THE SCIENCE OF LIQUISOLID COMPACTS: ENHANCING DRUG SOLUBILITY

Pankaj Khuspe*[1], Swapnil Phade[1a], Dipali Mane[1], Trushali Mandhare[2], Pooja Kashid[2], Abhaysinh Hole[3], Amol Raskar[4], Ritesh Vyavahare[5], Amol Ban[6], Pranjali Kharmate[7]

1. Associate Professor, Shriram Shikshan Sanstha's College of Pharmacy, Paniv-413113.
1a. Principal, Shriram Shikshan Sanstha's College of Pharmacy, Paniv-413113.
2. Assistant Professor, Navsahyadri Institute of Pharmacy, Naigaon- 412213.
3. Associate Professor, ADT's School of Pharmacy & Research Centre, Baramati- 413115
4. Head of Department, S. B. Patil College of Pharmacy, Indapur- 413106
5. Assistant Professor, SVERIs College of Pharmacy, Pandharpur-413304
6. Associate Professor, Vidya Niketan College of Pharmacy, Lakhewadi-413103
7. Lecturer, Anusaya Institute of Pharmacy, Bhigwan-413130

Article History: Received: 10/10/2022 Revised: 16/11/2022 Accepted: 28/11/2022

Abstract:

A liquisolid compact system for drug delivery utilizes a combination of liquid and solid forms of medication to enhance solubility and improve the bioavailability of the drug. The technique involves mixing a liquid drug with a solid excipients and compressing the mixture into a tablet or capsule form. This allows for the drug to be more easily dissolved in human body, increasing its absorption and effectiveness. Liquisolid compacts have been shown to be effective in increasing not only solubility but also bioavailability of drugs with poor water-solubility, making them a viable replacement for conventional drug delivery techniques. This review is having aim to provide an overview of the liquisolid compact technology, its advantages, and its potential in the pharmaceutical industry. It will cover the basic concepts and principles of liquisolid compact system, the different types of excipients used, and the various methods of preparation. Additionally, it will also highlight the potential of liquisolid compact system not only improves solubility but also improves bioavailability of drugs with poor water-solubility.

Keywords:

Liquisolid Compacts, Enhancing drug solubility, Drugs with poor water-solubility.

DOI: 10.48047/ecb/2022.11.11.58

Introduction:

Bioavailability is a measure of quantiy of a drug reaches to the systemic bloodstream and is available to the body after administration. It is a critical factor in determining drug effectiveness, as it determines amount of the active ingredient that is available to produce a therapeutic effect. The bioavailability of a drug can be affected by a number of factors, including its solubility, dissolution rate, and permeability through the gastrointestinal tract and the liver. Poorly water-soluble drugs, in particular, can have low bioavailability because they are difficult to dissolve in the body's fluids, leading to reduced absorption and effectiveness. The drug bioavailability can also be affected by the way it is

administered. For example, oral administration is the most popular method of medication administration. but it can be subject to a various number of factors that can affect bioavailability, such as the pH of the stomach, the presence of food, and the first-pass metabolism by the liver. In order to ensure that a drug is effective, it is important to optimize its bioavailability. This can be achieved through various different drug delivery methods, such as using a carrier to increase solubility or using a different route of administration, such as intravenous or transdermal, which can bypass the gastrointestinal tract and the liver. In summary, bioavailability is a measure quantity of the drug which reaches the systemic bloodstream and is available to produce a therapeutic effect, and it is a critical factor in determining the drug effectiveness. Low bioavailability of drugs with poorly water-solubility can be overcome by novel drug delivery methods such as liquisolid compacts and by optimizing route of administration[1-2].

Solubility is a major issue in the pharmaceutical industry, as it affects the effectiveness and safety of many drugs. Poorly water-soluble drugs, in particular, can be difficult to absorb and utilize in the body, leading to a number of problems. One main issue with drugs having poorly water-solubility is low bioavailability. Poorly water-soluble drugs have low bioavailability because they are difficult to dissolve in the body's fluids, leading to reduced absorption and effectiveness. This can require higher doses than the normal dose of drug to be administered, which can increase the risk of side effects and toxicity. Another issue with poorly water-soluble drugs is poor stability. These drugs can be highly susceptible to degradation, which can lead to reduced effectiveness over time. This can make it difficult to store and transport these drugs, as well as to ensure that they remain effective once they reach the patient[3-5].

Solubility enhancement refers to the process of increasing the solubility of a drug, which is the ability of a substance to dissolve in a solvent. This is an important property of drugs, as it determines how much of the drug can be absorbed into the bloodstream and how well it can be transported to its site of action. The drugs solubility can be limited by various factors such as pH, temperature, and the presence of other substances in the solution. Poor solubility in water can causes to low bioavailability, which means that only a small amount of the drug reaches the site of action, resulting in a weak or ineffective treatment. Solubility enhancement is important to increase the bioavailability of the drug and to make the drug more suitable for oral administration. There are different methods for solubility enhancement, such as physical methods (e.g. particle size reduction), chemical methods (e.g. salt formation, pH modification, complexation), and other methods like biotechnological and formulation engineering methods, etc[3, 6-7].

Physical Methods:

There are several physical methods used to improve the drugs solubility, including:

1. Micronization: This involves reducing the particle size of the drug, which increases the surface area and allows for better dissolution in the body's fluids. It can be achieved

through various techniques such as jet milling, ball milling, and high-pressure homogenization[8].

