Development of Liquisolid Technology to Overcome Dissolution/Absorption Limitations of Oral Drugs

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Abstract

Increasing influx of poorly water-soluble drugs poses a significant challenge to oral drug delivery. Conventional solubilization techniques such as solid dispersion and cyclodextrin inclusion, while capable of improving drug dissolution, suffer from a great predicament in subsequent formulation processing. A novel "powder solution technology," the liquisolid technique, has come to the forefront in dealing with drug solubilization and formulation of oral "problem" drugs. The liquisolid technique involves the adsorption of liquid medications onto suitable carrier and coating materials, followed by conversion into free-flowing, dry-looking, and compressible powders. In the liquisolid system, the drug is dispersed in an almost molecular state, which greatly contributes to drug dissolution and absorption. This review aims to present the fundamentals of liquisolid technology and update the concept of liquisolid processing to expand its applications. The trend of modern drug discovery, drug solubilization approaches, application of liquisolid technology in formulation innovation, formulation composition, and design of liquisolid systems were discussed in detail. Special emphasis was placed on the application of liquisolid technology to improve the dissolution and bioavailability of poorly water-soluble drugs. Accumulating evidence shows that the liquisolid technology has immense potential to improve oral delivery and facilitate the secondary development of insoluble drugs.

Keywords
- liquisolid
- poorly water-soluble drugs
- dissolution
- absorption
- bioavailability

Introduction

Rapid advances in science and technology have accelerated the discovery of biologically active molecules, while at the same time generating a large number of poorly soluble and insoluble drug candidates.[1] Oral administration is the preferred route of drug delivery and has been used for thousands of years. The solubility and dissolution of active pharmaceutical ingredients (APIs) continue to be a concern for pharmaceutical practitioners. Approximately 40% of approved drugs and nearly 90% of pipeline drug candidates under development are estimated to be poorly water-soluble compounds.[2] These insoluble molecules, especially Biopharmaceutical Classification System (BCS) II molecules, are invariably subject to absorption barriers due to limited dissolution in the gastrointestinal (GI) tract. Therefore, dissolution enhancement is particularly important to facilitate drug absorption.[3]

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A variety of formulation strategies have been explored to improve the dissolution of poorly water-soluble drugs, including micronization,[4] solid dispersion,[5] inclusion complexation,[6] co-crystal formation,[7] nanocrystal technology,[8] the use of ionic liquids,[9] liquisolid technology,[10] and other pharmaceutical dispersion techniques.[11] Of these approaches, some can lead to the development of solid dosage forms, while others can only be applied to develop liquid dosage forms. Micronization can barely increase the specific surface area (SSA) of coarse drugs to a certain extent, but particle agglomeration often plagues formulation development.[12] Although solid dispersions and cyclodextrin inclusion complexes can be processed into solid dosage forms in one step using certain techniques,[13,14] the solvents used to dissolve drugs usually have to be removed, which poses a major problem in subsequent processing due to the viscous nature of the resulting products. Nanocrystal preparation also confronts the challenges of desolvation and crystal growth. Drug-loaded ionic liquids and other colloidal dispersions must also be converted to solid formulations for use.[15] The subsequent processing of these preparative intermediates poses a serious challenge for the development of oral dosage forms. Interestingly, the liquisolid technique holds great promise for continuous production, providing a platform for the convenient conversion of liquid medications into a solid form.[16]

The liquisolid technology is an innovative and advanced solid dosage form approach that can convert liquid or dissolved drugs into apparently dry, nonadherent, free-flowing, and compressible powders.[17] The earliest concept of the liquisolid system can be traced back to the 1980s with the introduction of the powdered solution.[18] In the liquisolid system, the drug is in the highest form of dispersion with an absolutely large SSA that allows the drug to dissolve freely in a dissolution medium. Excellent wettability and miscibility due to the use of hydrophilic nonvolatile solvents further contribute to the dissolution enhancement. Liquisolid powders can either be made into immediate-release or sustained-release preparations.[19–21] Furthermore, the liquisolid technology is particularly suitable for solubilization and formulation development of amphiphobic drugs that tend to precipitate from nanoparticles or dispersion systems upon encapsulation. Due to its low production cost and ease of handling, the liquisolid technology is emerging as an innovative and promising formulation strategy to improve the dissolution and bioavailability of insoluble drugs.[22]

This work was intended to provide information on the potential of liquisolid technology in enhancing drug dissolution and absorption. We discussed the features of modern drug discovery, various strategies for dissolution enhancement, and formulation composition and design ideas for developing liquisolid systems with an emphasis on the practical applications of liquisolid technology in dissolution and absorption enhancement. Extended liquisolid technology concepts and application scenarios were also presented and commented.

Overview of Modern Drug Discovery

Drug discovery and development represents one of the most important medical activities that contribute to human health and well-being. The modality of drug discovery has dramatically evolved over the past century. From the initial serendipitous discovery of an active compound, it is transiting to the current pattern: a target- and mechanism-driven approach based on a deep understanding of a disease.[23] Drug discovery and synthesis are becoming increasingly computerized and automated. Genomics, proteomics, and metabolomics hasten the rate of drug discovery,[24] while molecular mimicry and molecular docking speed up the generation of new pharmacological active ingredients (APIs).[25] High affinity to a disease target inevitably comes at the expense of water solubility, as intermolecular interactions are dominated by hydrophobicity. This shift in drug discovery has led to mixed results (►**Fig. 1**).[26] On the one hand, computer-aided drug design, combinatorial chemistry, and high-throughput screening have greatly accelerated drug discovery; on the

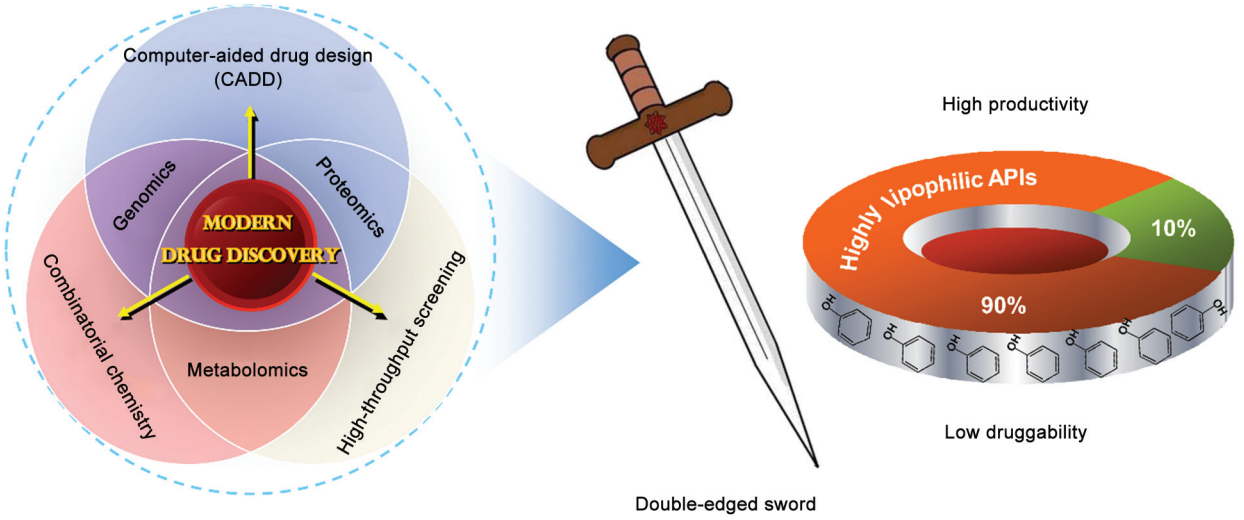

Fig. 1 Modern drug discovery.

other hand, this shift in drug discovery has also led to the emergence of an overwhelming number of highly hydrophobic active entities with poor druggability. In addition to those biodrugs, these newly discovered compounds are characterized by greater lipophilicity and/or high molecular weight. As reported,[27] approximately 40% of marketed drugs and 90% of drug candidates in the discovery pipeline are poorly water soluble or insoluble molecules, posing a serious challenge for formulation development.

