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Review Article

# Enhancing Furosemide Bioavailability Using Liquisolid Compacts With Mixed Solvency Approach

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## A B S T R A C T

Objective(s): To study the synergy of using both the Liquisolid Technique and the Mixed Solvency Approach for improving the solubility and oral bioavailability of Furosemide, which is a BCS Class IV drug.

Sources: An exhaustive review of literature from the field of pharmacy with regards to liquisolid techniques, mixed solvency approaches, and furosemide pharmacokinetics.

Summary: The liquisolid technique helps enhance the dissolution rate by incorporating the active substance molecularly in a non-volatile solvent, sometimes resulting in an amorphous state with high energy levels. On the other hand, the concept of mixed solvency resolves the problem of high doses in normal liquisolid techniques by using a combination of safe solvents to increase the amount of drug in the liquid matrix.

Conclusion: Integrated technology offers an efficient and flexible strategy for formulation of high dose oral formulations that dissolve faster than conventional drug forms.

**Keywords:** Furosemide, Liquisolid Technology, Mixed Solvency Concept, Poor Aqueous Solubility, Dissolution Enhancement, High-Dose Formulation.

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## INTRODUCTION

### The Existing Challenge of Poor Aqueous Solubility in Pharmaceutical Development:

Poor aqueous solubility creates a huge problem, during pharmaceutical development. Since it affects about 40% of all new medicines beyond affecting 60% of all compounds tested. A drug is not absorbed well by your gut without proper dissolving. This gives you an partial dose since the drug is weakened and tougher to provide as one simple tablet. This issue is prominent for drugs classified in either BCS Class II or Class IV category. These classes are characterized by low solubility along with poor absorption and to address these issues, advanced formulation strategies are essential. These advanced technique are now became an important part of drug development and its effectiveness.[1-2]

### Furosemide A Drug Profile and Rationale for Solubility Enhancement:

Strong loop diuretics like furosemide are commonly used to treat a number of illnesses, such as hypertension and pulmonary, cardiac, or hepatic oedema. Despite its clinical significance, furosemide poses a significant biopharmaceutical challenge. Because of its low intestinal permeability and low aqueous solubility, it is classified as a BCS Class IV drug. Furosemide is a perfect model compound to study sophisticated solubility enhancement methods because of these two limitations.[1,3,7]

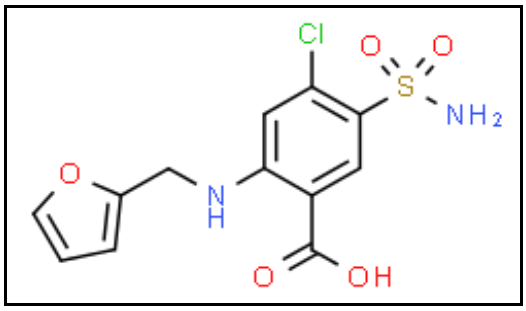


**Figure: 1** Structure of furosemide [1,4]

**Table: 1** Furosemide's Biopharmaceutical Profile[1]

| Parameter | Value / Description |
|---|---|
| BCS Class | Class IV (Low Solubility, Low Permeability) |
| Pharmacological Class | Loop Diuretic |
| Aqueous Solubility | Practically insoluble in gastric fluid (0.006 mg/mL) |
| pKa | 3.53 and 10.15 |
| Oral Bioavailability | Highly variable, ranging from 11% to 90% |
| Absorption Window | Narrow, primarily in the proximal small intestine |

## Foundational Principles: Synergistic Technologies

## THE LIQUISOLID TECHNOLOGY: AN OVERVIEW OF ITS PRINCIPLES AND MECHANISMS:

Liquisolid technology is a revolutionary formulation approach designed to convert a drug in a liquid state—be it a liquid drug, a drug solution, or a suspension—into an apparently dry, non-adherent, free-flowing, and readily compressible powder. This technique was first introduced by Spireas et al. to formulate water-insoluble drugs into solid dosage forms that exhibit rapid release kinetics.[2,19]

