands are submitted to preformulation experiments including differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR) for compatibility studies. To enhance water solubility and drug release, angle of repose, flow characteristics, solubility studies, and liquid load retention potential calculations are explored. One of the most promising methods for promoting drug disintegration and maintaining drug release is liquisolid technology, and its prospective applications in the pharmaceutical industry are still being explored [17-20].

2. Importance of Solubility Enhancement

- Therapeutic effectiveness is achieved by accurate bioavailability of drug that depends upon the solubility of drug[21].
- Solubility is an important parameter that is required to attain desired concentration of drug with in the blood circulation to obtain optimum therapeutic response[22].
- For better absorption of drug, it needs good solubility near to the absorption site (Gastrointestinal track)[23].
- Solubility of drug is related to dose of drug and its regimen timing as poor solubility of drug leads to high dosing at frequent time interval and vise-e-versa[24].
- Most of the liquid formulations requires water, hence aqueous solubility of drug is required [25].
- Poorly aqueous-soluble drugs show delayed absorption though absorption site that produces gastrointestinal mucosal toxicity and mucosal irritation[26].

S.NO.	DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED TO DISSOLVE ONE PART OF SOLUTE (ml)
1	Very soluble	Less than1
2	Freely soluble	More than 1 but less than 10
3	Soluble	More than 10 but less than 30
4	Sparingly soluble	More than 30 but less than 100
5	Slightly soluble	More than 100 but less than 1000
6	Very slightly soluble	More than 1000 but less than 10000
7	Insoluble	More than 10000

Table 1: Descriptive term for solubility as per Indian Pharmacopoeia

3. **Advantages:**
   - It is suitable technique for drugs with high permeability and poorly water soluble[27].
   - It is suitable technique for practically insoluble liquids and solid drugs[28].
   - It is suitable technique for enhancement of bioavailability of poorly water-soluble drugs[29].
   - It is suitable technique for enhancement of dissolution profiles[30].
   - It is suitable technique for improvement of exposed drug surface arca to the dissolutionmedium[31].
   - It is suitable technique, specifically for powdered liquid medications[32].
   - It is suitable technique for formulate into immediate release or sustained release dosage forms[33].
   - In this liquisolid technique, production expenditure is low compared to soft gelatincapsules[34].
   - It is used in controlled drug delivery systems[35].
   - Drug can be molecularly dispersed in the formulation[36].
   - The release of a drug can be altered by utilising the right formulation elements[37].
   - Make the dosage form stand out by adding colour to the liquid vehicle[38].
   - Industrial production capability is also conceivable[39].
   - To reduce the amount of excipients compared to other formulations, such as solid dispersions[40].
   - Leave out process techniques like nano- and micronization[41].
   - Medication is prepared as a tablet or encapsulated dosage form and maintained in a liquid condition that has been solubilized, giving it established or improved wetting qualities that improve drug dissolving profiles.[42].

4. **Disadvantages:**
   - Low drug loading capabilities are needed for liquidsolid systems[43].
   - It calls for excipients that are more effective, have more adsorption capacities, and should result in a faster drug release from a smaller tablet[44].
   - More carrier and coating materials are needed to maintain compatibility and flowability standards[45].
   - Drugs must be highly soluble in non-volatile liquid carriers in a liquidsolid system[46].
   - Water-insoluble medicines are typically administered using a liquidsolid method[47].
   - Liquisolid systems are not appropriate for the formulation of high doses of lipophilic, water-insoluble medicines[48].

