Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 1246-1253
DoI-10.004687/1000-9035.2025.166

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Unlocking the Potential of Liquisolid Tablets: A Review of Formulation and Therapeutic Benefits

Pranali Baburao Dangat[1]*, Dr. Maya Sharma[2], Prof. P. K. Chaudhury[3]
[1]Department of Pharmaceutics, Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan, India
[2]Associate Professor, Department of Pharmaceutical Chemistry, Pacific College of Pharmacy, Udaipur, Rajasthan, India
[3] Dean, Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan, India.

Article Information
Received: 08-10-2025
Revised: 12-11-2025
Accepted: 06-12-2025
Published: 30-12-2025

Keywords
Liquisolid technology, solubility enhancement, bioavailability, BCS Class II and IV, pharmaceutical formulation, controlled release, nanotechnology integration, personalized medicine.

ABSTRACT
The poor aqueous solubility and low bioavailability of many drugs, particularly those in Biopharmaceutical Classification System (BCS) Class II and IV, present significant challenges in pharmaceutical development. Liquisolid technology offers a promising solution by transforming liquid drug formulations into dry, free-flowing, and compressible powders without compromising their solubility. This novel approach utilizes non-volatile solvents, porous carriers, and coating materials to maintain drugs in a molecularly dispersed state, enhancing dissolution rates and therapeutic efficacy. Initially introduced in the late 1990s, this technique has since gained traction as a versatile and adaptable strategy for solubility enhancement. Liquisolid systems have been successfully applied to improve the bioavailability of poorly water-soluble drugs like carbamazepine and furosemide and have facilitated controlled or sustained-release formulations. Beyond oral delivery, emerging applications include topical, pediatric, and veterinary formulations, reflecting its adaptability across therapeutic areas. Additionally, the technology's potential for stability enhancement, reduced excipient use, and simplified manufacturing offers significant advantages over traditional methods such as particle size reduction and solid dispersions. Current research trends focus on integrating liquisolid technology with nanotechnology, developing eco-friendly systems, and exploring its use in personalized medicine and biologic formulations. Despite its benefits, wider adoption requires establishing regulatory frameworks and expanding its application to non-oral routes. This review highlights the formulation principles, therapeutic benefits, and future directions of liquisolid technology, emphasizing its role as an innovative solution to address solubility and bioavailability challenges in modern pharmaceutics.

INTRODUCTION:

In the world of pharmaceuticals, drug solubility and dissolution play crucial roles in determining the bioavailability and therapeutic efficacy of orally administered drugs. Despite numerous advancements in drug discovery, a significant proportion of newly developed chemical entities exhibit poor aqueous solubility, which translates into low bioavailability. These issues predominantly affect drugs classified under Biopharmaceutical Classification System (BCS) Class II and IV, characterized by poor solubility and poor permeability, respectively. In response to this challenge, various drug delivery technologies

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have emerged, among which the "liquisolid dosage form" has gained considerable attention. This novel formulation approach offers an innovative solution for enhancing the dissolution rate and bioavailability of poorly soluble drugs by converting liquid drug formulations into dry, non-adherent, and free-flowing powders suitable for direct compression into tablets or encapsulation.

The "liquisolid technology" was initially introduced by Spireas and Bolton in the late 1990s, aimed at addressing the limitations posed by hydrophobic drugs. It has since evolved into a widely researched area in pharmaceutical formulation, with numerous studies exploring its potential to enhance the performance of drugs with solubility challenges. This technique utilizes a combination of solid carriers, coating materials, and non-volatile solvents to transform a drug in liquid form into a compactable powder. This allows the drug to remain in a solubilized or molecularly dispersed state, thereby improving its wettability, surface area, and overall dissolution rate.