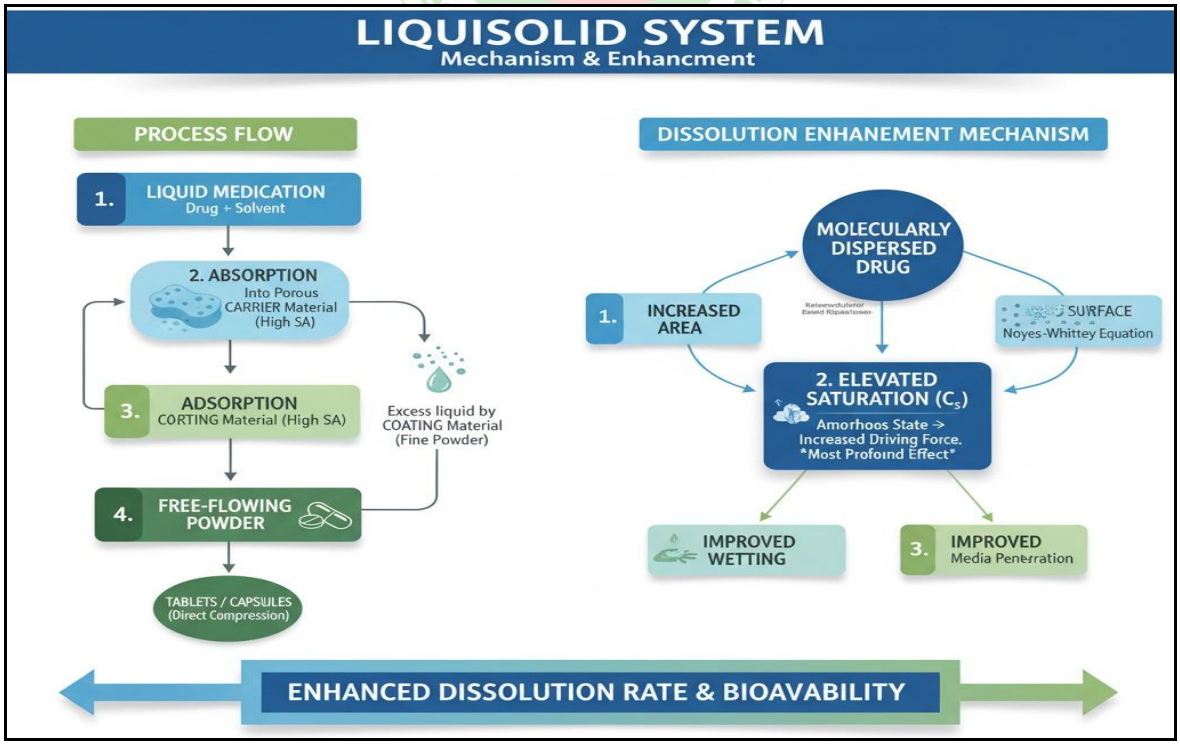

**Figure: 2** The liquisolid technology-principle and its mechaninsm

The mixed solvency concept is an innovative and environmentally conscious method proposed by Maheshwari for improving the aqueous solubility of poorly soluble drugs.