2. Lyophilization: This is a freeze-drying process that used to improve the drugs solubility by removing the solvent. The drug is frozen, and the solvent is removed through sublimation[9].
3. Hot Melt Extrusion: This is a method where a drug substance is melted and extruded in a specific shape, this method is useful in increasing the solubility of lipophilic drugs[10-11].
4. Spray drying: This is a method where a liquid solution or suspension of a drug is atomized into small droplets which are then dried to form powder[12].
5. Co-precipitation: This involves the formation of a solid precipitate of the drug in the presence of a precipitation agent[13].
6. Spray congealing: This is a method where a liquid solution or suspension of a drug is atomized into small droplets which are then solidified by adding a solidifying agent[14].
7. Supercritical fluid technology: This involves dissolving the drug in a supercritical fluid, such as carbon dioxide, which can increase its solubility[15].
8. Solid Dispersions: This method involves preparing a solid dispersion of the drug in a hydrophilic carrier to increase its solubility[16, 17].
9. Physical Mixing: This is a simple method where a drug is mixed with excipients to increase its solubility[18, 19].

Chemical methods:

There are several chemical methods used to improve the solubility of drugs, including:

1. Salt formation: This involves forming a salt of the drug, which can increase its solubility. Commonly used counter-ions for salt formation include hydrochloride, sulfate, and fumarate[20, 21].
2. pH modification: This involves adjusting the pH of the drug to a more favorable value, which can increase its solubility. For example, weak acids can be converted to their more soluble conjugate bases by raising the pH[22].
3. Solubilization: This involves using solvents or surfactants to dissolve the drug, which can increase its solubility and bioavailability. Commonly used solvents include polyethylene glycol, ethanol, and propylene glycol [23].
4. Complexation: This involves forming a complex between the drug and a water-soluble excipient, such as cyclodextrins, which can increase the solubility of the drug[24, 25].
5. Prodrugs: This involves chemically modifying the drug to make it more water-soluble, which can increase its bioavailability[26, 27].
6. Lipid-based systems: This involves using lipids, such as liposomes, to encapsulate the drug, which can increase its solubility and stability[28].
7. Polymer-based systems: This involves using polymers, such as

polyvinylpyrrolidone, to increase the solubility of drugs[29, 30].

8. Hydrate formation: This is a method where anhydrous forms of drugs are converted to their hydrates form to increase the solubility[31, 32].

Other Methods

In addition to physical and chemical methods, there are also several other methods used to improve the solubility of drugs, including:

1. Biotechnology: This involves using biological systems, such as enzymes, to increase solubility of drugs. For example, enzymes can be used to convert insoluble prodrugs into their active forms[26].
2. Formulation engineering: This involves optimizing the formulation of the drug to improve its solubility and bioavailability[33].
3. In silico modeling: This involves using computer simulations and modeling to predict and optimize the solubility of drugs[34].

A Liquisolid Compact

A drug delivery system called a liquisolid compact is used to increase not only solubility but also bioavailability of medications that aren't particularly soluble. A liquisolid compact is a unit solid dosage form consist of a liquid vehicle, a solid excipient, and a finely ground drug combination. The medicine is solubilized using the liquid vehicle, and the solid excipient serves as a carrier and binder to create a free-flowing powder. The liquid vehicle is present in the powder in a small amount, typically less than 20% by weight, and is adsorbed onto the surface of the solid excipient particles. The drug is then dispersed within the powder as a fine dispersion, which improves its solubility and bioavailability. Liquisolid compacts have several advantages over other solubility enhancement techniques. They are easy to prepare and can be used with a wide range of drugs and excipients. They also have a high loading capacity, which means that a large drug amount can be incorporated into the powder. In addition, liquisolid compacts are stable and can be stored for long periods of time without losing their effectiveness[35-37].

The concept of liquisolid compacts was first proposed in the 1998s by Spireas as a way to improve both solubility as well as bioavailability of drugs with poorly soluble. Over the following decades, researchers around the world have continued to study and develop liquisolid compacts, exploring different drugs, liquid vehicles, and excipients to improve their effectiveness and applicability. The technology has been continuously improved, and today, it has become a widely accepted method for solubility enhancement and bioavailability enhancement of poorly water-soluble drugs. Nowadays, liquisolid compacts are being investigated for various therapeutic applications and have been shown to be a promising and effective drug delivery system[37, 38].

Liquisolid compacts are a type of drug delivery system that is derived from powdered solutions. This is because they are formed by mixing a liquid drug with a solid carrier, such as a powder or a granule, in order to create a solid, free-flowing mixture. This mixture can then be compressed into a

compact tablet form. This strategy aims to enhance the bioavailability and solubility of weakly water-soluble medicines, which can be challenging to administer in their original form. Therefore, liquisolid compacts are considered to be a descendant of powdered solutions as they build on the concept of mixing a liquid and a solid to create a new form of drug delivery. "Liquisolid compacts" is a general term that refers to a specific type of drug delivery system that involves mixing a liquid drug with a solid carrier to create a free-flowing powder or granule, which can then be compressed into a compact tablet form. There are four different types of formulation systems that fall under the category of liquisolid compacts, which are:

1. Liquisolid powder: This is the most common form of liquisolid compacts, where a liquid drug is mixed with a solid carrier such as microcrystalline cellulose or lactose, and then compressed into a tablet.
2. Liquisolid granules: In this formulation, the liquid drug is mixed with a solid carrier such as granulated sugar or spray-dried lactose to form granules, which are then compressed into a tablet.
3. Liquisolid capsules: This formulation involves filling a capsule with a liquisolid powder or granule, which allows for easy administration of the drug.
4. Liquisolid coating: This involves coating a solid drug core with a liquisolid film, which can improve the dissolution and bioavailability of the drugs[39, 40].