Over the past few decades, significant advancements in drug development have addressed many challenges related to drug delivery. However, one of the most persistent obstacles remains the poor aqueous solubility of many active pharmaceutical ingredients (APIs), which directly affects their bioavailability and therapeutic efficacy. Approximately 40% of new chemical entities (NCEs) and more than 90% of drugs in development belong to Biopharmaceutical Classification System (BCS) Class II and IV, both characterized by poor solubility. To combat this issue, various approaches have been investigated, one of the most promising beings "liquisolid technology". This innovative drug delivery technique has garnered attention for its ability to enhance the dissolution rate and bioavailability of poorly water-soluble drugs, which is vital for oral drug delivery.[1]

Liquisolid technology" is a formulation strategy in which a poorly soluble drug is dissolved or suspended in a non-volatile liquid vehicle (such as propylene glycol, polyethylene glycol, or glycerin) and then converted into a free-flowing, compressible, and dry-looking powder by adsorption onto a suitable carrier (e.g., microcrystalline cellulose) and a coating material (such as colloidal silica). The resultant powder can be compacted into tablets or filled into capsules without compromising the drug's dissolution profile. This technology is especially effective in enhancing the dissolution and bioavailability of BCS Class II and IV drugs by converting them into a solubilized or molecularly dispersed form within a solid dosage matrix.

Spireas and Bolton (1999) pioneered this approach, emphasizing the potential of l iquisolid technology to improve the dissolution rates of poorly soluble drugs. Since then, it has become an attractive formulation technique for various hydrophobic drugs, offering numerous advantages over conventional methods such as particle size reduction, solid dispersion, and complexation with cyclodextrins. [2]

Principle of Liquisolid Technology:

At its core, liquisolid technology is designed to improve the dissolution rate of hydrophobic drugs. By maintaining the drug in a molecularly dispersed state within the liquid phase, the technique ensures that the drug's surface area for dissolution is maximized, significantly enhancing its bioavailability when compared to traditional solid dosage forms. Liquisolid technology involves the use of non-volatile solvents (like glycerin, propylene glycol, or PEG 400), carriers (e.g., microcrystalline cellulose, starch, or lactose), and coating materials (such as colloidal silicon dioxide). The non-volatile solvent maintains the drug in a solution or suspension, while the porous carrier adsorbs the liquid, forming a dry, non-sticky powder. The coating material, typically colloidal silica, ensures that the powder remains free-flowing and compressible.

This transformation from a liquid state into a solid form without any phase change increases the drug's surface area and improves its wettability, both of which are key factors in enhancing drug dissolution. As the drug dissolves faster, its bioavailability in the gastrointestinal (GI) tract is also improved, leading to more effective therapeutic outcomes.[3]

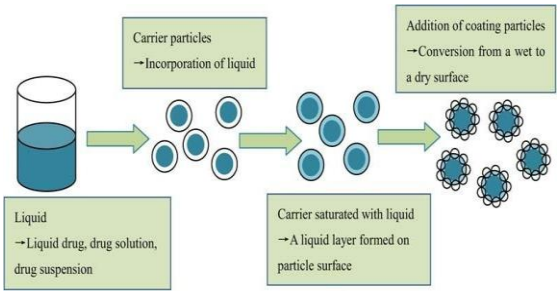

Figure 1 Principle of Liquisolid Technology

Liquisolid systems are based on the conversion of a liquid drug or a drug solution/suspension in a non-volatile solvent into a dry, free-flowing, and compressible powder mixture. The drug in a liquid state is first absorbed onto a porous carrier material, typically microcrystalline cellulose or lactose, which acts as the backbone of the system.

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This carrier material provides the necessary flow properties, while the addition of a coating material, such as colloidal silica, ensures that the powder remains free-flowing and non-sticky. This combination enables the conversion of liquid formulations into solid dosage forms, which can be directly compressed into tablets or filled into capsules.