According to the BCS,[28] poorly water-soluble drugs include BCS II and IV compounds. They are all characterized by a dissolution-limited process after oral administration. Most cases of failure in new drug research and development (R&D) can be ascribed to their poor or inadequate water solubility. Troubles associated with poor solubility of drugs can result in low bioavailability, hence inferior oral drug delivery efficacy. For BCS IV drug candidates, oral formulations are generally not encouraged to develop, since the issue of insufficient absorption is difficult to overcome even if a formulation technique solves the dissolution limitation. Oral dosage forms are the best options for BCS II drugs for their clinical application once the dissolution limitation is addressed. As far as conventional oral preparations are concerned, dosage escalation is necessary to achieve effective treatment goals. However, this dose escalation may cause adverse GI reactions, even enterotoxicity, upon oral administration.[29] To this end, dissolution improvement is the key to solving the challenge in the oral delivery of lipophilic drugs, both for old and newly discovered APIs.

Approaches for Improving Drug Dissolution

According to the specification of China Pharmacopeia, the solubility of drugs is specified as very soluble, freely soluble, soluble, sparingly soluble, slightly soluble, very slightly soluble, and practically insoluble or insoluble. APIs with a solubility of less than 1 mg/mL are considered poorly water-soluble drugs, including very slightly soluble and practically insoluble or insoluble ones. Eligible oral formulations must be satisfied by the solubility—the highest dose of API able to be completely dissolved in 250 mL of GI fluids, i.e., matching the sink condition for dissolution.[30] For poorly water-soluble drugs, the sink condition is difficult to achieve with conventional formulations. This predicament requires the use of advanced formulation technology to achieve formulation innovation.

A variety of pharmaceutical techniques have been explored to improve a drug's solubility or dissolution, including chemical modification, particle downsizing, amorphization, crystal engineering, nanometerization, and liquisolid technique, as shown in ►**Fig. 2**. Chemical modification improves drug solubility and dissolution by changing the chemical structure of the drug such as salt formation and introduction of a hydrophilic group.[31] It is the use of medicinal chemistry to improve the dissolution of a drug from the perspective of pharmaceutics. A drug salt can ionize in an aqueous solution, increasing its water solubility and dissolution rate. The attachment of a hydrophilic group, on the one hand, can improve the solubility of the drug itself, and on the other hand, a long hydrophilic chain (e.g., polyethylene glycol [PEG]) enables the

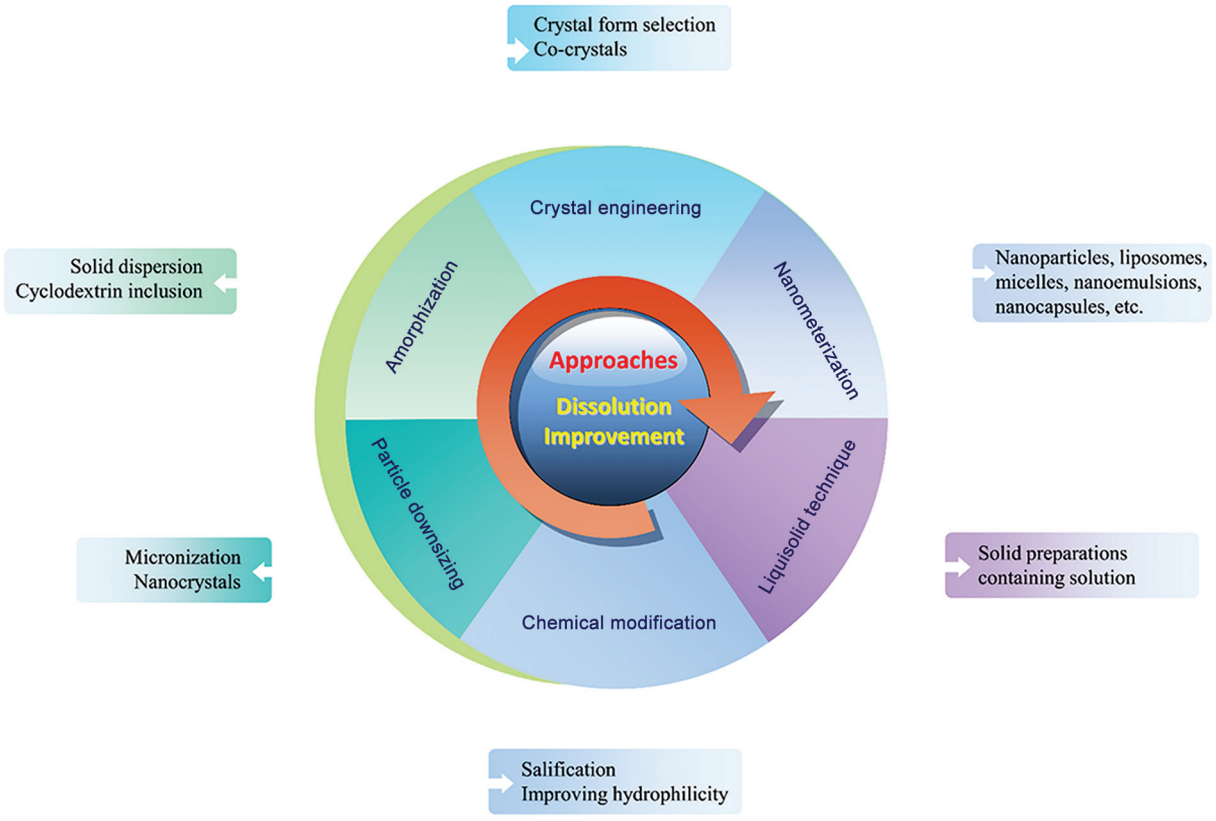

Fig. 2 Pharmaceutical techniques for improving drug dissolution.

self-assembly of molecules upon conjugation with the parent compound, thus facilitating the dissolution.[32]

Reducing the particle size of a drug is the most commonly used approach to improve its dissolution. According to the Noyes–Whitney equation,[33] the dissolution rate of a drug is proportional to the surface area and the saturation solubility of the drug, which can be achieved by the particle size reduction. There are typically two techniques available to reduce the size of drugs, i.e., micronization and nanocrystallization. Micronization is a mechanical and high-shear process to reduce the size of drug particles to the micron scale.[34] Nanocrystal technology is a method of obtaining drug nanocrystals by top-down or bottom-up techniques.[35] The nanocrystal technology is more feasible in improving drug dissolution than micronization. Amorphization is a formulation technique for obtaining amorphous drugs that can be achieved through solid dispersion and cyclodextrin inclusion. For example, revaprazan has been separately produced in solid dispersions, solid SNEDDS, and inclusion compounds with the crystalline drug being converted to an amorphous state in all formulations. All formulations significantly increased the drug solubility, dissolution, plasma drug concentration, and area under the curve compared with revaprazan powders.[36]