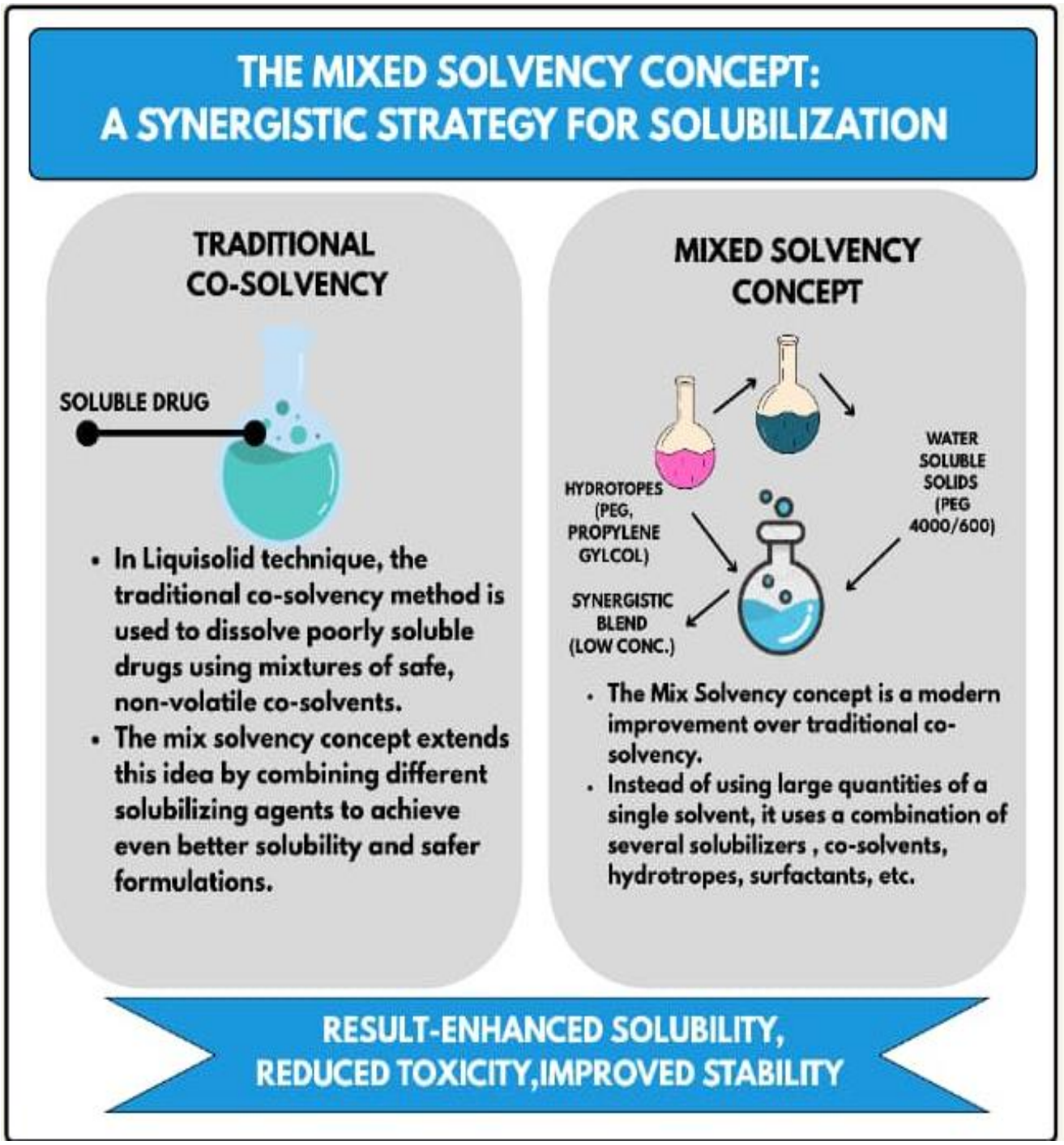


**Figure: 2** The Mixed Solvency Concept: A Synergistic Strategy for Solubilization[15,17,19]

The mixed solvency concept is a powerful pre-formulation tool. It addresses the fundamental problem of how to get a high dose of a poorly soluble drug into solution using a minimal volume of a safe and effective solvent system. This ability to create a highly concentrated "liquid medication" is a critical prerequisite for the successful application of liquisolid technology, as will be detailed in the following section.

**Table 2:** Common Excipients and Solvents in Combined Formulations

| Excipient Type | Examples | Function in Liquisolid Systems | Function in Mixed Solvency |
|---|---|---|---|
| Carrier Materials | Microcrystalline cellulose (Avicel PH 101, Avicel PH 102), Neusilin | Adsorption of liquid medication, compression enhancement | Not a direct component; used as a solid matrix |
| Excipient Type | Examples | Function in Liquisolid Systems | Function in Mixed Solvency |
| Coating Materials | Fumed silica (Cab-O-Sil M-5, Aerosil 200), Aeroperl 300 | Adsorption of liquid layer on carrier surface, flow enhancement | Not a direct component |
| Liquid Vehicles / Solvents | Polyethylene glycol (PEG 400), Propylene glycol, Glycerin, Synperonic PE/L 81 | Medium for drug dissolution, liquid medication component | Co-solvent / Solubilizer |
| **Mixed Solvency Solubilizers** | Sodium citrate, Sodium benzoate, Urea, Nicotinamide, L-arginine, Sodium caprylate | N/A | Hydrotrope / Co-solvent for synergistic action |