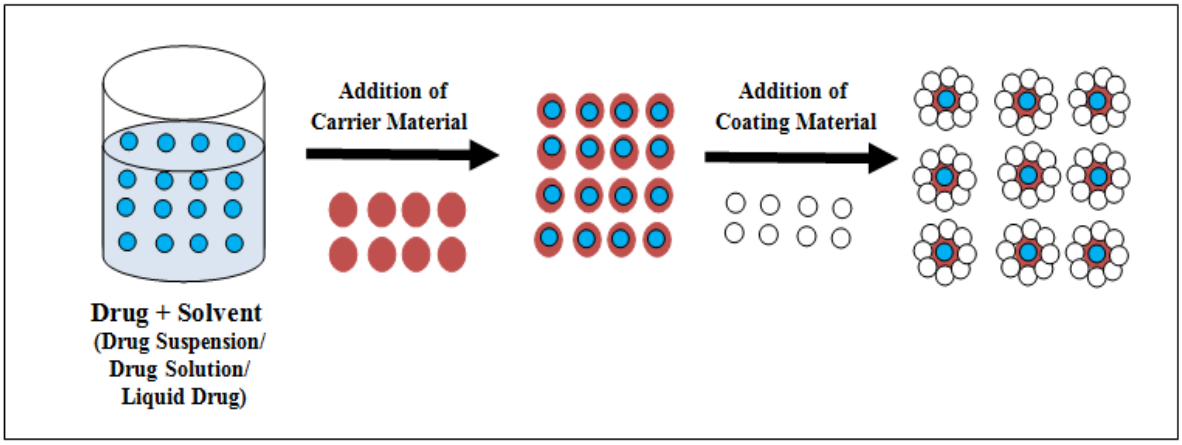

Figure No: 1: Formation of liquisolid compact of liquid drugs using porous carriers and coating materials

Theory:

Only a small portion of a liquid drug may be adequately preserved in a powder while maintaining flowability and compressibility. In order to create a liquisolid system with suitable flowable and compressible properties, it is advised to apply a mathematical model developed and validated by Spireas to estimate the required proportions of carrier and coating material. The flowable liquid retention potential (value) and compressible liquid retention potential (value), two essential features of a powder, are the foundation of the liquisolid

model. The and values of powder excipients indicate how much liquid vehicle may be maintained in the majority of the powder without compromising flow ability and compressibility. Measuring the liquid-powder mixture's sliding angle is the primary way for figuring out value. Value can be ascertained by doing an experiment called pactisity, which is defined as the maximum crushing strength of a tablet with a weight of one gram under sufficiently strong compression.

The following is the definition of excipients ratio (R), often known as carrier/coating ratio:

$$R = Q\ q \quad (a)$$

R is the proportion of carrier (Q) and coating material weights as a result (q). Higher carrier and lower coating material amounts result from an increase in R value. An ideal value of R is suggested to be 20 since the R value is connected to the liquisolid system's flowability, compressibility, disintegration, and dissolution rates.

Another crucial factor known as liquid loading of the liquisolid system. The loading factor (Lf), often known as the liquid's weight to its volume. The system contains the drug (W) and the carrier material (Q).

$$Lf = W\ Q \quad (b)$$

The factor for liquid loading in the creation of a liquisolid. A system's suitability for flowability can be assessed by:

$$\Phi L\ \Phi\ f = +\phi\ R \quad (c)$$

where Φ and ϕ values flowable liquid is represented by the values of and the carrier's and the coating's relative retention capacities.

In line with this, the liquid loading factor is used to liquisolid system's allowable compressibility can be established by:

$$^{\Psi}L\ \Psi\ f = +\psi R \quad (d)$$

Where Ψ and ψ values represent the carrier's and the coating material's capacity to retain compressible liquid, respectively.

Therefore, lowest value is the optimal liquid loading factor L_0, which results in a liquisolid system with adequate proper compressibility as well as flowability. Since the values for Φ, Ψ, ϕ, and ψ are constants for each powder-liquid combination, the ideal liquid loading factor for excipients ratio R can be determined using Equations (c) or (d). Then, different weights of liquid medication (W) will be employed in accordance with various drug concentrations. Thus, using Equations (a) and (b), the appropriate amount of carrier Q_o and coating material q_o may be determined based on predicted L_0 and W[35-40, 48].

Advantages of the liquisolid technique include:

1. Improved flowability and compressibility of liquid drugs, which allows for their easy handling and tablet formation.
2. Enhanced dissolution rate of drugs, which can lead to faster onset of action and improved bioavailability.
3. Increased stability of liquid drugs, as they are incorporated into a solid matrix.
4. Possibility of achieving controlled release of drugs, by choosing

appropriate solid carriers and coating materials.

5. Cost-effective technique as it utilizes small amounts of excipients[41-44].

Disadvantages of the liquisolid technique include:

1. Limited applicability to certain types of drugs, as the technique may not be suitable for all types of liquid drugs.
2. Complex formulation process, as the selection of appropriate excipients and the optimization of their ratios is critical for the successful formation of the compact.
3. High viscosity liquids may be difficult to handle and may require further processing steps.
4. Potential for reduced drug content uniformity and stability if not properly prepared.
5. The potential for toxicity due to inappropriate excipient selection and lack of toxicity testing[45-47].