Crystal engineering involves the selection of the crystal form and formation of the eutectic crystals (co-crystals). Some drugs may be polycrystalline during recrystallization due to different crystallization processes. Differences in solubility exist in different crystal forms, and the optimal crystal form can be determined based on their solubility. Eutectic crystals have a lower dissolution potential energy due to the presence of crystalline defects, which favors the improvement of drug dissolution. Nanometerization refers to the preparation of a natural, incidental, or manufactured material-containing particles, in an unbound state or as aggregates or as agglomerates with a nanoscale size. Nanometerization is a broader concept that refers to various nanotechniques involved in the preparation of polymeric nanoparticles, lipid-based nanoparticles, liposomes, micelles, nanoemulsions, nanocapsules, etc. In pharmaceutics, it refers specifically to formulation processing that allows the incorporation of nanocarriers or nanoparticles. Although nanometerization does not directly improve drug dissolution, it creates a supersaturated drug concentration in the GI tract that facilitates drug absorption. The liquisolid technique is based on solid dispersions, which is a pharmaceutical technology used to formulate drug-containing liquid or preparative intermediate into a solid dosage form. The liquisolid technique lends strong support for the development of oral formulations of poorly water-soluble drugs.[37]

Liquisolid Technology in Formulation Innovation

The liquisolid technology involves the conversion of a liquid drug into a dry, nonadherent, free-flowing, and compressible powder mixture by mixing the liquid drug with suitable excipients.[38] Indeed, the liquisolid technology should not be confined to converting liquid-containing drugs into a processable solid form but specifically refers to a technology that can solidify liquid drugs. It allows the liquids that aid in the dissolution of a drug to remain in the liquid system or to be promptly removed from the system. Likewise, liquid medications are also not limited to a true solution of the drug, which can be a solid dispersion solution, a cyclodextrin inclusion solution, a self-emulsifying system, or an ionic liquid. Both pure drug solutions and carrier excipient-containing drug solutions can be loaded into liquisolid systems. Volatile solvents can be removed from the system via drying or evaporation after drug loading, leaving dried drug or drug dispersions in the system.[39,40] The liquisolid technology not only serves as a platform for the solidification of liquid medications, but also has deeper application scenarios in pharmaceutical processing. In a broad sense, the liquisolid technology, as depicted in ►**Fig. 3**, should encompass all aspects of technologies capable of solidifying liquid drugs, including liqui-pellet and extrusion-spheronization techniques originating from the liquisolid concept.[22,41,42]

The liquisolid technology offers many advantages over other dissolution-enhancing techniques. The liquisolid technology appropriately integrates liquid solubilization, solid dispersion, and formulation processing. The preparative process is largely simplified beyond low production cost and easy industrialization. An enormous number of poorly water-soluble drugs can be formulated into liquisolid systems for dissolution and bioavailability enhancement.[43] This technology is expected to convert solid dispersions and cyclodextrin inclusion complexes into tablets and capsules. The use of nonvolatile and anhydrous solvents is also of great promise to improve the chemical stability of water-labile drugs. Hydrolysis and oxidation are the predominant chemical degradation pathways of drugs.[44] Drug degradation in the liquid system is inhibited in an anhydrous medium due to the absence of moisture, while nonvolatile solvents also insulate drugs from oxygen exposure. The liquisolid technique circumvents the problems of downstream processing caused by the presence of liquid residues in other solubilization approaches. It transforms preparative intermediates such as solid dispersions and inclusion complexes into specific dosage forms, showing unique potential in formulation innovation. Of course, there are also disadvantages associated with the liquisolid technique. The technique is exclusively applied for poorly water-soluble drugs with a low dose, whereas the loading of high-dose drugs into liquisolid systems becomes difficult due to limitation capacity. The incorporation of hydrophilic liquids in the liquisolid systems can also cause problems with hygroscopicity, which may be detrimental to the stability of formulation as well as drugs.

Formulation and Design of A Liquisolid System

The smallest dimension of the drug in a formulation is manifested by its molecularity dispersed in suitable carrier excipients. In terms of solid dispersions, coarse poorly water-soluble drugs can be converted to solid solution upon complete dispersion in a selected carrier.[13,45] Likewise, liquefied medications can also be converted into dry-like,

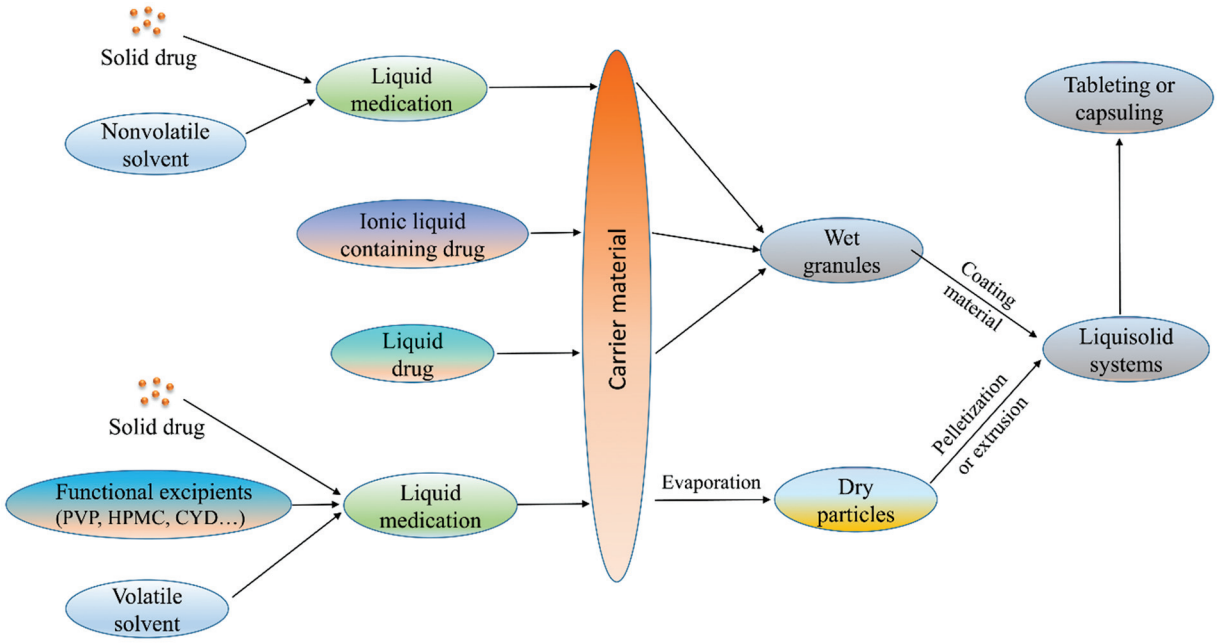

Fig. 3 Schematic illustration of liquisolid systems.

free-flowing, and compressible or fillable powders or granules by mixing with adsorptive excipients and subsequent formulation. A liquisolid system provides the molecular dispersion of drugs and creates the most favorable conditions for rapid dissolution. A liquisolid system is designed to convert a liquid drug into a processable solid form. Apart from the basic excipients used in tablets or capsules, a classical liquisolid dispersion system typically consists of a nonvolatile solvent, carrier material, coating material, and other excipients.[11] In the case of liquisolid compacts, the drug is first completely dissolved in the minimum amount of nonvolatile solvent necessary to make a liquid drug, then the liquid drug is mixed with carrier material to produce wet powders or granules, followed by the addition of coating material to form dry, free-flowing, and compressible mixtures, and finally compressed into tablets. The formulation composition of a liquisolid dispersion system (liquisolid compacts) is shown in ►**Table 1**.