## SYNERGY IN ACTION: APPLYING THE COMBINED APPROACH TO FUROSEMIDE

### Justification for Combining Mixed Solvency and Liquisolid Technology:

The standard Liquisolid method's primary drawback is its limited capacity to store large amounts of medication, such as 40 mg of furosemide. This occurs as a result of the excipients' limited capacity to hold liquid before the powder ceases to flow and compress effectively. This restricts the amount of medication that can be included in a single dosage of the finished powder. Mixed Solvency is useful in this situation. The amount of Furosemide that dissolves in the liquid portion of the formulation can be significantly increased by combining a number of substances known as solubilizers. For instance, scientists discovered that they could make furosemide more soluble in simple propylene glycol, increasing its solubility from a low level (e.g., 25 mg/mL)

Everything is altered by this massive increase in drug solubility:

- High Dose in a Small Space: It makes it possible for a significant amount of medication to dissolve in a tiny amount of liquid.
- Effective Liquisolid: The excipients readily retain this tiny liquid volume, producing a free-flowing, compressible powder that can be formed into a high-dose tablet.
- Patient-Friendly: The final tablet is easy for the patient to take and has sufficient strength. The drug's poor dissolving (dissolution) and absorption (bioavailability) issues
- are resolved by the Liquisolid process when the dosage limit is resolved by Mixed Solvency. Together, they build a strong, effective system.

**Practical Implementation: Formulation Design And Mathematical Modeling: Key Formulation Ratios:**

| Parameter | Symbol | Formula |
|---|---|---|
| Liquid Loading Factor | Lf | Lf=W/Q |
| Excipients Ratio | R | R=Q/q |

W: weight of liquid medication Q: weight of carrier material q: weight of coating material .[3,12,14]

## EVALUATION OF THE FORMULATION

### Evaluation of Powder Properties: Flowability and Compressibility:

An effective formulation must be processable into a stable solid dosage form, requiring acceptable powder flow and compaction characteristics.

**Flowability**: Commonly assessed by the angle of repose. It's a prerequisite for successful processing on high-speed tablet presses.

**Compressibility:** Evaluated using Carr's index and Hausner's ratio. Quantifies the powder's ability to be compacted into a strong, cohesive tablet without liquid exudation ("liquid squeezing out"). [13,11,21,]

### In Vitro Dissolution Profile and Its Dependence on Formulation Variables:

The major aim of converting furosemide into a liquisolid system is to accelerate its dissolution rate.

A best liquisolid formulation with drug content released 90% of the drug in 10 minutes, well surpassing a standard Directly Compressed Tablet (DCT) which released only 65% during the same time.

- pH Dependence: Dissolution is greater in neutral media (pH 6.4–6.6) compared to acidic media (pH 1.2). As furosemide is a weakly acidic drug, greater solubility is to be expected at higher pH values.

- Critical Role of Liquid Vehicle: The nature of the liquid vehicle significantly controls the drug release rate, which implies that the mechanism of dissolution goes beyond the mere general liquisolid effect. [5]

## PHYSICOCHEMICAL CHARACTERIZATION: DSC, FTIR, AND PXRD ANALYSES:

To comprehend the basic transformations in the physical state of the drug, different physicochemical characterization methods are used. Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD) analysis of furosemide liquisolid compacts revealed a transformation of the crystalline state of the drug. The crystalline furosemide's characteristic endothermic peaks and sharp diffraction patterns were greatly diminished or lost in liquisolid formulations, an unambiguous evidence for the conversion of the drug into a less ordered, amorphous state. This change is the result of the dispersion of the drug's molecules into the liquidvehicle and its stabilization in the excipient matrix of the liquisolid system.[14]