Liquisolid Compacts Formulation

Liquid Vehicle:

It's crucial to remember that these processes may change based on the unique features of the liquid medicine and the desired attributes of the compact. In the formulation design of a liquisolid system, choosing the liquid vehicle is a crucial step. The liquid vehicle should have the following characteristics:

1. It should be chemically and physically stable, non-toxic, and compatible with the liquid drug and excipients used in the formulation.
2. It should have a suitable viscosity and surface tension, which allows for good mixing with the solid carrier and coating material.
3. It should have low volatility and a low tendency to form crystals, which can affect the flowability and compressibility of the compact.
4. It should be pharmaceutically acceptable and should not interact with the drug or excipients in a way that affects the stability or bioavailability of the drug.
5. It should be able to solubilize the drug, if the drug is sparingly soluble in water.
6. It should be a good solvent for the excipients used in the formulation[48-53].

Carrier material:

Carriers play a crucial role in the formulation design of a liquisolid system, as they are responsible for providing the physical structure to the compact and influencing the release rate of the drug. The selection of the carrier should take into account the following factors:

1. Compatibility: The carrier should be compatible with the liquid drug and excipients used in the formulation.
2. Flowability: The carrier should have good flow properties, which allows for easy handling and tablet formation.
3. Compressibility: The carrier should have good compressibility, which allows for the formation of tablets with adequate hardness and friability.
4. Surface area: The carrier should have a high surface area to volume ratio, which enhances the dissolution rate of the drug.

5. Cost: The carrier should be readily available and cost-effective.
6. Safety and toxicity: The carrier should be non-toxic and should not interact with the drug or excipients in a way that affects the stability or bioavailability of the drug.

Examples of carriers used in liquisolid systems formulation include microcrystalline cellulose, lactose, starch, and dicalcium phosphate. The selection of a carrier would depend on the specific characteristics of the liquid drug and the desired properties of the compact[54-56].

Coating material

Coating materials play a critical role in the formulation design of a liquisolid system, as they provide a protective barrier around the solid carrier-liquid drug particles, which helps to control the drug release rate. The selection of the coating material should take into account the following factors:

1. Hydrophobicity: The coating material should be hydrophobic in nature, which allows it to form a film around the solid carrier-liquid drug particles and prevent the drug from leaching out.
2. Film-forming properties: The coating material should have good film-forming properties, which allows it to form a uniform, continuous, and stable film around the solid carrier-liquid drug particles.
3. Compatibility: The coating material should be compatible with the liquid drug and excipients used in the formulation.
4. Cost: The coating material should be readily available and cost-effective.
5. Safety and toxicity: The coating material should be non-toxic and should not interact with the drug or excipients in a way that affects the stability or bioavailability of the drug.

Examples of coating materials used in liquisolid systems formulation include Neusilin®, talc, calcium silicate, magnesium stearate, magnesium aluminometasilicates, silicon dioxide, polyethylene glycol and Aerosil® 200. The selection of a coating material would depend on the specific characteristics of the liquid drug and the desired properties of the compact[36, 48, 57, 58].

Other additives:

Additives added to liquisolid formulation to enhance its properties and performance include:

1. Disintegrants: It is added to liquisolid formulation to improvement in surface area of the compact, which imparts and improve the dissolution rate of the drug. Examples of disintegrants include cellulose derivatives such as sodium starch glycolate and cross-linked polyvinylpyrrolidone.
2. Lubricants: It is added to liquisolid formulation for minimizing the friction between the compact and the die wall during compression, which improves the flow properties of the formulation and prevents sticking. Examples of lubricants include magnesium stearate, talc, and silicon dioxide.
3. Wetting agents: It is added to liquisolid formulation to minimizing surface tension of the liquid vehicle,

which allows for better wetting and mixing of the solid carrier and coating material. Examples of wetting agents include polysorbate 80 and sodium lauryl sulfate.

4. Plasticizers: These additives are added to the formulation to increase the flexibility of the compact and prevent cracking. Examples of plasticizers include glycerol and propylene glycol.
5. Buffers: These additives are added to the formulation to control the pH of the liquid vehicle and improve the stability of the drug. Examples of buffers include sodium citrate and citric acid [48, 59, 60].

Preparation Procedure for a Liquisolid System:

The procedure for a liquisolid preparation typically involves the following steps:

1. Selection of the drug: The first step in the preparation of a liquisolid system is to select the drug that will be used in the formulation. The drug should be stable and have adequate solubility in liquid vehicle.
2. Choosing the carrier and coating material: The choice of the carrier and coating material comes next. The coating material should be hydrophobic and have good film-forming capabilities, and the carrier should have good flow and compressibility characteristics.
3. Selection of the liquid vehicle and additives: The liquid vehicle should be selected based on the solubility of the drug and the desired properties of the compact. Additives such as disintegrants, lubricants, wetting agents, plasticizers, and buffers can also be added to the formulation at this stage.
4. Mixing of the ingredients: The ingredients, including the liquid drug, carrier, coating material, liquid vehicle, and additives, are mixed together in a suitable equipment such as a planetary mixer or a high-speed mixer to form a homogenous blend.
5. Compression of the blend: The homogenous blend is then compressed into tablets using a suitable tablet press. The compression parameters such as the pressure and speed are adjusted to achieve the desired tablet properties.
6. Evaluation of the tablets: The tablets are evaluated for physical properties such as hardness, friability, and weight variation, as well as for dissolution rate and bioavailability.
7. Optimization and Stability studies: If the results of the evaluations are not satisfactory, the formulation can be optimized by adjusting the ratio of ingredients and/or compression parameters. Finally, the stability of the liquisolid compacts is studied in appropriate conditions before commercialization[48, 54, 61-63].