The solvents used to dissolve poorly water-soluble drugs for developing liquisolid systems are normally nonvolatile liquids, meanwhile biologically inert, lowly viscous, and preferably water-miscible, in addition to strong solvent powder. A variety of hypotoxic solvents are employed to produce liquisolid systems, including PEG, propylene glycol, glycerin, and polysorbate. Mixed solvents or cosolvents can also be used to solubilize insoluble drugs. In liquisolid

Table 1 Components generally involved in a liquisolid formulation

Excipient type	Characteristics	Function	Examples
Nonvolatile solvent	Inert, water-miscible, compatible with drug candidates, and has excellent dissolution capacity	The nonvolatile solvent acts as a solvent and a binding agent in a liquisolid system	PEG, glycerin, propylene glycol, polysorbate, Cremophor EL, Transcutol HP, Capryol 90, 2-pyrrolidone, Labrasol
Carrier material	Porous, large specific surface area, sufficient adsorption ability, good flowability, and compressibility	Carrier material plays a fundamental role in forming the dry powders from liquid medication	Microcrystalline cellulose (MCC; e.g., Avicel, Ceolus, Vivapur, Emcocel), lactose, mannitol, magnesium aluminometasilicate (Neusilin), dibasic calcium phosphate anhydrous (Fujicalin)
Coating material	Ultrafine and highly adsorptive particles, good flow-enhancing effect	Coating material contributes to covering the wet surface of particles by adsorbing excess liquid to ensure a good flowability of powders	Colloidal silicon dioxide (e.g., Aerosil, Cab-O-Sil M5), Neusilin, Calcium silicate (Florite)
Other excipients	Disintegrant, lubricant, release modifiers, flavoring, and coloring agents	The selected agents can improve the quality of solid dosage forms	Sodium starch glycolate (CMS-Na), crospovidone, L-HPC, PVP k25, PEG 6000, HPMC, Eudragit

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systems, the liquid vehicle works as both a solvent and a binder.[46] Other hydrophilic or amphiphilic solvents such as Transcutol, Maisine 35-1, Labrafac CC, and Solutol are occasionally used in the liquisolid systems.[47] Carrier materials play a crucial role in changing liquid drugs into dry powders. They should have a porous microstructure and a large SSA.[48] The most commonly used carrier materials in liquisolid systems include microcrystalline cellulose (e.g., Avicel and Ceolus), mesoporous silicate, lactose, sorbitol, anhydrous dibasic calcium phosphate (Fujicalin), and amorphous magnesium aluminometasilicate (Neusilin). Fujicalin and Neusilin are inorganic functional materials, which display large SSAs, up to 40 and 300 m^2/g, respectively.[49] Neusilin is not only used as a carrier material but also as a coating material due to its excellent adsorption and flowability.[50] Coating materials help cover the wet particles to result in dry powders with sufficient flowability. They are characterized by fine micromeritic properties and a high adsorptive capacity that can adsorb excess liquid from the admixture. The coating materials currently used in liquisolid systems include colloidal silicon dioxide (e.g., Aerosil and Cab-O-Sil M5), amorphous silica gels (e.g., Syloid), calcium silicate (Florite), Neusilin, etc.[51] In addition to the excipients mentioned above, a liquisolid system usually involves the use of other additives to facilitate formulation development, such as disintegrants, lubricants, and release modifiers.[52,53]

In addition to the dissolution enhancement, liquisolid technology has also been employed as an innovative formulation strategy to develop sustained- or extended-release dosage forms. The rationale behind liquisolid technology to prolong drug release lies in the involvement of hydrophobic excipients (e.g., Eudragit RL and RS) instead of hydrophilic excipients or the incorporation of retarding agents (e.g., polyvinylpyrrolidone [PVP] and hydroxypropyl-methyl cellulose [HPMC]) or the use of viscous or liposoluble liquid vehicles (e.g., glycerin and polysorbate) in the liquisolid formulations, where a sustained release profile can be achieved.[53–55] The hydrophobicity and lower SSA of hydrophobic excipients compared to Avicel contribute to delayed drug release. Macromolecular polymers such as HPMC can form a gelatinous diffusion layer that delays drug release from liquisolid compacts. Viscous or liposoluble liquids as nonvolatile solvents used in the liquisolid systems can also control drug release in the presence of diffusion and insolubility barriers. A major advantage of applying liquisolid technology to extend drug release is the possibility of obtaining liquisolid systems with zero-order release kinetics. For instance, Pavani et al produced sustained-release tablets of trimetazidine dihydrochloride using Tween 80 as a nonvolatile vehicle and a binary mixture of ethyl cellulose (F1, F2, and F3), Eudragit L-100 (E1, E2, and E3) or RS-100 (S1, S2, and S3) and Aerosil as carrier-coating materials.[56] The dissolution profile of formulation E3 followed the Higuchi and Peppas model, showing a nearly zero-order release. Similarly, Hussain et al developed aceclofenac-loaded Eudragit L-100 and RS-100-based sustained-release tablets characterized by a zero-order release pattern using glycerin as the liquid vehicle upon the coating material Aerosil.[57] These studies indicate that the liquisolid technology has the potential to successfully develop sustained-release formulations. While the technology may seem straightforward for oral drugs that require sustained release, there are hurdles in the transition to industrialization due to poor flowability and compactibility as a result of the high proportion of controlled-release materials. A workable approach was proposed by Javadzadeh et al to increase the loading factor whereby to reduce the amount of carrier and coating materials,[52] thus obtaining liquisolid powders with acceptable flowability and compactibility. By introducing hydrophilic polymers such as PVP, HPMC, and PEG 35000, the loading factor can be increased. Either way, the liquisolid technology can be used to develop both immediate-release and sustained-release formulations to meet the challenges of oral drug delivery.

The liquisolid technology discussed in this section is not conceptually equivalent to the liquisolid system. Liquisolid systems are truly solid-like dispersion systems containing a liquid component, which can only address the formulation challenges of small-dose drugs and have a limited selection of nonvolatile solvents. The liquisolid technology is a specialized technique that converts a liquid drug into a solid form. It can overcome the limitations of drug dose and solvent selection, providing more options for oral drug delivery. For low-dose drugs, we can develop liquisolid compact formulations using a nonvolatile good solvent. However, for high-dose drugs, the amount of solvent needed to dissolve a poorly water-soluble drug often exceeds the maximum loading capacity of the excipient. At this point, formulation design will become particularly critical for the development of a liquisolid system. To improve the solubility of a high-dose drug, we can also utilize an ionic liquid as an alternative to a nonvolatile solvent to solubilize the drug, thereby reducing the liquid volume in the final formulation.[58] Furthermore, we can use a volatile solvent plus functional materials to achieve molecular dispersion of poorly water-soluble drugs in the pseudo-liquisolid system via drying in solid technique.[59] For example, it is an advisable strategy to combine a precursor solution containing solid dispersion carriers, inclusion materials, or self-emulsifying constituents with liquisolid technology for synchronous drug wrapping and loading via timely evaporation of volatile solvents.[60–63] With the help of these technologies, the criteria for drug candidates to develop liquisolid systems have been extended from low-dose drugs to some high-dose drugs and amphiphobic drugs. Fortunately, these novel formulation designs have slowly made their way into the minds of formulators to develop novel liquisolid systems.