One of the most important aspects of the liquisolid technology is the use of non-volatile solvents, such as polyethylene glycol, propylene glycol, or glycerin, which act as solubilizing agents for the drug. These solvents enhance the dissolution of the drug by maintaining it in a molecularly dispersed state, thereby increasing the surface area available for dissolution. As a result, the dissolution rate of the drug is significantly enhanced, leading to improved bioavailability.

Mechanism of Dissolution Enhancement:
The key advantage of liquisolid systems lies in their ability to enhance the dissolution rate of poorly soluble drugs. This is achieved through multiple mechanisms, including increased surface area, improved wettability, and enhanced molecular dispersion of the drug. In a liquisolid system, the drug is maintained in a non-crystalline, solubilized state within the carrier matrix, allowing for rapid dissolution once it comes into contact with gastrointestinal fluids.

One of the primary mechanisms of action is the increased surface area provided by the porous carrier materials. By adsorbing the liquid drug onto these carriers, the system ensures that the drug is distributed over a larger surface area, which accelerates the dissolution process. In addition, the use of non-volatile solvents ensures that the drug remains in a molecularly dispersed state, further enhancing its dissolution rate compared to conventional solid dosage forms, where the drug may exist in a crystalline form that dissolves slowly.

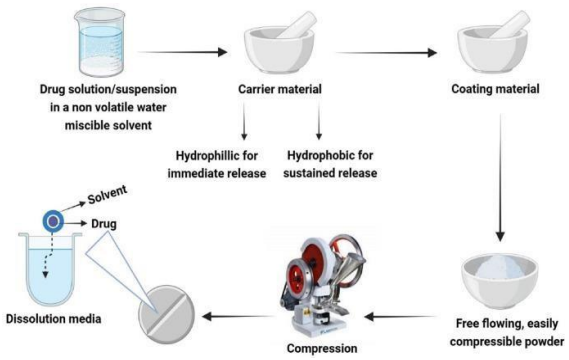

Figure 2 Effect of the liquisolid system on dissolution rate enhancement and drug release from the liquisolid system.

Another important factor is the improved wettability of the drug particles. In a liquisolid system, the liquid layer surrounding the drug particles facilitates their wetting in the gastrointestinal environment, allowing for faster and more efficient dissolution. This is particularly beneficial for hydrophobic drugs, which often exhibit poor wettability and slow dissolution rates in aqueous media.[4]

Background of Solubility Challenges:
Drug solubility is a critical factor in ensuring adequate absorption in the gastrointestinal tract, particularly for orally administered drugs. Poorly soluble drugs often face significant challenges in achieving therapeutic plasma concentrations, resulting in poor clinical outcomes. The solubility-dissolution-permeability interplay is a cornerstone of successful drug formulation, particularly for drugs administered via the oral route, which must first dissolve in the gastrointestinal fluids before absorption into systemic circulation. Drugs classified as BCS Class II and IV present particular difficulties, as they exhibit low aqueous solubility, leading to poor dissolution in the gastrointestinal environment.

Various techniques have been developed to improve the solubility and dissolution rates of these drugs, including micronization, solid dispersions, cyclodextrin inclusion complexes, and the use of surfactants. However, each of these approaches comes with its limitations in terms of scalability, stability, and applicability across different drug molecules. The liquisolid technique presents a promising alternative that overcomes some of these challenges, offering a unique way to enhance the solubility of hydrophobic drugs without altering their chemical structure.[5]

Benefits of Liquisolid Technology:
1. Enhanced Solubility and Dissolution Rates:
One of the primary benefits of liquisolid technology is its ability to significantly increase the solubility of poorly water-soluble drugs. Through this approach, drugs are dissolved in non- volatile solvents, making them more readily available for absorption. As a result, the dissolution rate of the drug in the gastrointestinal tract is enhanced, which in turn improves bioavailability. A study by Javadzadeh et al. demonstrated that liquisolid formulations improved the dissolution rate of piroxicam compared to its conventional counterparts.[6]

2. Improved Bioavailability:
Liquisolid systems offer a superior alternative to traditional formulations due to the increased surface area of the drug particles. When these