5. Components for liquisolid compact

a) Drug

They might not dissolve at all in water. Drugs utilised in liquisolid systems ought to be low dosage, water insoluble, or poorly soluble medicines. It must fall under BCS classes II or IV [49].

b) Non-Volatile solvent

Non-volatile solvent is frequently used in liquisolid systems, which improves wettability, ensures molecular dispersion of the medicine in the formulation, and increases solubility. This method allows one to control the release (sustained release) of drugs by using hydrophobic carriers (non-volatile solvents). Depending on the formulation type, such as instant release or sustained release, they may be either hydrophilic or lipophilic in nature. The most typical preferred organic solvent systems should be water-miscible, inert high boiling point, and not very viscous. Non-volatile solvents are frequently used to dissolve drugs since the liquid vehicle does not evaporate, allowing the medicine to remain present throughout the product. It must be miscible with inert water, not very viscous, and have a high boiling point. Vehicles utilised in liquisolid systems include Poly Ethylene Glycol (PEG)-400, PEG-200, PEG-4000, PEG-6000, Tween-80, Span 20, Propylene Glycol (PG), N, N dimethylacetamide, Fixed oils, glycerine, etc[50].

- It should not participate in changing the chemical properties of drug by some kind of bonding and other (Inert in nature).
- Non-volatile vehicle should have high boiling point.
- It should not be too much viscous so that compact will dry with least carrier.
- It should have ability to solubilize the drug completely.
- It should be water soluble[51].

c) Carrier

For a suitable flow, they are favoured to have coarser granules. They are a porous material with good absorption capabilities. These materials are highly porous, have a large surface area, and are advised for drug absorption. As carriers, MCC, starch, sorbitol, and lactose are utilised. For prolonged release, use Eudragit RL and RS, Ethocel, Methyl cellulose (MC), Ethyl cellulose (EC), HPMC K4M, etc[52].

d) Coating material

It is a material with extremely small coating particles (10 nm to 5,000 nm in diameter) that are highly adsorptive and help the flow. By adsorbing any extra liquid, these help to cover the wet carrier particles and present a dry-looking powder. Coating materials include Acrosil PH 200, Colloidal Silica, Talc, Syloid244FP, and Cab-O-sil RTM M5[53].

e) Super Disintegrates

They are employed to separate the compacts into more manageable pieces. Super Disintegrates are made using sodium starch glycolate (SSG), Explotab, pre-gelatinized starch, crospovidone, and sodium croscarmellose [54].

f) Lubricants

They are designed to lessen friction. For instance, stearic acid, its salts, and Tale, etc[55].

g) Glidants

By lowering friction, these are designed to encourage the movement between particles. For instance: Talc, corn starch, and compounds of silica [56].

6. Classification of liquisolid system

A. ***Liquisolid systems can be divided into three classes based on the sort of liquid medication they include:***

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

The latter is created by turning liquid drugs into liquisolid systems after the first two are created by converting drug solutions or drug suspensions. The liquid vehicle does not evaporate since non-volatile solvents are employed to make the drug solution or suspension; as a result, the medication is carried within the liquid system, which is then spread throughout the finished product [57,58].

B. ***Liquisolid systems can be divided into two types based on the formulation method utilised:***

- Liquisolid compacts
- Liquisolid Microsystems Liquisolidcompacts: The term "liquisolid systems" refers to instantaneous sustained-release tablets or capsules.

When an additive is added to "liquisolid systems" to create capsules, the resulting unit size can be up to five times smaller than that of a liquisolid compact. This is known as a "liquisolidMicrosystem." [59].

7. Mechanisms to Enhance Drug Release

To improve the medication release, several mechanisms have been developed. Included among three key mechanisms are:

a) An improvement in the efficiency of drug surface area,

b) A rise in aqueous solubility

c) Increased drug wettability[60].

I. An improvement in the efficiency of drug surface area

Increased drug solubility with the liquid carrier is caused by increasing the drug's effective surface area[61].

II. A rise in aqueous solubility

The complete amount of medication cannot be solubilized with just a tiny amount of liquid carrier. However, it is possible that a small amount of liquid vehicle diffuses from the total quantity along with the drug at the solid-liquid interface between the particles and the dissolution medium. If this small quantity of liquid acts as a co-solvent, it will be enough to increase the drug's aqueous solubility[62].