Liquisolid Technology for Dissolution/Absorption Improvement

Liquisolid technology can be deemed as a pragmatic pharmaceutical dispersion technique.[11] In liquisolid systems, poorly water-soluble drugs are molecularly dispersed in the solid excipients,[21,64] and thus liquisolid technology has enormous potential for improving dissolution. For the

majority of poorly soluble drugs, the liquisolid technology can solve dissolution problems and improve oral bioavailability. BCS II drugs are particularly well suited to be developed as liquisolid compacts or capsules because the rate-limiting step for absorption is related to dissolution.[65,66] The absorption issues of BCS IV drugs can also be addressed to some extent by liquisolid technology in combination with the use of absorption enhancers.[67,68] In recent years, a great many poorly water-soluble drugs have been formulated into liquisolid systems for dissolution and/or bioavailability enhancement, including telmisartan,[69] raloxifene hydrochloride,[70] risperidone,[71] curcuma,[72] erlotinib,[73] efavirenz,[74] etodolac,[75] ritonavir,[76] itraconazole,[77] simvastatin,[78] silymarin,[79] cannabidiol,[40] clopidogrel,[80] loratadine,[81] rivaroxaban,[82] and cannabis sativa extracts.[83] ►**Table 2** shows the properties of the above APIs, the composition of their liquisolid systems, and the results obtained after *in vitro*/*vivo* testing. Significantly improved biopharmaceutical attributes (e.g., dissolution, permeability, or absorption) have been investigated using the liquisolid technology.

Using propylene glycol as a nonvolatile solvent, microcrystalline cellulose as a carrier, and silicon dioxide as a coating material, Naureen et al developed liquisolid compacts using a central composite design to improve the dissolution of mirtazapine.[84] The results showed that the crystallinity of mirtazapine in the liquisolid formulation vanished and the drug was completely dissolved in the nonvolatile solvent and thoroughly dispersed within the powders composed of carrier and coating materials. In addition, the dissolution of the drug was found to be higher from liquisolid compacts than from the conventional tablets compressed directly. In another study,[85] ketoprofen, a BCS II drug, was made into liquisolid formulation with PEG 200 as a solvent and microcrystalline cellulose and Aerosil 200 as carrier and coating material, respectively, in an attempt to improve the dissolution rate of ketoprofen and thereby its bioavailability. Differential scanning calorimetry and powder X-ray diffraction confirmed the amorphous nature of ketoprofen in the liquisolid system, which resulted in a significant improvement in its dissolution and anti-

Table 2 Reported liquisolid systems: API, formulation, and *in vitro*/*vivo* performance

API	Physical state	Excipients	*In vitro*/*vivo* outcomes	Ref.
Telmisartan	Partially amorphous /reduced crystallinity	Transcutol HP, Avicel PH 102, and Aerosil PH 200	pH-independent release with significant improvement in dissolution	69
Raloxifene	Molecular/amorphous state	Vehicle (Cremophor EL, Capmul PG-8, or Transcutol HP), Avicel PH 102, and Aerosil PH 200	Enhanced dissolution and intestinal permeability	70
Risperidone	Low crystallinity	Labrasol/Labrafil (1:1), Avicel PH 102, nanosized amorphous silicon dioxide (SiO_2)	Higher dissolution and increased oral bioavailability	71
Curcuma	Not characterized	Ethanol (removed in the final products), Avicel PH 102, and Aerosil PH 200	Improvement in dissolution with increased release	72
Erlotinib	Molecularly solubilized state	PEG 400 and Florite PS 200	Enhancement in dissolution, oral bioavailability, and therapeutic effect	73
Efavirenz	Amorphous/molecularly dispersed state	Transcutol HP, Neusilin US2, and Aerosil PH 200	Higher dissolution rate than tablets containing pure drug	74
Etodolac	Amorphous/molecularly dispersed state	PEG 400, Avicel PH 200, Aerosil PH 200	Enhanced oral bioavailability	75
Ritonavir	Amorphous form	PEG 400, Transcutol HP, Labrasol, Labrasol/Labrafil (1:1), Avicel PH 102, and nanosized amorphous SiO_2	Solubility enhancement effect at the absorption site	76
Itraconazole	Molecularly dispersed state	PEG 600, Alfacel PH 200, and Aerosil PH 200	Significantly higher drug dissolution and enhanced oral bioavailability were achieved	77
Simvastatin	Not characterized	Tween 80, Avicel PH 101, fumed silica, and Ac-Di-Sol	Increase of dissolution rate and overall enhancement in pharmacokinetics and pharmacodynamics	78
Silymarin	Partially amorphous form	Propylene glycol (PG), Avicel PH 102, Aerosil 200, HPMC K4M, and PVP K30	Improved dissolution and cardioprotective efficacy	79
Clopidogrel	Not characterized			80

(*Continued*)

Table 2 (*Continued*)

API	Physical state	Excipients	*In vitro*/*vivo* outcomes	Ref.
		The mixture of propylene glycol and water (2:1), MCC, starch maize, PVP, HPMC, and Aerosil 200	Fast and sustained releases of clopidogrel were achieved through the proper selection of excipients	
Loratadine	Not characterized	Propyleneglycol, glycerin, PEG 400, Avicel PH 102, and Aerosil (not specified)	Dissolution was significantly enhanced	81
Rivaroxaban	Amorphous state	PEG 400, Avicel PH 200, and Aerosil 200	Both dissolution rate and oral bioavailability were improved	82
Cannabis sativa extracts	Crystalline state (physically deposited onto carrier material)	Volatile vehicle (ethanol) and nonvolatile vehicles (Labrasol, PEG 400, Labrafil M 1944 CS, and Tween 20), Avicel PH 102, and Aerosil 200	More than 90% cannabinoid dissolution was achieved via liquisolid formulations using liquids with low polarity	83

Abbreviation: API, active pharmaceutical ingredient.

inflammatory activity *in vivo*. Continuous manufacturing is also a key component in realizing industrialized production of liquisolid formulations. To achieve this technical transformation, Zakowiecki et al employed a twin-screw processor to continuously produce liquisolid tablets containing either simethicone (oily API) or a combination of simethicone with loperamide hydrochloride.[86] Liquid-loaded powders that could be processed into tablets were continuously output using porous tribasic calcium phosphate as a carrier and the settings of the twin-screw processor. Raman imaging was used to visually observe the drug distribution of each component in the liquisolid tablets. In addition to dramatically enhanced dissolution, the liquid drugs (loperamide hydrochloride as the marker molecule) were uniformly distributed in the tablets but varied in particle size as shown in ►**Fig. 4**, which can be attributed to the difference in droplet size adsorbed by the excipient.

The *in vivo* studies also demonstrate an excellent performance of liquisolid formulation in improving oral bioavailability. Andrographolide, a major bioactive component from *Andrographis paniculata*, exhibits poor water solubility and low dissolution rate. When formulated into liquisolid powders, good powder fluidity and compressibility characteristics were achieved by solubilization in the mixture of *N*-methylpyrrolidone, PEG 6000, and Soluplus followed by adsorption with porous starch.[87] The liquisolid formulation not only increased the drug dissolution rate but also improved the *in vivo* pharmacokinetic behaviors, resulting in significantly enhanced oral bioavailability, up to 311.62 and 137.10% relative to commercial guttate pills and raw drugs. A clinical pharmacokinetic study conducted in healthy human volunteers also provided evidence that liquisolid formulations hold great promise for bioavailability enhancement.[88] In this work, liquisolid tablets containing tadalafil (TDL) and dapoxetine (DPX) were developed aiming to improve their bioavailability and potentiate their therapy for male sexual dysfunction. As a result, pharmacokinetic parameters of both TDL and DPX with liquisolid formulation were optimized after oral administration (►**Fig. 5**). The relative oral bioavailability of TDL and DPX was calculated to be 170.6 and 117.05%, respectively, compared to the marketed tablets. Taken together, the *in vitro*/*vivo* studies have demonstrated the tremendous potential of liquisolid technology to address the formulation challenges of poorly water soluble drugs. The rate and extent of drug absorption are closely related to their dissolution and surface area available for absorption in the intestinal lumen. APIs dissolved in nonvolatile solvents or molecularly dispersed in solid excipients can overcome the dissolution limitation, thus promoting oral drug absorption. The future development of liquisolid technology should focus on simplification and continuous manufacturing through technology integration. The emerging liqui-pellet