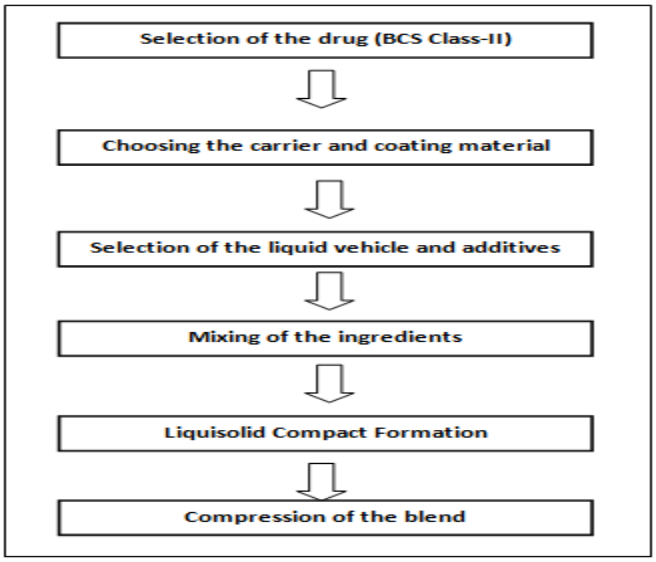

Figure No: 2: Preparation Procedure for a Liquisolid System

Applications of the liquisolid system

Liquisolid systems are a promising method for formulating liquid medications with poor solubility, bioavailability, or stability problems. The following are some examples of liquisolid method applications in pharmaceutics:

1. Medications with poor water solubility can have their solubility improved using the liquisolid approach, which increases the drugs' bioavailability and lowers the dosage needed to produce a therapeutic effect.
2. Controlled release: The liquisolid approach can be utilised to regulate the rate at which pharmaceuticals are released from the compact, enabling sustained release and targeted drug administration to particular parts of the body.
3. Liquisolid technology can be used to enhance the stability of liquid medications, which lowers the need for refrigeration and lengthens the shelf life of the drug
4. Taste masking: By using the liquisolid approach, bitter or unpleasant-tasting medications can be disguised, increasing patient compliance.
5. Transdermal administration: Liquisolid formulation can be utilised to provide liquid medications for transdermal administration, enabling non-invasive administration and enhancing patient compliance[48, 64].

Conclusion:

In conclusion, the liquisolid technique is a promising approach for the formulation of liquid drugs that have poor solubility, bioavailability, or stability issues. The liquisolid technique utilizes a hydrophobic coating material and a hydrophilic carrier to form a solid compact that contains a high amount of liquid drug. This results in an increase in the solubility and dissolution rate of the drug, which improves its bioavailability and reduces the dose required to achieve the therapeutic effect. Additionally, the liquisolid technique can be

used for controlled release, stability improvement, taste masking, and transdermal delivery of liquid drugs. The liquisolid compacts can be prepared using various carrier and coating materials, and the formulations can be optimized to achieve the desired properties. Overall, the liquisolid technique offers a novel approach for the formulation of liquid drugs and has the potential to improve patient compliance and treatment outcomes.

Sr. No	**Name of drug**	**Carrier material**	**Coating Material**	**Liquid Vehicle**
1	Cadesartan cilexetil	Microcrystalline cellulose	silica	Tween 80
2	Trimetazidine Di hydrochloride	Binary mixture of carrier coating (F1, F2 and F3), Eudragit L-100 (E1, E2 and E3) and RS-100 (S1, S2 and S310	Ethyl cellulose	Polysorbate 80
3	Paliperidone	Avicel PH 102	Aerosil 200	PEG 400
4	Carbamazepine	Neusilin, Fujicalin	--	Nonvolatile solvents
5	Nimesulide	Microcrystalline cellulose, Hydroxypropyl methylcellulose-E15, Starch	Silica gel	Polyethylene glycol-400
6	BCS class II drug	Avicel PH 102	Aerosil 200	Nonvolatile solvent
7	Amlodipine Besylate	Avicel PH-101	Aerosil	Propylene Glycol
8	Piroxicam	Avicel PH 102	Aerosil 200	--
9	Olmesartan medoxomil	Avicel PH 102, Fujicalin and Neusilin	Aerosil	Acrysol EI 135
10	Carvedilol	Avicel PH 101 and 102	Aerosil	PEG, PG, glycerin
11	Meloxicam	Avicel PH102	Aerosil 200	Polyethylene glycol 400
12	Candesartan	Avicel PH102	Aerosil	PEG 400, propylene glycol
13	Telmisartan	Avicel PH102	Aerosil 200	Transcutol HP
14	Flubiprofen	Avicel PH102 or starch or HPMC or PEG 4000 or PEG 6000	Aerosil 200	Polyethylene Glycol 400
15	Lovastatin	Avicel PH 200	Cab-O-Sil	Polyethylene

				Glycol 400
16	Spironolactone	Microcrystalline cellulose	Silica	PEG 400 and glycerin
17	Risperidone	Neusilin and Fugicalin	Aerosol 200	Propylene glycol