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particles are suspended in the liquid vehicle, the drug becomes molecularly dispersed, enhancing absorption upon administration. Research on poorly soluble drugs like carbamazepine and furosemide has shown that liquisolid technology significantly improves bioavailability by promoting rapid dissolution.[7]

3. Versatility and Adaptability:
Liquisolid technology can be employed across various types of drugs, including those with lipophilic and hydrophilic properties. This adaptability provides formulators with more options to enhance drug delivery profiles, regardless of the drug's solubility characteristics. For example, Vranikova et al. noted that the technology could be tailored to enhance delivery of both immediate-release and sustained-release formulations by adjusting the carrier and coating materials used in the formulation.[8]

4. Simplified Manufacturing Process:
Compared to other solubility enhancement techniques like solid dispersions or micronization, liquisolid technology offers a simpler manufacturing process. This simplicity can lead to cost savings and reduced production times in pharmaceutical manufacturing. The ease of scaling up liquisolid formulations without requiring complex machinery makes it a favorable option for industrial applications.[9]

5. Potential for Controlled Release:
Liquisolid systems can be modified to enable sustained or controlled release of drugs. By using hydrophobic carriers and adjusting the excipient ratios, formulators can create liquisolid systems that provide a slower, more controlled release, improving patient compliance and therapeutic outcomes. For example, Madhav et al. developed sustained-release formulations of nifedipine using liquisolid technology, showcasing its potential to modulate drug release profiles.

6. Increased Stability:
Drugs that are prone to degradation in certain environmental conditions benefit from liquisolid formulations as they are stabilized in a liquid form within a solid matrix. This increases the stability of drugs that may otherwise be sensitive to environmental factors like moisture and light. The stability of formulations can be particularly advantageous for drugs with narrow therapeutic windows or those susceptible to degradation.[10]

7. Reduction of Excipient Use:
Liquisolid technology requires minimal excipients compared to other formulations, allowing for a purer drug product with fewer inactive ingredients. This can be beneficial in minimizing potential interactions between the drug and excipients, leading to an overall safer and more effective drug product.[10]

Applications of Liquisolid Dosage Forms:

1. Enhanced Oral Bioavailability of Poorly Water-Soluble Drugs
Liquisolid systems have proven highly effective in enhancing the oral bioavailability of drugs with low water solubility, which is crucial for drugs classified under Biopharmaceutical Classification System (BCS) Class II and IV. By solubilizing the drug in a liquid vehicle, liquisolid technology enhances its wettability and surface area, leading to improved dissolution rates. For instance, research on carbamazepine, a poorly soluble drug, demonstrated a marked increase in bioavailability when formulated as a liquisolid dosage form. This application is particularly beneficial for drugs like glipizide, piroxicam, and furosemide, which have shown substantial improvements in absorption and bioavailability with liquisolid formulations.[11]

2. Controlled and Sustained Release Formulations:
Beyond solubility enhancement, liquisolid technology can be used to design controlled-release and sustained-release formulations. By adjusting the carrier and coating materials, along with the type and amount of liquid vehicle, liquisolid systems can be engineered to release drugs slowly over an extended period. This is particularly advantageous for drugs with short half-lives, where maintaining therapeutic blood levels over time can be challenging. Studies on nifedipine and diltiazem have shown that liquisolid systems can provide extended- release profiles by selecting hydrophobic carriers that delay drug dissolution. This application is highly beneficial for chronic conditions requiring consistent blood levels, such as hypertension and diabetes.[12]

3. Development of Immediate-Release Dosage Forms:
Liquisolid technology is not limited to controlled-release applications; it can also be used to develop immediate-release formulations. By employing hydrophilic carriers and coating materials, liquisolid systems can deliver rapid drug release, ideal for drugs requiring a quick onset of action. A study on naproxen, a non-steroidal anti-inflammatory drug (NSAID), demonstrated that liquisolid formulations achieved a faster dissolution rate, allowing for more immediate pain relief. This application is useful for drugs intended for acute conditions where rapid therapeutic effects are desired, such as pain management and acute allergic reactions.[13]