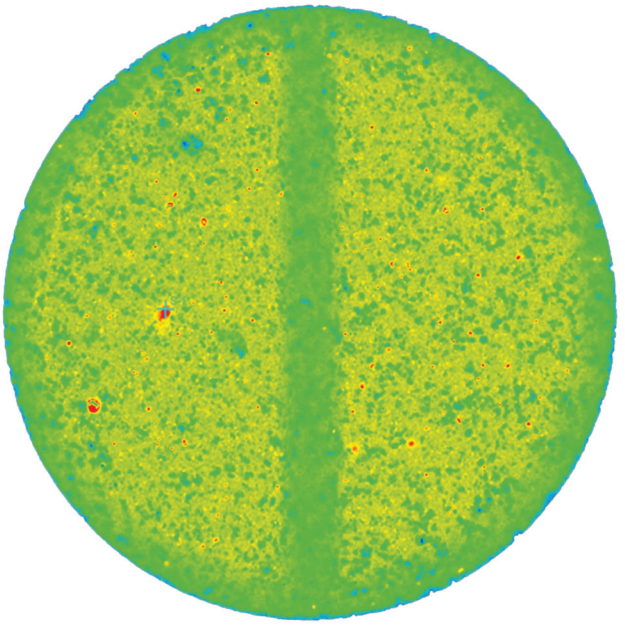

Fig. 4 Raman correlation map showing the spatial distribution of loperamide hydrochloride (in *red*). (Reproduced with permission from Zakowiecki et al,[86] copyright 2023 MDPI, Basel, Switzerland.)

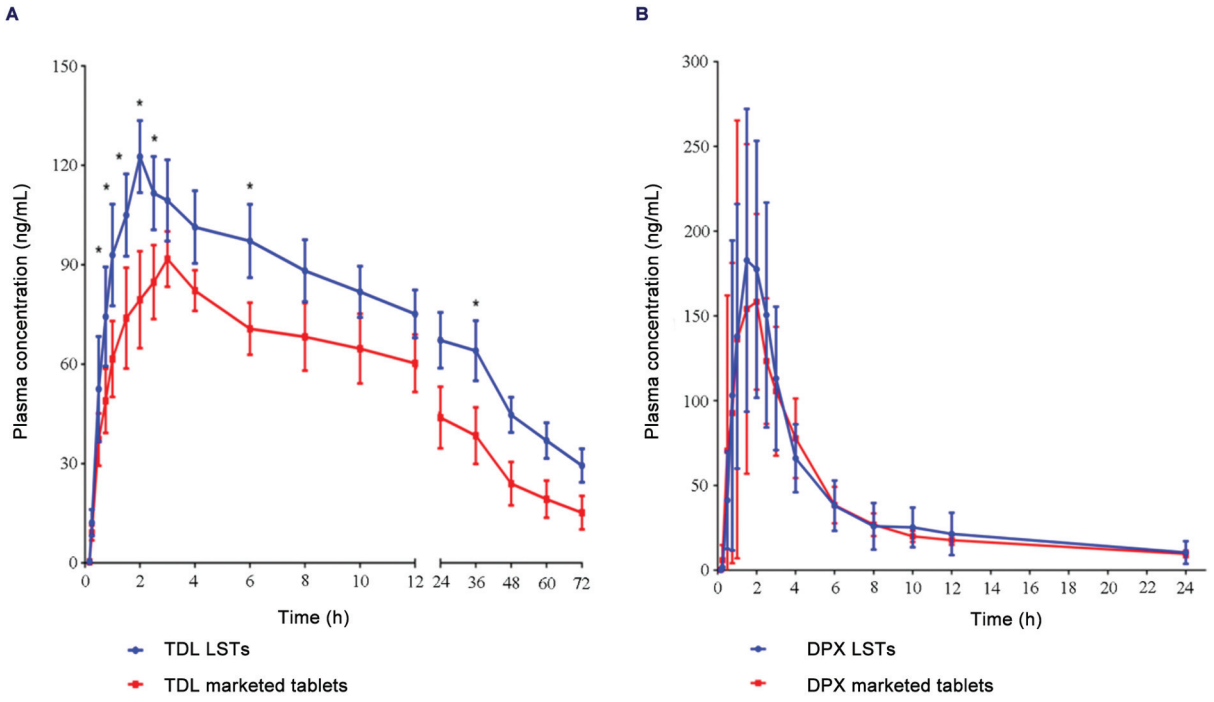

Fig. 5 The mean plasma concentration–time profiles of (**A**) marketed TDL tablets and optimized TDL LSTs at an oral dose of 5 mg and (**B**) marketed DPX tablets and optimized DPX LSTs at an oral dose of 30 mg. DPX, dapoxetine; LSTs, liquisolid tablets; TDL, tadalafil. *Significant difference at $p < 0.05$. (Reproduced with permission from Alotaibi et al,[88] copyright 2020 MDPI, Basel, Switzerland.)

technology (derived from the extrusion/palletization technology) and liquiground technology (combining liquisolid and co-grinding technologies) represent the next generation of liquisolid systems. These novel technologies enable the continuous manufacture of liquisolid formulations with high drug loading and reduced excipient limitations.

Conclusion

Liquisolid technology is a promising preparative process that enables the solidification of a liquid drug and allows the dissolution of the payload in the final formulation. Liquisolid technology maximizes drug dispersion (molecular form), thereby improving drug dissolution, and hence the oral bioavailability. Numerous studies have demonstrated rapid dissolution and drug absorption occurring with liquisolid formulations. The problems of dissolution and absorption of poorly water-soluble drugs, especially BCS II drugs, can be easily solved by liquisolid technology compared with other solubilization methods. It combines the advantages of solvent solubilization and solidification in one step that facilitates the production of an innovative solid dosage form. Liquisolid technology is not only limited to the solidification of liquid drugs or self-emulsifying formulations into a dry form, but it also includes dehydration and solidification of solutions containing solid dispersions, inclusion complexes, and other drug solubilization systems. In the future, liquisolid technology should move toward continuous manufacturing with the support of advanced equipment. It is imperative to develop novel solvents with strong solubilizing potential and carrier materials with high adsorption capacity so as to cope with the increasing number of insoluble drugs.

Conflict of Interest

None declared.

References

1 Vinarov Z, Abrahamsson B, Artursson P, et al. Current challenges and future perspectives in oral absorption research: an opinion of the UNGAP network. Adv Drug Deliv Rev 2021;171:289–331
2 Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B 2015;5 (05):442–453
3 Jambhekar SS, Breen PJ. Drug dissolution: significance of physicochemical properties and physiological conditions. Drug Discov Today 2013;18(23–24):1173–1184
4 Behzadnia M, Salmanpour M, Heidari M, et al. Sorafenib tosylate incorporation into mesoporous starch xerogel for *in-situ* micronization and oral bioavailability enhancement. Drug Dev Ind Pharm 2022;48(08):343–354
5 Srinarong P, de Waard H, Frijlink HW, Hinrichs WL. Improved dissolution behavior of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations. Expert Opin Drug Deliv 2011;8(09):1121–1140
6 Zhong Z, Yang X, Fu XB, et al. Crystalline inclusion complexes formed between the drug diflunisal and block copolymers. Chin Chem Lett 2017;28(06):1268–1275
7 Wang H, Yang D, Zhang W, et al. An innovative rhein-matrine cocrystal: synthesis, characterization, formation mechanism and pharmacokinetic study. Chin Chem Lett 2023;34(02):107258
8 Qiao Y, Wei Z, Qin T, et al. Combined nanosuspensions from two natural active ingredients for cancer therapy with reduced side effects. Chin Chem Lett 2021;32(09):2877–2881