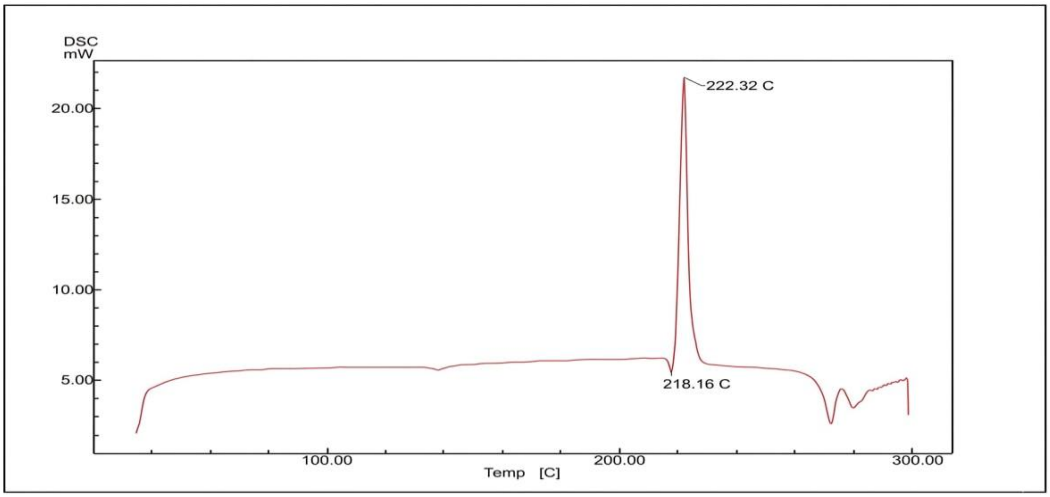


**Figure: 4 DSC of Furosemide** [14]

Fourier-Transform Infrared (FTIR) spectroscopy is employed to investigate possible chemical interactions between the excipients and the drug. Various furosemide liquisolid formulation studies indicated no interaction and inferred that the dissolution improvement mechanism was mainly physical in nature. Other analyses indicated a "possible interaction" of the drug with excipients, which was speculated to account for the resulting dissolution outcomes. This seeming inconsistency is no contradiction but a subtle result. The lack of new spectral peaks generally does not indicate new covalent bonds, but lesser interactions, like hydrogen bonding between the vehicle or excipients and drug, can be strong enough to stabilize the amorphous state and affect dissolution without resulting in a complete chemical reaction. This reflects the intricate interaction of forces that dictate the performance of the end product.