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4. Topical Drug Delivery:
Liquisolid technology has also been explored for topical drug delivery systems. By incorporating the drug into a liquid vehicle and embedding it into a liquisolid matrix, enhanced penetration of the active ingredient through the skin can be achieved. This is particularly useful for drugs with poor skin permeability, as the liquisolid approach can enhance their solubility and, consequently, their penetration through the skin barrier. An example of this application is seen in the formulation of topical anti-inflammatory agents, which benefit from improved skin absorption and targeted delivery to inflamed tissues.[14]

5. Formulation of Insoluble Natural Compounds:
Many natural compounds, such as curcumin, resveratrol, and quercetin, possess health benefits but are limited by poor water solubility and bioavailability. Liquisolid technology offers a promising approach to formulating these compounds, thereby enhancing their absorption and effectiveness. Studies on curcumin liquisolid formulations, for example, have shown significantly improved bioavailability compared to traditional formulations, which could enhance its therapeutic effects in anti-inflammatory and antioxidant therapies. This application is particularly relevant in the nutraceutical and functional food industries, where the efficacy of natural compounds is often constrained by poor bioavailability.[15]

6. Enhanced Stability of Sensitive Drugs:
Liquisolid systems can also improve the stability of drugs that are prone to degradation under environmental conditions, such as moisture or light. By incorporating the drug into a non- volatile liquid vehicle and embedding it within a solid matrix, the drug is protected from external factors that may cause degradation. This has been demonstrated with drugs like vitamin C and ascorbic acid, which are sensitive to oxidation and light. The liquisolid approach provides a protective environment, reducing degradation and extending shelf life. [16]

7. Application in Pediatric and Geriatric Dosage Forms:
Liquisolid technology enables the preparation of dosage forms that can be easily adapted for pediatric and geriatric patients, who often face challenges with swallowing solid dosage forms. By incorporating the drug into a liquid matrix and then converting it into a powder form, liquisolid systems can be used to develop rapidly disintegrating tablets or powders that can be reconstituted in water. This is especially beneficial for pediatric patients who may have difficulty swallowing tablets, as well as elderly patients with dysphagia. Research on liquisolid pediatric formulations of acetaminophen and ibuprofen has shown promising results in terms of ease of administration and improved palatability.[17]

8. Use in Veterinary Medicine:
Veterinary medicine has also adopted liquisolid technology to address the solubility issues of certain drugs used in animal care. Liquisolid formulations can enhance the absorption of drugs administered to animals, where bioavailability is often a concern due to the variability in animal gastrointestinal physiology. For example, liquisolid formulations of fenbendazole, an antiparasitic drug, have shown improved efficacy in animals due to enhanced solubility and bioavailability (Prasad et al., 2014). This application can reduce the required dose frequency in animals, improving treatment adherence and outcomes in veterinary practices.[18]

Examples of Liquisolid Technology:
1. Carbamazepine:
Pharmaceutical Category: Anticonvulsant Marketed Formulation Name:Tegretol Applications in Liquisolid Technology:
Solubility Enhancement: Carbamazepine is a poorly water-soluble drug, which limits its bioavailability when administered orally. Liquisolid technology effectively improves its dissolution rate by dispersing it in a non-volatile solvent and then adsorbing it onto a carrier matrix.
Bioavailability Improvement: Liquisolid formulations of carbamazepine have shown a significant improvement in bioavailability, which is crucial for maintaining therapeutic blood levels in epilepsy management.[19]

2. Piroxicam:
Pharmaceutical Category: Nonsteroidal Anti-Inflammatory Drug (NSAID) Marketed Formulation Name: Feldene
Applications in Liquisolid Technology:

Improved Dissolution and Onset of Action: Piroxicam, used for pain and inflammation, benefits from liquisolid technology by achieving a faster dissolution rate, which results in a quicker onset of action for pain relief.