Table No:1 Formulations of Liuisolid Compact[48-64]

Future prospective:

The future prospects of the liquisolid technique are promising, as it offers a viable solution for the formulation of liquid drugs that have poor solubility, bioavailability, or stability issues. Some potential future developments in the field of liquisolid compacts include:

1. Development of novel carrier and coating materials: Researchers are currently exploring new carrier and coating materials that can improve the solubility, dissolution rate, and stability of liquid drugs. For example, the use of natural polymers such as cellulose derivatives and chitosan as carrier materials is being investigated.
2. Optimization of formulation parameters: Researchers are also working on optimizing the formulation parameters such as the ratio of carrier to coating material and the particle size of the carrier to achieve optimal drug release and bioavailability.
3. Use of smart polymers: Use of smart polymers in liquisolid systems could be a great step for targeted drug delivery, for example, pH-sensitive polymers can be used to release drugs at specific pH values in the body.
4. Development of liquisolid systems for specific drug classes: Researchers are also focusing on developing liquisolid systems for specific drug classes, such as anticancer drugs, anti-inflammatory drugs, and antiviral drugs, which have poor solubility and bioavailability.
5. Development of liquisolid systems for transdermal delivery: Researchers are also focusing on developing liquisolid systems for transdermal delivery of liquid drugs which can be a great step in non-invasive drug delivery.

Overall, the liquisolid technique has the potential to become a widely-used approach for the formulation of liquid drugs and future research will likely lead to new and improved formulations with better solubility, dissolution rate, and stability.

References:

1. Price G, Patel DA. Drug Bioavailability. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557852/.
2. Alagga AA, Gupta V. Drug Absorption. [Updated 2022 Jun 23].

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557405/

3. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727. Epub 2012 Jul 5. PMID: 22830056; PMCID: PMC3399483.
4. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012 Jan;2(1):12-7. doi: 10.4103/2230-973X.96921. PMID: 23071955; PMCID: PMC3465159
5. Tran P, Pyo Y-C, Kim D-H, Lee S-E, Kim J-K, Park J-S. Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs. Pharmaceutics. 2019; 11(3):132. https://doi.org/10.3390/pharmaceutics11030132
6. Coltescu A.R, Butnariu M, Sarac I. The Importance of Solubility for New Drug Molecules. Biomed Pharmacol J 2020;13(2). https://dx.doi.org/10.13005/bpj/1920
7. Bremmell KE, Prestidge CA. Enhancing oral bioavailability of poorly soluble drugs with mesoporous silica based systems: opportunities and challenges. Drug Dev Ind Pharm. 2019 Mar;45(3):349-358. doi: 10.1080/03639045.2018.1542709
8. Loh, Zhi Hui, et al. "Overview of Milling Techniques for Improving the Solubility of Poorly Water-soluble Drugs." Asian Journal of Pharmaceutical Sciences, vol. 10, no. 4, Elsevier BV, July 2015, pp. 255–74. https://doi.org/10.1016/j.ajps.2014.12.006.
9. Dixit M, Kulkarni PK. Lyophilization monophase solution technique for improvement of the solubility and dissolution of piroxicam. Res Pharm Sci. 2012 Jan;7(1):13-21. PMID: 23181075; PMCID: PMC3500553.
10. Repka MA, Majumdar S, Kumar Battu S, Srirangam R, Upadhye SB. Applications of hot-melt extrusion for drug delivery. Expert Opin Drug Deliv. 2008 Dec;5(12):1357-76. doi: 10.1517/17425240802583421.
11. Patil H, Tiwari RV, Repka MA. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation. AAPS PharmSciTech. 2016 Feb;17(1):20-42. doi: 10.1208/s12249-015-0360-7.
12. Patel BB, Patel JK, Chakraborty S, Shukla D. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharm J. 2015 Sep;23(4):352-65. doi: 10.1016/j.jsps.2013.12.013.
13. Sertsou G, Butler J, Hempenstall J, Rades T. Solvent change co-precipitation with hydroxypropyl

methylcellulose phthalate to improve dissolution characteristics of a poorly water-soluble drug. J Pharm Pharmacol. 2002 Aug;54(8):1041-7. doi: 10.1211/002235702320266181.

14. Bertoni S, Albertini B, Passerini N. Spray Congealing: An Emerging Technology to Prepare Solid Dispersions with Enhanced Oral Bioavailability of Poorly Water Soluble Drugs. Molecules. 2019 Sep 25;24(19):3471. doi: 10.3390/molecules24193471.
15. Misra SK, Pathak K. Supercritical fluid technology for solubilization of poorly water soluble drugs via micro- and naonosized particle generation. ADMET DMPK. 2020 Jun 29;8(4):355-374. doi: 10.5599/admet.811.
16. Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs. Pharmaceutics. 2019 Mar 19;11(3):132. doi: 10.3390/pharmaceutics11030132.
17. Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs. Adv Pharm Bull. 2020 Jul;10(3):359-369. doi: 10.34172/apb.2020.044.
18. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. 2022; 10(9):2055. https://doi.org/10.3390/biomedicines10092055
19. Sneha Jagtap et al, Solubility Enhancement Technique: A ReviewJ. Pharm. Sci. & Res. Vol. 10(9), 2018, 2205-2211
20. Serajuddin AT. Salt formation to improve drug solubility. Adv Drug Deliv Rev. 2007 Jul 30;59(7):603-16. doi: 10.1016/j.addr.2007.05.010.
21. Gupta D, Bhatia D, Dave V, Sutariya V, Varghese Gupta S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations. Molecules. 2018 Jul 14;23(7):1719. doi: 10.3390/molecules23071719
22. Badawy, S.I.F. and Hussain, M.A. (2007), Microenvironmental pH modulation in solid dosage forms. J. Pharm. Sci., 96: 948-959. https://doi.org/10.1002/jps.20932
23. Yeh MK, Chang LC, Chiou AH. Improving tenoxicam solubility and bioavailability by cosolvent system. AAPS PharmSciTech. 2009;10(1):166-71. doi: 10.1208/s12249-009-9189-2.
24. Saokham P, Muankaew C, Jansook P, Loftsson T. Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes. Molecules. 2018 May 11;23(5):1161. doi: 10.3390/molecules23051161.
25. Shalaby KS, Ismail MI, Lamprecht A. Cyclodextrin Complex Formation with Water-Soluble Drugs: Conclusions from Isothermal