9 Jiang L, Sun Y, Lu A, Wang X, Shi Y. Ionic liquids: promising approach for oral drug delivery. Pharm Res 2022;39(10):2353–2365
10 Aleksić I, German Ilić I, Cvijić S, Parojčić J. An investigation into the influence of process parameters and formulation variables on compaction properties of liquisolid systems. AAPS PharmSciTech 2020;21(07):242
11 Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. Pharmaceutics 2018;10(03):74
12 Saravanan D, Muthudoss P, Khullar P, Venis AR. Micronization and agglomeration: understanding the impact of API particle properties on dissolution and permeability using solid state and biopharmaceutical "Toolbox". J Pharm Innov 2021;16(01):136–151
13 Zhang XW, Sun NY, Wu BJ, et al. Physical characterization of lansoprazole/PVP solid dispersion prepared by fluid-bed coating technique. Powder Technol 2008;182(03):480–485
14 Zhang X, Wu D, Lai J, Lu Y, Yin Z, Wu W. Piroxicam/2-hydroxypropyl-beta-cyclodextrin inclusion complex prepared by a new fluid-bed coating technique. J Pharm Sci 2009;98(02):665–675
15 Liu R, Luo C, Pang Z, et al. Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment. Chin Chem Lett 2023;34(02):107518
16 Chaudhary N, Tripathi D, Rai AK. A technical approach of solubility enhancement of poorly soluble drugs: liquisolid technique. Curr Drug Deliv 2020;17(08):638–650
17 Spireas S, Sadu S, Grover R. *In vitro* release evaluation of hydrocortisone liquisolid tablets. J Pharm Sci 1998;87(07):867–872
18 Spireas SS, Jarowski CI, Rohera BD. Powdered solution technology: principles and mechanism. Pharm Res 1992;9(10):1351–1358
19 Prajapat MD, Butani SB, Gohel MC. Liquisolid: a promising technique to improve dissolution efficiency and bioavailability of poorly water soluble nimodipine. J Drug Deliv Sci Technol 2019;53:101135
20 Nnamani PO, Ugwu AA, Ibezim EC, et al. Sustained-release liquisolid compact tablets containing artemether-lumefantrine as alternate-day regimen for malaria treatment to improve patient compliance. Int J Nanomedicine 2016;11:6365–6378
21 Nokhodchi A, Hentzschel CM, Leopold CS. Drug release from liquisolid systems: speed it up, slow it down. Expert Opin Drug Deliv 2011;8(02):191–205
22 Vasiljević I, Turković E, Nenadović S, et al. Investigation into liquisolid system processability based on the SeDeM Expert System approach. Int J Pharm 2021;605:120847
23 Eder J, Herrling PL. Trends in modern drug discovery. Handb Exp Pharmacol 2016;232:3–22
24 Russell C, Rahman A, Mohammed AR. Application of genomics, proteomics and metabolomics in drug discovery, development and clinic. Ther Deliv 2013;4(03):395–413
25 Saikia S, Bordoloi M. Molecular docking: challenges, advances and its use in drug discovery perspective. Curr Drug Targets 2019;20 (05):501–521
26 Williams HD, Trevaskis NL, Charman SA, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev 2013;65(01):315–499
27 Khan KU, Minhas MU, Badshah SF, Suhail M, Ahmad A, Ijaz S. Overview of nanoparticulate strategies for solubility enhancement of poorly soluble drugs. Life Sci 2022;291:120301
28 Ku MS. Use of the Biopharmaceutical Classification System in early drug development. AAPS J 2008;10(01):208–212
29 Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm 2011;420(01):1–10
30 Phillips DJ, Pygall SR, Cooper VB, Mann JC. Overcoming sink limitations in dissolution testing: a review of traditional methods and the potential utility of biphasic systems. J Pharm Pharmacol 2012;64(11):1549–1559
31 Das B, Baidya ATK, Mathew AT, Yadav AK, Kumar R. Structural modification aimed for improving solubility of lead compounds in early phase drug discovery. Bioorg Med Chem 2022;56:116614
32 Khajeei A, Masoomzadeh S, Gholikhani T, Javadzadeh Y. The effect of PEGylation on drugs' pharmacokinetic parameters; from absorption to excretion. Curr Drug Deliv 2024;21(07):978–992
33 Noyes A, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897;19(12):930–934
34 Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods Find Exp Clin Pharmacol 1998;20(03):211–215
35 Mohammad IS, Hu H, Yin L, He W. Drug nanocrystals: fabrication methods and promising therapeutic applications. Int J Pharm 2019;562:187–202
36 Park JH, Kim DS, Mustapha O, et al. Comparison of a revaprazan-loaded solid dispersion, solid SNEDDS and inclusion compound: Physicochemical characterisation and pharmacokinetics. Colloids Surf B Biointerfaces 2018;162:420–426
37 Rashad A, Louis D. An overview on liquisolid technique: its development and applications. Ther Deliv 2022;13(12):577–589
38 Agiba AM. Liquisolid Technology: a state-of-the-art review on the current state, challenges, new and emerging technologies for next generation. Curr Drug Deliv 2020;17(09):736–754
39 Anzilaggo D, O'Reilly Beringhs A, Pezzini BR, Sonaglio D, Stulzer HK. Liquisolid systems: Understanding the impact of drug state (solution or dispersion), nonvolatile solvent and coating material on simvastatin apparent aqueous solubility and flowability. Colloids Surf B Biointerfaces 2019;175:36–43
40 Limpongsa E, Tabboon P, Pongjanyakul T, Jaipakdee N. Preparation and evaluation of directly compressible orally disintegrating tablets of cannabidiol formulated using liquisolid technique. Pharmaceutics 2022;14(11):2407
41 Lam M, Ghafourian T, Nokhodchi A. Liqui-pellet: the emerging next-generation oral dosage form which stems from liquisolid concept in combination with pelletization technology. AAPS PharmSciTech 2019;20(06):231
42 Muley S, Nandgude T, Poddar S. Extrusion–spheronization a promising pelletization technique: in-depth review. Asian J Pharm Sci 2016;11(06):684–699
43 Lu M, Xing H, Jiang J, et al. Liquisolid technique and its applications in pharmaceutics. Asian J Pharm Sci 2017;12(02):115–123
44 Zelesky T, Baertschi SW, Foti C, et al. Pharmaceutical forced degradation (stress testing) endpoints: a scientific rationale and industry perspective. J Pharm Sci 2023;112(12):2948–2964
45 Karolewicz B, Górniak A, Probst S, Owczarek A, Pluta J, Zurawska-Płaksej E. Solid dispersions in pharmaceutical technology. Part I. Classification and methods to obtain solid dispersions. Polim Med 2012;42(01):17–27
46 Karmarkar AB, Gonjari ID, Dhabale PN, et al. Dissolution rate enhancement of fenofibrate using liquisolid tablet technique. Lat Am J Pharm 2009;28:219–225
47 Siju VV, Soniwala M, Nagar S. A novel technique to enhance dissolution rate of cilnidipine using liquisolid compact and wet granulation. Int J Pharm Sci Drug Res 2017;9:160–168
48 Karmarkar AB, Gonjari ID, Hosmani AH. Liquisolid technology for dissolution rate enhancement or sustained release. Expert Opin Drug Deliv 2010;7(10):1227–1234
49 Hentzschel CM, Sakmann A, Leopold CS. Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug Dev Ind Pharm 2011;37(10):1200–1207
50 Vraníková B, Svačinová P, Marushka J, et al. The importance of the coating material type and amount in the preparation of liquisolid systems based on magnesium aluminometasilicate carrier. Eur J Pharm Sci 2021;165:105952
51 Vraníková B, Gajdziok J. Liquisolid systems and aspects influencing their research and development. Acta Pharm 2013;63(04): 447–465