Enhanced Patient Compliance: Rapid onset provided by the liquisolid formulation improves patient satisfaction, especially in acute conditions.[18]

3. Furosemide:
Pharmaceutical Category: Diuretic Marketed Formulation Name: Lasix Applications in Liquisolid Technology:
Increased Solubility and Bioavailability:

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Furosemide has low solubility in aqueous solutions, impacting its absorption. Liquisolid technology enhances its solubility, allowing for more efficient diuretic action.

Application in Controlled Release: Researchers have also explored using hydrophobic carriers to slow the release, useful in cases requiring extended diuretic action.[20]

4. Nifedipine:
Pharmaceutical Category: Calcium Channel Blocker Marketed Formulation Name: Adalat
Applications in Liquisolid Technology:

Sustained-Release Potential: Liquisolid formulations can be modified for sustained release, allowing nifedipine to maintain therapeutic plasma levels over longer periods, which is beneficial for treating chronic hypertension.

Enhanced Stability: Liquisolid formulations have been shown to improve the stability of nifedipine, which is sensitive to light and oxidation.[21]

5. Glibenclamide:
Pharmaceutical Category: Antidiabetic Marketed Formulation Name: Daonil Applications in Liquisolid Technology:
Improved Solubility for Consistent Blood Glucose Control For diabetic patients, it's critical to have a steady and predictable effect. Liquisolid technology aids in achieving consistent dissolution and bioavailability of glibenclamide.

Reduced Dose Variation: By enhancing the dissolution profile, liquisolid technology reduces the variability in plasma levels, allowing for more reliable glycemic control.[22]

6. Atorvastatin:
Pharmaceutical Category: Lipid-Lowering Agent Marketed Formulation Name: Lipitor
Applications in Liquisolid Technology:
Enhanced Solubility and Absorption: Atorvastatin is a poorly water-soluble drug, making it a good candidate for liquisolid technology, which enhances its bioavailability and absorption in the gastrointestinal tract.
Potential for Lower Dosing: With improved absorption, liquisolid formulations may allow for reduced dosing without compromising therapeutic efficacy.[23]

7. Hydrochlorothiazide Pharmaceutical Category: Diuretic:
Marketed Formulation Name: Microzide
Applications in Liquisolid Technology:
Enhanced Bioavailability: Hydrochlorothiazide's limited solubility can lead to erratic absorption. Liquisolid formulations can improve the drug's bioavailability for more predictable diuretic action.

Extended-Release Option: Modifications in the liquisolid system can create extended-release formulations, beneficial for hypertension management.[24]

8. Indomethacin:
Pharmaceutical Category:Nonsteroidal Anti-Inflammatory Drug (NSAID) Marketed Formulation Name:Indocin
Applications in Liquisolid Technology:

Enhanced Solubility and Faster Action: Indomethacin, often used for inflammation and pain, benefits from improved solubility via liquisolid technology, providing quicker relief.

Sustained Release for Chronic Conditions: Liquisolid systems also enable controlled release, making it suitable for patients with chronic pain or arthritis.[25]

9. Prednisolone:
Pharmaceutical Category: Corticosteroid Marketed Formulation Name: Orapred Applications in Liquisolid Technology:

Improved Dissolution Rate: Prednisolone, used in inflammatory and autoimmune diseases, shows better dissolution in liquisolid form, which improves therapeutic efficacy.

Reduced Gastrointestinal Side Effects: Liquisolid formulations can minimize direct contact with the gastrointestinal lining, potentially reducing irritation, a common issue with corticosteroids.[26]

10. Spironolactone:
Pharmaceutical Category: Diuretic Marketed Formulation Name: Aldactone Applications in Liquisolid Technology:
Enhanced Solubility for Effective Diuresis: Liquisolid technology can improve the dissolution rate of spironolactone, ensuring more consistent diuretic action.