Titration Calorimetry and Molecular Modeling. AAPS PharmSciTech. 2021 Aug 31;22(7):232. doi: 10.1208/s12249-021-02040-8.

26. Jornada DH, dos Santos Fernandes GF, Chiba DE, de Melo TR, dos Santos JL, Chung MC. The Prodrug Approach: A Successful Tool for Improving Drug Solubility. Molecules. 2015 Dec 29;21(1):42. doi: 10.3390/molecules21010042.
27. Markovic M, Ben-Shabat S, Dahan A. Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products. Pharmaceutics. 2020 Oct 29;12(11):1031. doi: 10.3390/pharmaceutics12111031.
28. Kalepu, Sandeep, et al. "Oral Lipid-based Drug Delivery Systems – an Overview." Acta Pharmaceutica Sinica B, vol. 3, no. 6, Elsevier BV, Dec. 2013, pp. 361–72. https://doi.org/10.1016/j.apsb.2013.10.001.
29. Franco P, De Marco I. The Use of Poly(N-vinyl pyrrolidone) in the Delivery of Drugs: A Review. Polymers (Basel). 2020 May 13;12(5):1114. doi: 10.3390/polym12051114.
30. Liechty WB, Kryscio DR, Slaughter BV, Peppas NA. Polymers for drug delivery systems. Annu Rev Chem Biomol Eng. 2010;1:149-73. doi: 10.1146/annurev-chembioeng-073009-100847.
31. Jurczak E, Mazurek AH, Szeleszczuk Ł, Pisklak DM, Zielińska-Pisklak M. Pharmaceutical Hydrates Analysis-Overview of Methods and Recent Advances. Pharmaceutics. 2020 Oct 11;12(10):959. doi: 10.3390/pharmaceutics12100959.
32. Thi Nhat Phuong Nguyen and Kwang-Joo Kim, Transformation of Monohydrate into Anhydrous Form of Risedronate Monosodium in Methanol−Water Mixture, Industrial & Engineering Chemistry Research 2010 49 (10), 4842-4849 DOI: 10.1021/ie901677n
33. Gupta, Shweta, et al. "Formulation Strategies to Improve the Bioavailability of Poorly Absorbed Drugs With Special Emphasis on Self-Emulsifying Systems." ISRN Pharmaceutics, vol. 2013, Hindawi Limited, Dec. 2013, pp. 1–16. https://doi.org/10.1155/2013/848043.
34. Khadka, Prakash, et al. "Pharmaceutical Particle Technologies: An Approach to Improve Drug Solubility, Dissolution and Bioavailability." Asian Journal of Pharmaceutical Sciences, vol. 9, no. 6, Elsevier BV, Dec. 2014, pp. 304–16. Crossref, https://doi.org/10.1016/j.ajps.2014.05.005.
35. Sayyad, Fahim Jahangir, et al. "Design and Development of Liquisolid Compact of Candesartan Cilexetil to Enhance Dissolution." Journal of Pharmacy Research, vol. 7, no. 5, Elsevier BV, May 2013, pp. 381–88.https://doi.org/10.1016/j.jopr.2013.05.012.