52 Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm 2007;341;(1–2):26–34
53 Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN. Evaluation of *in vitro* dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets. Drug Discov Ther 2010;4 (01):26–32
54 Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm 2008;362(1–2):102–108
55 Nokhodchi A, Aliakbar R, Desai S, Javadzadeh Y. Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release. Colloids Surf B Biointerfaces 2010;79(01):262–269
56 Pavani E, Noman S, Syed IA. Liquisolid technique based sustained release tablet of trimetazidine dihydrochloride. Drug Invent Today 2013;5(04):302–310
57 Hussain Y, UrRehman A, Shah MN. Liquisolid technique: a novel tool to develop aceclofenac-loaded Eudragit L-100 and RS-100-based sustained release tablets. J Pharm Innov 2021;16(04):659–671
58 Zhang Y, Liu C, Wang J, et al. Ionic liquids in transdermal drug delivery system: current applications and future perspectives. Chin Chem Lett 2023;34(03):107631
59 De Mohac LM, Caruana R, Cavallaro G, Giammona G, Licciardi M. Spray-drying, solvent-casting and freeze-drying techniques: a comparative study on their suitability for the enhancement of drug dissolution rates. Pharm Res 2020;37(03):57
60 Sharma V, Pathak K. Effect of hydrogen bond formation/replacement on solubility characteristics, gastric permeation and pharmacokinetics of curcumin by application of powder solution technology. Acta Pharm Sin B 2016;6(06):600–613
61 Cirri M, Righi MF, Maestrelli F, Mura P, Valleri M. Development of glyburide fast-dissolving tablets based on the combined use of cyclodextrins and polymers. Drug Dev Ind Pharm 2009;35(01):73–82
62 Daware S, Patki M, Saraswat A, Palekar S, Patel K. Development of a safe pediatric liquisolid self-nanoemulsifying system of triclabendazole for the treatment of fascioliasis. Int J Pharm 2022; 626:122163
63 El-Say KM, Alamri SH, Alsulimani HH, et al. Incorporating valsartan in sesame oil enriched self-nanoemulsifying system-loaded liquisolid tablets to improve its bioavailability. Int J Pharm 2023; 639:122966
64 Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2008;69(03):993–1003
65 Tsume Y, Matsui K, Searls AL, et al. The impact of supersaturation level for oral absorption of BCS class IIb drugs, dipyridamole and ketoconazole, using *in vivo* predictive dissolution system: gastrointestinal simulator (GIS). Eur J Pharm Sci 2017;102:126–139
66 Takano R, Furumoto K, Shiraki K, et al. Rate-limiting steps of oral absorption for poorly water-soluble drugs in dogs; prediction from a miniscale dissolution test and a physiologically-based computer simulation. Pharm Res 2008;25(10):2334–2344
67 Ghadi R, Dand N. BCS class IV drugs: Highly notorious candidates for formulation development. J Control Release 2017;248:71–95
68 Saha SK, Joshi A, Singh R, et al. An investigation into solubility and dissolution improvement of alectinib hydrochloride as a third-generation amorphous solid dispersion. J Drug Deliv Sci Technol 2023;81:104259
69 Chella N, Narra N, Rama Rao T. Preparation and characterization of liquisolid compacts for improved dissolution of telmisartan. J Drug Deliv 2014;2014:692793
70 Komala DR, Janga KY, Jukanti R, et al. Competence of raloxifene hydrochloride loaded liquisolid compacts for improved dissolution and intestinal permeation. J Drug Deliv Sci Technol 2015; 30:232–241
71 Khames A. Investigation of the effect of solubility increase at the main absorption site on bioavailability of BCS class II drug (risperidone) using liquisolid technique. Drug Deliv 2017;24 (01):328–338
72 Jaipakdee N, Limpongsa E, Sripanidkulchai BO, Piyachaturawat P. Preparation of Curcuma comosa tablets using liquisolid techniques: *in vitro* and *in vivo* evaluation. Int J Pharm 2018;553;(1–2):157–168
73 Patel K, Doddapaneni R, Patki M, Sekar V, Bagde A, Singh M. Erlotinib-valproic acid liquisolid formulation: evaluating oral bioavailability and cytotoxicity in erlotinib-resistant non-small cell lung cancer cells. AAPS PharmSciTech 2019;20(03):135
74 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;28(06):737–745
75 Pathak BK, Raghav M, Thakkar AR, Vyas BA, Shah PJ. Enhanced oral bioavailability of etodolac by the liquisolid compact technique: optimisation, *in vitro* and *in vivo* evaluation. Curr Drug Deliv 2021;18(04):471–486
76 Bonthagarala B, Dasari V, Kotra V. Solubility enhancement effect at absorption site on bioavailability of ritonavir using liquisolid technique. Ther Deliv 2019;10(05):295–310
77 Thakkar HP, Vasava D, Patel AA, Dhande RD. Formulation and evaluation of liquisolid compacts of itraconazole to enhance its oral bioavailability. Ther Deliv 2020;11(02):83–96
78 El-Say KM, Ahmed TA, Ahmed OAA, Elimam H. Enhancing the hypolipidemic effect of simvastatin in poloxamer-induced hyperlipidemic rats via liquisolid approach: pharmacokinetic and pharmacodynamic evaluation. AAPS PharmSciTech 2020;21(06):223
79 Sheta NM, Elfeky YA, Boshra SA. Cardioprotective efficacy of silymarin liquisolid in isoproterenol prompted myocardial infarction in rats. AAPS PharmSciTech 2020;21(03):81
80 Ali B, Khan A, Alyami HS, et al. Evaluation of the effect of carrier material on modification of release characteristics of poor water soluble drug from liquisolid compacts. PLoS One 2021;16(08): e0249075
81 Eryani MC, Hendradi E, Siswandono. Variation concentration effect of propyleneglycol, glycerin, and polyethyleneglycol 400 to physical properties and dissolution rate of loratadine liquisolid tablet. J Basic Clin Physiol Pharmacol 2021;32(04):583–587
82 Shah P, Desai H, Vyas B, Lalan M, Kulkarni M. Quality-by-design-based development of rivaroxaban-loaded liquisolid compact tablets with improved biopharmaceutical attributes. AAPS PharmSciTech 2023;24(07):176
83 Jaipakdee N, Tabboon P, Limpongsa E. Application of a liquisolid technique to cannabis sativa extract compacts: Effect of liquid vehicles on the dissolution enhancement and stability of cannabinoids. Int J Pharm 2022;612:121277
84 Naureen F, Shah Y, Shah SI, et al. Formulation development of mirtazapine liquisolid compacts: optimization using central composite design. Molecules 2022;27(13):4005
85 Devi S, Kumar S, Verma V, Kaushik D, Verma R, Bhatia M. Enhancement of ketoprofen dissolution rate by the liquisolid technique: optimization and *in vitro* and *in vivo* investigations. Drug Deliv Transl Res 2022;12(11):2693–2707
86 Zakowiecki D, Richter M, Yuece C, et al. Towards the continuous manufacturing of liquisolid tablets containing simethicone and loperamide hydrochloride with the use of a twin-screw granulator. Pharmaceutics 2023;15(04):1265
87 Liu MK, Chen HL, Chen LL, et al. Andrographolide liquisolid using porous-starch as the adsorbent with enhanced oral bioavailability in rats. J Pharm Sci 2023;112(02):535–543
88 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;12 (12):1187