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A Comprehensive Review: Advantages and Limitations of Liquisolid Compacts Over Conventional Formulation Approaches

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Abstract

Low aqueous solubility remains one of the dominant challenges limiting the clinical performance of modern drug molecules. As nearly 40% of marketed drugs and more than 70% of new chemical entities fall into Biopharmaceutics Classification System (BCS) Class II or IV, formulation scientists continue to seek reliable and scalable strategies to improve dissolution behavior and oral bioavailability. Liquisolid compact technology has emerged as a promising method capable of enhancing the dissolution performance of poorly water-soluble drugs by converting liquid medications into compressible, free-flowing powders. This review provides an expanded, in-depth evaluation of the scientific principles, technological advancements, excipient selection, formulation considerations, micromeritic evaluations, and performance outcomes associated with liquisolid systems. Mechanistic insights into wettability enhancement, increased surface area, and molecular drug dispersion are examined. Applications in sustained-release design, supersaturable systems, and solid-state transformation are highlighted. The review also synthesizes contemporary findings, discusses manufacturing scalability, and explores future directions involving nanotechnology integration and predictive computational modelling. The evidence suggests that liquisolid technology represents a versatile, cost-effective, and industrially feasible strategy for improving the pharmaceutical performance of challenging drug candidates.

KEYWORDS: Liquisolid compact technology; Solubility enhancement; Wettability; Molecular dispersion; Supersaturation.

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INTRODUCTION

The limitations posed by poor aqueous solubility have become increasingly significant in modern drug development. A majority of newly discovered molecules display high lipophilicity, low dissolution rates, and poor absorption from the gastrointestinal tract. These characteristics often translate into suboptimal therapeutic performance, dose escalation, and variable patient outcomes. Solubility improvements through salt formation, micronization, solid dispersion [1], nano-formulation, and lipid-based carriers have achieved varying degrees of success, yet each strategy faces intrinsic limitations including stability issues, complex processing, and scale-up barriers [2-7].

Liquisolid compact technology offers an innovative approach whereby liquid drugs or liquid drug solutions are converted into dry, nonadherent, free-flowing powders suitable for tableting or encapsulation [8]. Originally introduced by Spireas and Bolton, the liquisolid technique relies on the capability of selected carrier and coating materials to absorb and adsorb significant quantities of liquid medications while retaining acceptable flow and compressibility. Over the past decade, this approach has gained substantial attention due to its simplicity [9-16], low processing cost, compatibility with industrial equipment, and superior dissolution enhancement.

This review expands upon existing literature to present a detailed scientific exploration of liquisolid compacts, emphasizing

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formulation science, material selection, dissolution mechanisms, advanced applications, and emerging research trends. The goal is to provide a comprehensive body of knowledge suitable for researchers, industrial formulators, and academic investigators seeking to apply or advance liquisolid techniques for solubility improvement [17].

COMPREHENSIVE REVIEW

Scientific Basis of Liquisolid Technology

The liquisolid concept revolves around transforming a liquid drug or drug solution into a dry, compressible, and flowable form by utilizing a porous solid carrier blended with a fine coating material [18]. The fundamental aspect lies in the ability of powders such as microcrystalline cellulose, silica derivatives, and other polysaccharides to retain liquid within their internal structures without exhibiting wetness [19-25].

A "liquid medication" in this context refers not only to drugs already in liquid form but also solid drugs dissolved or dispersed in nonvolatile solvents such as PEG 400, propylene glycol, glycerin, fixed oils, or surfactant-based vehicles. These solvents facilitate molecular drug dispersion, reduce crystallinity, and often improve thermodynamic activity, contributing to enhanced dissolution. Carriers such as Avicel PH 102 and coating materials like colloidal silicon dioxide collectively determine the flow, compressibility, and overall feasibility of the liquisolid powder blend. Their specific surface area, porosity, and absorption capacity influence performance (Tables 1 and 2). The Spireas liquid load factor (Lf) provides guidance for determining the maximum solvent content that can be held within acceptable flow and compression limits [26].

The main advantages of liquisolid systems is the substantial improvement in drug wettability. Solvents with inherent surface-tension-lowering properties allow the hydrophobic drug particles to maintain a high degree of hydration during dissolution testing. At the same time, the effective surface area of the drug increases due to molecular dispersion within the liquid vehicle. Liquisolid systems often result in partial or complete conversion of crystalline drugs into amorphous forms due to their solvati on within the solvent matrix [27]. Reduction in crystallinity significantly boosts dissolution, though stability considerations must be addressed.

Formulation Design and Excipients

A successful liquisolid system requires careful selection of excipients based on physical, chemical, and technological properties. Commonly employed solvents include PEGs, propylene glycol, Transcutol P, Labrafils, and polysorbates. Solvent selection depends on the solubility of the drug, compatibility, viscosity, and ability to enhance final dissolution. Microcrystalline cellulose is the most widely used carrier due to its porous structure and high adsorption capacity.

Other carriers include lactose, dextrin, and certain modified starches. Colloidal silicon dioxide (Aerosil 200) remains the standard coating excipient due to its ultra-fine particle size and massive surface area [28-31]. It "locks" the liquid within the carrier matrix and provides enhanced flowability. Superdisintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate help overcome any dissolution retardation caused by the presence of liquid vehicles. Incorporating surfactants may improve drug solubilization and aid rapid dissolution, especially for highly lipophilic molecules.