III. Increased drug wettability

By serving as a surface-active agent or by lowering the surface tension, the liquid vehicle can improve the wettability of the liquid-solid primary particle. By measuring contact angles and water rising times, wettability of liquisolid systems has been proven [63].

Preparation of liquisolid compacts:

Non-volatile solvents and carrier coating ingredients like Avicel PH 102, Aerosil 200, and cross povidone were used to create the LS formulations. The liquid vehicle and the desired amounts of the previously weighed solid medication were combined in a beaker, and the mixture was heated to 80–900 °C while being constantly stirred to create a uniform drug solution. Three steps were taken in the mixing process:

***Step I*:** To properly disperse the liquid medication into the powder, a weighed quantity of the carrier substance (Avicel PH 102) was combined with the liquid medication.

Step II:The mixing stage involved adding determined amounts of the coating material (Aerosil 200) to the system and blending it for two minutes. To allow the medication solution to be absorbed into the interior of the powder particles, the liquid powder admixture was kept undisturbed for around 5 min.

***Step III*:** To create the final LS formulation, the powder was combined for additional 30 seconds with a calculated amount of superdisintegrant (5%). The mixture was compacted into tablets using a rotary tablet punching machine with an 11 mm punch size. Each batch of 20 tablets was manufactured[64-67].

Preparation of solid dispersion by kneading method Drug and carrier in various (1:1).

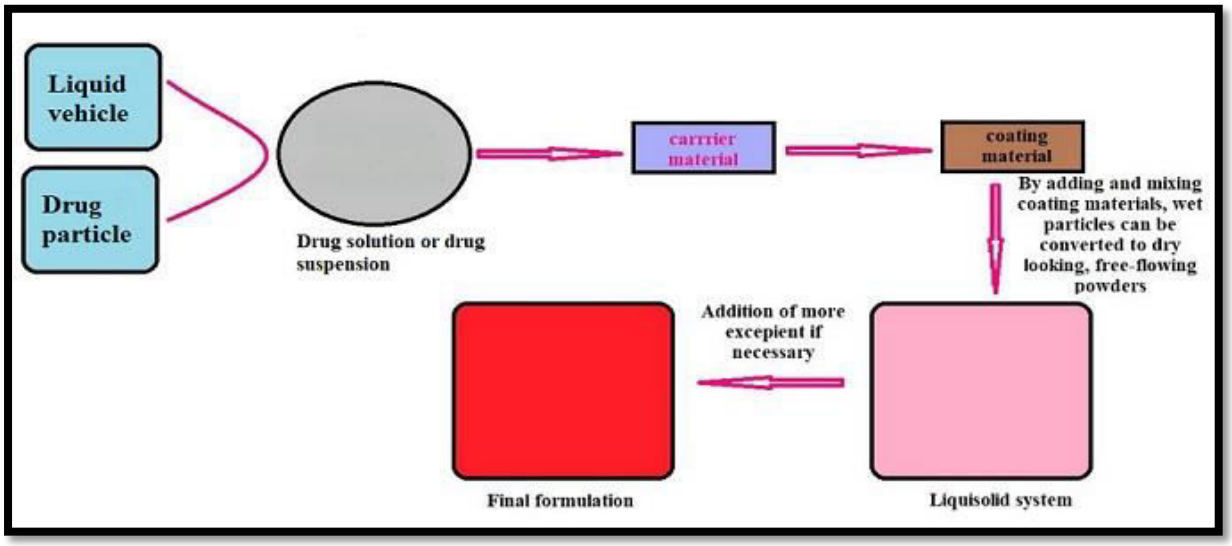

Figure 1: Layout Diagram for preparation of liquisolid compact

8. Liquid-solid formulations as a means of delaying the onset of a medicine

It is helpful for the reader to have a short understanding of sustained release matrix tablets since the excipients (polymeric materials) utilised in the design of liquisolid tablets are comparable to those used in the design of simple sustained release matrix tablets[68].