36. Jaydip B, Dhaval M, Soniwala MM, Chavda J. Formulation and optimization of liquisolid compact for enhancing dissolution properties of efavirenz by using DoE approach. Saudi Pharm J. 2020 Jun;28(6):737-745. doi: 10.1016/j.jsps.2020.04.016.
37. Tiong N, Elkordy AA. Effects of liquisolid formulations on dissolution of naproxen. Eur J Pharm Biopharm. 2009 Nov; 73(3):373-84. doi: 10.1016/j.ejpb.2009.08.002.
38. Spireas, S., Sadu, S. Enhancement of prednisolone dissolution properties using liqui- Solid compacts. Int.J. Pharm. 1998; 166: 177-88.
39. El-Say KM, Samy AM, Fetouh MI. Formulation and evaluation of rofecoxib liquisolid tablets. Int J Pharm Sci Rev Res 2010; 3:135-42.
40. Kulkarni AS, Gaja JB. Formulation and evaluation of liquisolid compacts of diclofenac sodium. PDA J Pharm Sci Technol 2010; 64:222-32.
41. Elkordy AA, Tan XN, Essa EA. Spironolactone release from liquisolid formulations prepared with Capryol™ 90, Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles. Eur J Pharm Biopharm 2013;83:203–223.
42. Khames A. Liquisolid technique: a promising alternative to conventional coating for improve ment of drug photostability in solid dosage forms. Drug Delivery 2013;10:1335–1343.
43. Gubbi SR, Jarag R. Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian J Pharm Sci, 2010;5:50–60.
44. Karmarkar AB, Gonjari ID, Hosmani AH, et al. Evaluation ofin vitro dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets. Drug Discov Ther 2010;4:26–32.
45. Singh SK, Srinivasan KK, Gowthamarajan K, et al. Influence of formulation parameters on dissolution rate enhancement of glyburide using liquisolid technique. Drug Dev Ind Pharm 2012;38:961–970.
46. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A, et al.Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm 2007;341:26–34.
47. Alotaibi FO, Alhakamy NA, Omar AM, El-Say KM. Clinical Pharmacokinetic Evaluation of Optimized Liquisolid Tablets as a Potential Therapy for Male Sexual Dysfunction. Pharmaceutics. 2020 Dec 7; 12(12):1187. doi: 10.3390/pharmaceutics12121187.
48. Mei Lu, Haonan Xing, Jingzheng Jiang, Xiao Chen, Tianzhi Yang, Dongkai Wang, Pingtian Ding,Liquisolid technique and its applications in pharmaceutics,Asian Journal of Pharmaceutical Sciences,Volume 12, Issue 2,2017,Pages 115-123,ISSN 1818-0876,https://doi.org/10.1016/j.ajps.2016.09.007.

49. Charman, S. A., & Charman, W. N. (2002). Oral Modified-Release Delivery Systems. In Modified-release drug delivery technology (pp. 25-34). CRC Press.
50. Saeedi, M., Akbari, J., Morteza-Semnani, K., Enayati-Fard, R., Sar-Reshteh-dar, S., & Soleymani, A. (2011). Enhancement of dissolution rate of indomethacin: using liquisolid compacts. Iranian journal of pharmaceutical research: IJPR, 10(1), 25.
51. Elkordy, A. A., Tan, X. N., & Essa, E. A. (2013). Spironolactone release from liquisolid formulations prepared with Capryol™ 90, Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles. European journal of pharmaceutics and biopharmaceutics, 83(2), 203-223.
52. Pavani, E., Noman, S., & Syed, I. A. (2013). Liquisolid technique based sustained release tablet of trimetazidine dihydrochloride. Drug invention today, 5(4), 302-310.
53. Spireas, S., & Sadu, S. (1998). Enhancement of prednisolone dissolution properties using liquisolid compacts. International Journal of Pharmaceutics, 166(2), 177-188.
54. Spireas, S. (2002). U.S. Patent No. 6,423,339. Washington, DC: U.S. Patent and Trademark Office.
55. Ali B, Khan A, Alyami HS, Ullah M, Wahab A, Badshah M, Naz A. Evaluation of the effect of carrier material on modification of release characteristics of poor water soluble drug from liquisolid compacts. PLoS One. 2021 Aug 2;16(8):e0249075. doi: 10.1371/journal.pone.0249075.
56. Hentzschel, C. M., Sakmann, A., & Leopold, C. S. (2011). Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug development and industrial pharmacy, 37(10), 1200-1207.
57. Hentzschel, C. M., Alnaief, M., Smirnova, I., Sakmann, A., & Leopold, C. S. (2012). Enhancement of griseofulvin release from liquisolid compacts. European Journal of Pharmaceutics and Biopharmaceutics, 80(1), 130-135
58. Sahil, M. G., Sharad, S. P., Shirish, V. S., Kisan, R. J., & Vilasrao, J. K. (2011). Liquisolid compact: a new technique for enhancement of drug dissolution. Int. J. Res. Pharm. Chem, 1(3).
59. Akinlade B, Elkordy AA, Essa EA, Elhagar S. Liquisolid systems to improve the dissolution of furosemide. Sci Pharm. 2010 Apr-Jun;78(2):325-44. doi: 10.3797/scipharm.0912-23. Epub 2010 Apr 23
60. Vraníková, B., Gajdziok, J., & Vetchý, D. (2015). Modern evaluation of Liquisolid systems with varying amounts of liquid phase prepared using two different methods. BioMed Research International, 2015, 1–12. https://doi.org/10.1155/2015/608435

61. Kulkarni, Ajit & Aloorkar, Nagesh & Mane, Madhav & Gaja, Jayashree. (2010). Liquisolid Systems: A Review. Int J Pharm Sci Nanotechnol. 3. 10.37285/ijpsn.2010.3.1.1.
62. Chella, Naveen, et al. "Preparation and Characterization of Liquisolid Compacts for Improved Dissolution of Telmisartan." Journal of Drug Delivery, vol. 2014, Hindawi Limited, Oct. 2014, pp. 1–10. Crossref, https://doi.org/10.1155/2014/692793.
63. Kasturi, Madhavi. 'Development of Liquisolid Compacts: An Approach for Dissolution Enhancement of Poorly Aqueous Soluble Drugs'. Drug Formulation Design [Working Title], IntechOpen, Nov. 2022. doi:10.5772/intechopen.108706
64. Pankaj Rajdeo, Amey Sukhia, Akash Nirware, Ravi Rajdeo, Liquisolid Technique: A Novel Approach to Enhance Solubility of Poorly Soluble Drugs, nternational Journal of Science and Research (IJSR), ISSN: 2319-7064, Volume 8 Issue 10, October 2019, 631-64