Mechanisms of Solubility and Dissolution Enhancement

Liquisolid compacts improve dissolution through multiple interrelated mechanisms:

Drugs dissolved in vehicles present in molecularly dispersed form exhibit significantly faster dissolution compared to micronized

Table 1: Key Components Used in Liquisolid Compact Systems and Their Functional Roles.

Component Type	Examples Commonly Used	Primary Functional Role in Liquisolid Systems	Scientific Rationale
Non-volatile solvents (liquid vehicles)	Propylene glycol, PEG-400, Glycerin, Polysorbate-80, Labrasol	Improve drug solubility and convert drug into a liquid medication	Non-volatile vehicles increase wetting, facilitate molecular dispersion, and maintain adequate flow by being absorbed into the carrier matrix
Carrier materials	Microcrystalline cellulose (MCC), Lactose monohydrate, Starch, Neusilin®	Adsorb liquid medication and convert it into a dry, free-flowing powder	Carriers with a high specific surface area and porosity allow incorporation of large quantities of solvent while maintaining compressibility
Coating materials	Colloidal silicon dioxide (Aerosil® 200), Magnesium aluminum silicate	Coat carrier particles and improve flowability, uniformity, and powder handling	Coating particles create a thin film around adsorbed carrier particles, increasing surface roughness and decreasing interparticle friction
Disintegrants	Sodium starch glycolate, Crospovidone, Croscarmellose sodium	Facilitate rapid tablet disintegration and dissolution	They enhance water penetration and assist in breaking the compact to release the drug-laden carrier
Lubricants	Magnesium stearate, Talc	Ensure smooth compression and ejection from tooling	Lubricants reduce die-wall friction and preserve tablet integrity
Polymeric additives (optional)	HPMC, PVP K-30, PEG derivatives	Modify release rate, stabilize supersaturation, or control viscosity	Polymers help maintain drug in solubilized or amorphous form and reduce precipitation tendency

Table 2: Performance Evaluation of Liquisolid Compacts and Conventional Solid Dosage Forms in Drug Delivery Applications.

Feature	Liquisolid Compact Systems	Conventional Solid Dosage Forms (Tablets/Capsules)	Implications for Drug Delivery
Solubility enhancement	High—drug remains molecularly dispersed in a liquid vehicle	Often limited due to crystalline solid state	Superior for BCS Class II drugs requiring solubility enhancement
Dissolution rate	Rapid, due to increased wetting and surface area	Moderate to slow depending on drug powder characteristics	Leads to improved onset of action and potential bioavailability increase
Manufacturing complexity	Requires careful optimization of liquid load factor, flowability, and compressibility	Relatively simple and established	May require more technical expertise and formulation screening
Physical stability	Stable when optimized; risk of solvent migration if poorly designed	Generally stable for crystalline drugs	Requires proper carrier–coating ratio and storage conditions
Drug loading capacity	Moderate; limited by carrier porosity and liquid retention capacity	High—can incorporate large quantities of drug powders	May be challenging for high-dose drugs
Release modification	Adjustable using polymers and hydrophobic carriers	Widely achievable using common excipients	Can be tuned for immediate, sustained, or controlled release
Suitability for scale-up	Achievable but requires validation of flow, compression, and uniformity	Highly scalable	Modern processing equipment supports large-scale liquisolid production

drug particles. Solvents reduce interfacial tension between drug particles and dissolution media, enhancing hydration and facilitating faster penetration of aqueous fluids. Amorphization leads to higher Gibbs free energy and improved dissolution. Some liquisolid formulations suppress recrystallization upon storage. Drug-rich layers may form around the tablet upon contact with dissolution medium, enhancing concentration gradient–driven transport.

Evaluation of Liquisolid Compacts

Flowability, angle of repose, compressibility index, and Hausner ratio must remain within acceptable limits for robust manufacturing [32].

The presence of liquid vehicles sometimes affects mechanical strength; hence optimization is essential. Comparative dissolution studies between liquisolid compacts, conventional tablets, and pure drug are essential to demonstrate enhancement. X-ray diffraction (XRD), differential scanning calorimetry (DSC), FTIR spectroscopy, and SEM imaging help evaluate physical transformations.

Applications of Liquisolid Technology

Most liquisolid formulations aim to improve dissolution of BCS Class II drugs. Drugs like carbamazepine, naproxen, ibuprofen, and ketoprofen have shown remarkable improvement in dissolution performance using this technique. By adjusting carrier–coating ratios and using hydrophilic polymers, liquisolid systems can be engineered to release drugs slowly.

The integration of nanosuspensions or nanocrystals within liquisolid matrices is a developing area with potential for ultra-high dissolution efficiencies. These systems prevent precipitation during dissolution, allowing higher solubility beyond equilibrium. Liquisolid technology has recently been applied to curcumin, quercetin, and other phytoconstituents to address bioavailability challenges [34].

Industrial Feasibility and Manufacturing Considerations

One of the major advantages of liquisolid compact technology lies in its adaptability to existing tablet manufacturing lines. No special equipment is necessary, and the process can be scaled with minor modifications in blending and mixing procedures. Moisture sensitivity, solvent retention, and stability parameters must be monitored to ensure long-term product quality.

CONCLUSION

Liquisolid compact technology represents a versatile and effective formulation strategy that addresses the persistent challenge of poor aqueous solubility. By enabling molecular dispersion, enhancing wetting, reducing crystallinity, and providing greater surface exposure, liquisolid systems significantly improve dissolution behavior and potentially oral bioavailability. The technique is notable for its simplicity, cost-effectiveness, and industrial compatibility. As research advances, liquisolid technology is expected to play a critical role in developing next-generation formulations for highly insoluble drug molecules.

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