8.1 Background

Contrary to normal dosage forms, Extended release dosage forms are constructed in a way that makes the medicine they contain available for a longer length of time after administration. They also do not dissolve. Theoretically, compared to a traditional dose form, an oral sustained release matrix should provide a reduction in dosing frequency [69].

In terms of clinical efficacy and patient compliance, sustained release dosage formulations have advanced significantly during the past 20 years. One of the simplest methods for delivering medication in a temporal pattern into the systemic circulation is the direct compression of a mixture of drug, retardant material, and additives to create drug-embedded matrix tablets. As they are simple to produce, matrix systems are frequently employed as sustained release dosage forms. Many polymeric materials have been investigated as retarding agents in matrix systems, and each of them offers a unique perspective on the matrix idea. These orally delivered matrix may often be classified into one of the following categories. There are issues that can occur if the device is consumed orally, despite the fact that there has been a lot of basic study committed to the development of the following sorts of devices and a lot of trial under idealised settings that implies they will function[70-73].

8.1.1 A fatty matrix (digestible base)

These matrices are made by mixing the medication with the excipients in molten fat or wax, allowing it to solidify, then granulating and compressing it into cores. Carnauba wax, fatty alcohol, glycerol palmitostearate, stearyl alcohol, beeswax, aluminium monostearate, and glycerol monostearate are among the substances that create these matrices [74]. On the one hand, the medication may diffuse through solvent-filled holes as the mechanism of release from these matrices. On the other hand, they have the ability to erode and regulate medication release by combining erosion and diffusion[75].

8.1.2 Materia plastic or inert (non-digestible base)

Similar methods are used to produce plastic or inert matrices as well as fatty matrices. Via water-filled pores, simple diffusion causes drug release from these matrices. If channelling agents like PEG are not utilised, water penetration into the matrix is the rate-limiting phase in such systems. Water enters the matrix, and the medication can disperse through the same pores, leaving a skeleton of the matrix behind. Polyethylene, methylacrylate, methylmethacrylate, ethylcellulose, polyvinyl chloride, and polyvinyl acetate are a few examples of polymers used to create this sort of matrix[76].

8.1.3 Hydrophilic matrix

In 1966, hydrophilic polymers were originally presented as a possible possibility for prolonged release. These matrices are arguably the simplest and least expensive to create [77]. To help with flow, the materials can either be immediately crushed or granulated. Hydrophilic polymers hydrate when they come into contact with water, generating a gel layer. A combination of drug diffusion and erosion is the method by which drugs are released from hydrophilic matrices[78]. The following polymers are utilised in the production of hydrophilic matrices:

- Cellulose derivatives such as sodium carboxymethylcellulose, hydroxymethylcellulose, and hydroxypropylcellulose, as well as methylcellulose [79].
- Natural non-cellulose polysaccharides such carrageenan, alginates, and guar gum[80].
- Polymers made from acrylic acid, include polyacrylamide and polymethacrylamide[81].

9. Evaluation

A. Evaluation of flow properties of liquisolid compact.

The flow properties of LSC are evaluated on following parameters:

• ***Angle of repose****:*The funnel is gradually raised in order to maintain a fixed height between the powder tip and the bottom of the funnel when powder is allowed to fall on a flat surface from a funnel that has been placed at a specific height. The angle of repose is created by the powder on the surface. The alternative is to let powder escape via a flat-bottomed container's centre hole. The angle of repose is the slope created by the residual powder at the bottom of the container. Furthermore, the angle of repose can be measured using a rotating drum. The material is evenly poured into the drum, where it is allowed to revolve for a number of rotations. The angle is then measured.

$$\theta = tan\text{-}1(2h/d)$$

where, "θ" is angle of repose, "h" is height of heap&"r" is radius of heap[82].