Application in Sustained Release: Research has also explored using liquisolid systems to create extended-release spironolactone, which could be beneficial in chronic heart failure and hypertension management.[27]

Future Directions and Research Trends:
Liquisolid technology, an innovative approach to improving drug solubility and bioavailability, is expanding into numerous promising areas in

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pharmaceutical research. Future advancements in this field are likely to involve the development of novel excipients and liquid vehicles, allowing a broader range of drugs—especially highly lipophilic compounds—to benefit from this technology. Researchers are focusing on exploring new biodegradable and biocompatible liquid vehicles that could enhance the versatility of liquisolid systems. The development of these novel excipients is expected to open up possibilities for more stable, efficient, and safer formulations.

Another important area of exploration is targeted drug delivery, where liquisolid technology could be tailored to release drugs at specific sites within the body. By incorporating targeting ligands or designing the particles to respond to certain triggers, such as pH or temperature, liquisolid systems may provide site-specific drug release for more effective treatments. This application is particularly promising for diseases requiring localized therapy, such as cancers or inflammatory conditions.

Combining liquisolid technology with nanotechnology represents a significant research trend, with nano-liquisolid systems showing potential to enhance absorption and bioavailability even further. This combination may be particularly beneficial for transdermal, nasal, or other non- oral routes of administration. Through nanoscale modifications, liquisolid systems can deliver drugs more efficiently across barriers, making them suitable for a wider range of therapeutic applications.

Traditionally focused on oral dosage forms, liquisolid technology is now being investigated for use in topical, nasal, and ophthalmic formulations. These new applications aim to improve drug delivery through non-oral routes, making this technology more versatile and expanding its impact in areas like dermatology and ophthalmology, where solubility and stability challenges are prevalent.

As the industry focuses on sustainability, there is a rising interest in developing biodegradable and environmentally friendly liquisolid systems. Researchers are actively exploring eco- friendly solvents and carriers to reduce the environmental impact of drug manufacturing while maintaining therapeutic efficacy.

In line with the movement toward personalized medicine, liquisolid technology may soon be customized to create individualized dosage forms. Technologies like 3D printing enable on- demand manufacturing, allowing specific doses to be tailored for unique patient needs. This customization is especially valuable for populations requiring precise dosing, such as pediatric or geriatric patients, who often face challenges with standardized dosages.

Advances in artificial intelligence and machine learning are also impacting the field, providing improved mathematical modeling tools that aid in predicting formulation parameters for liquisolid systems. These computational models streamline the development process by identifying optimal excipient ratios and formulation conditions, reducing the need for extensive trial-and-error experimentation.

Wider adoption of liquisolid technology in the pharmaceutical industry will also benefit from the establishment of regulatory frameworks and quality standards. Currently, limited guidelines exist for evaluating the safety and efficacy of liquisolid formulations. As regulatory bodies introduce specific protocols, the acceptance and commercialization of liquisolid dosage forms are expected to increase, encouraging broader use of this technology.

Stability enhancement remains an area of active research within liquisolid technology. Researchers are experimenting with various coating materials and encapsulation techniques to protect sensitive drugs from environmental degradation. This is crucial for expanding the application of liquisolid systems to a broader range of pharmaceuticals, including drugs that are prone to instability under certain conditions.

Additionally, adapting liquisolid technology for macromolecules, such as peptides and proteins, offers another exciting opportunity. Traditionally challenging to formulate due to their sensitivity, these biologics could be stabilized within a liquisolid matrix, opening up new therapeutic possibilities in fields like biotechnology and personalized medicine. As research continues, liquisolid technology is poised to offer increasingly sophisticated and adaptable drug delivery solutions, reflecting its expanding role in modern pharmaceutical innovation.

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