• ***Bulk density****:*Bulk density, also known as apparent density or volumetric density in the field of materials science, is a characteristic of powders, granules, and other "divided" solids. It is particularly relevant to mineral components (soil, gravel), chemical compounds, (pharmaceutical) ingredients, food, or any other masses of corpuscular or particulate matter (particles).

The mass of the material's many particles divided by the entire volume they inhabit is how bulk density is calculated. Particle volume, inter-particle void volume, and internal pore volume are all included in the overall volume.

Bulk density is a quality that can change based on how a material is handled; it is not an intrinsic attribute of a substance. When powder is placed into a cylinder, for instance, it will have a certain bulk density; if the cylinder is shaken, however, the powder particles will move and usually settle closer together, increasing the bulk density. Due to this, "freely settled" (also known as "poured") density and "tapped" density are typically used to describe the bulk density of powders.

Particle density, on the other hand, does not account for the volume of spaces between particles and is a fundamental feature of the solid[83,84].

• ***Tapped density****:*The powder sample was contained in a container that was mechanically tapped to enhance the bulk density, which is known as the tapped density. By mechanically tapping a graduated measuring cylinder or vessel containing the powder sample, the tapped density is produced[85].
• ***Carr's index****:*T he compressibility of a powder is usually determined using the Carr index in pharmaceutics. The bulk density and tapped density in a free-flowing powder would be near in value, resulting in a low Carr index. On the other hand, the discrepancy between the measured bulk and tapped densities would be greater in a poorly flowing powder where there are more interparticle interactions, leading to a bigger Carr index. A Carr index above 25 is seen as a sign of poor flowability, and one below 15 as a sign of high flowability[86].

$$C=(\nu B-\nu T/\nu B) * 100$$

• ***Hausner ratio****:* The Hausner ratio is the ratio of tapped density W/V50 to fluffy density (W/V0 g/ml). A Hausner ratio greater than 1.25 indicates a healthy flow, whereas a number of 1.5 may suggest a bad flow[87].
• ***Liquid load factor****:*It speaks of the proportion of the amount of liquid medicine to the amount of carrier substance in the body [88].

B. Characterization of liquisolid compact

Various characterization methods are used to identify the interaction between active pharmaceutical ingredient and excipients used within the formation of liquisolid.

- ***FTIR (Fourier-Transform Infrared Spectroscopy)***

It is a method for obtaining an infrared emission spectrum, or we may say an infrared spectrum of absorption, of liquid, solid, and gas. It simultaneously gathers high-resolution spectral data across a wide spectrum. chemical conformation determination, intermolecular interaction, and integrated API investigation. The FTIR method is used to analyse API, conformers, and excepients across the wavelength range of 400–4000 cm-1. This method is rapid and straightforward for the discovery of functional groups [89].

- ***Differential scanning calorimetry (DSC)***

The most used approach of thermal analysis is this one. The sample and reference are kept at the same temperature while using the DSC technique, and the heat flow necessary to keep the temperatures equal is measured. This technique is used to determine how a medicine interacts with excipients used to create liquisolid compacts via exothermic and endothermic crest [90].

- ***Powder X-Ray Diffraction (PXRD)***

It is a common non-destructive analytical method for figuring out how crystalline a powder would behave in a three-dimensional structure. This analytical method is also often used for stability testing, medication discovery, and quality control of the finished product. While creating a liquisolid compact formulation, the PXRD is utilised to assess how the physicochemical characteristics of the medication and excipients have changed [91].

10. Conclusion

There are new chemical molecules on the market today with huge molecular weights that have poor permeability and solubility. It is a problem for researchers to improve a drug's water solubility and rate of dissolution in order to boost bioavailability. A possible method to improve the solubility of a poor water-soluble medication candidate is the liquidsolid compact procedure. The wetting ability and surface area of the drug particle that is available for dissolution are increased by the liquidsolid approach, which improves solubility and speeds up the dissolving process.

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Corresponding Email: ***mneharathore1997@gmail.com***