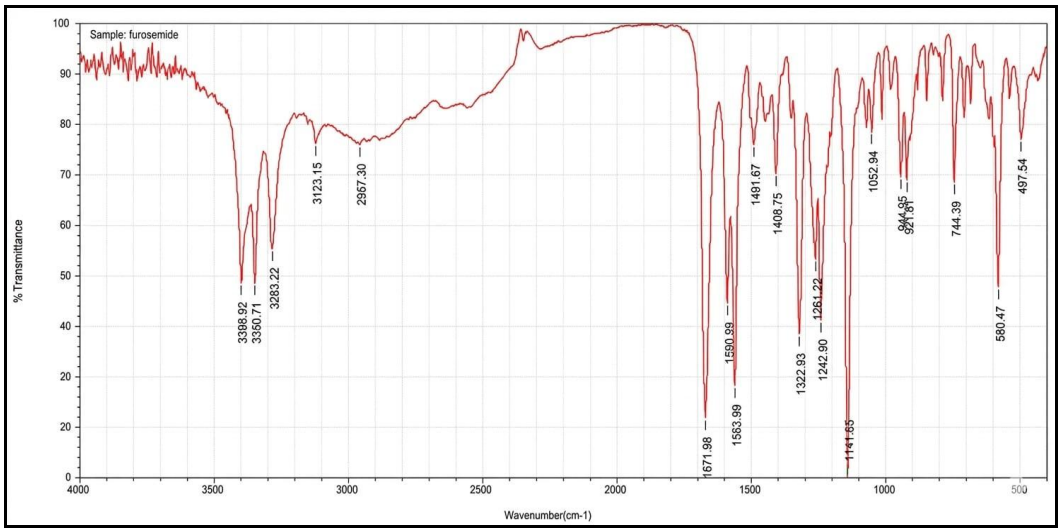


**Figure 4:** FTIR of Furosemide

## Comparative Biopharmaceutical Strategies and Outcomes

## Comparison With Other Solubility Enhancement Techniques:[4,11]

**Tablet: 5** Comparative Performance of Furosemide Solubility Enhancement Techniques[8,22]

| Technique | Dissolution Performance | Key Advantages | Key Disadvantages |
|---|---|---|---|
| Liquisolid | 90% release in 10 min for optimized formulation | Simple process, cost-effective, easily scalable, uses conventional equipment, enhances flowability | High-dose limitations, potential for stability issues (amorphous state) |
| Solid Dispersion | Up to 100% release in 30 min | Highly effective dissolution enhancement, proven method | Poor physical, stability, difficult to scale-up, limited commercial products |
| Complexation | Up to 100% release in 30 min | Highly effective, well-understood mechanism | Can be costly, may have stability concerns, potential for large dosage forms |
| Micronization | Increased dissolution rate compared to pure drug | Simple concept, readily available equipment | Particle aggregation, limited effectiveness in |
| Soft Gelatin Capsules | High bioavailability due to pre-dissolved drug | Highly effective for absorption | Costly, requires specialized production equipment |

## PRACTICAL AND INDUSTRIAL CONSIDERATION

## ADVANTAGES:

**Table: 6** Advantages [4,11]

| Points | Classification |
|---|---|
| Simplicity | The process is straightforward, involving the simple admixture of a liquid medication with excipients. |
| Low Production Costs | The technology has the potential for low production costs. |
| Potential for Industrial Scale-Up | The process can be accomplished using standard pharmaceutical equipment. |
| Quantifiable Framework | The existence of a robust mathematical model provides a framework for reproducible production and quality control |

## DISADVANTAGES:[4]

**Table: 6** Disadvantages [4]

| Points | Classification |
|---|---|
| Limited Applicability to High-Dose Drugs | High-dose drugs (like Furosemide at 40 mg) require a substantial amount of liquid, carrier, and coating material |
| Large, Heavy Tablets | The need for large amounts of excipients often results in the production of large, heavy tablets that can reduce patient compliance (harder to swallow**).** |
| Long-Term Stability Concerns | The drug is in a high-energy amorphous state, which is thermodynamically less stable than the crystalline form. |
| Recrystallization Risk | The amorphous drug has a tendency to revert back to its more stable crystalline state (recrystallization), potentially decreasing the dissolution rate over the product's shelf life**.** |
| Limited Commercial Adoption | The technology has not yet been widely commercialized, and the number of marketed products is very limited |
| Lack of Extensive In Vivo Clinical Data | There is a lack of extensive clinical data to conclusively prove enhanced bioavailability, leading to the pharmaceutical industry's hesitant embrace. |

## CONCLUSION

The overall description establishes that the integration of liquisolid technology with the mixed solvency approach gives a robust solution to furosemide, a low-solubility, low-permeability BCS Class IV drug with a narrow window for absorption. Liquisolid Technology Role: It aids dissolution by changing the drug into a highly soluble, molecularly dispersed, amorphous form such that there is quick availability within the restricted absorption window.

Role of Mixed Solvency: It breaks the dose constraint of liquisolid technology. Through the employment of more than one synergistic solubilizer, it forms a highly concentrated liquid drug vehicle. This enables the manufacturing of high-dose liquisolid tablets with requisite flowability and compressibility. Mixed solvency facilitates high-dose formulation, with liquisolid technology able to maximize its potential for increasing dissolution and bioavailability

### Recommendations for Future Research and Practical Application:

Despite the highly promising in vitro results, several key areas require further investigation to facilitate the widespread clinical and commercial adoption of this technology.

- In Vivo Bioavailability Studies: The most essential follow-up step is to perform sound in vivo studies to definitively prove that the increased in vitro dissolution directly results in enhanced and more predictable bioavailability in animal models and, eventually, in humans. This is the one most vital piece of missing data that will instill confidence in the technology.
- Stability Studies: Detailed long-term stability studies are required to assess the likelihood of recrystallization of the amorphous drug. Studies should aim to find best combinations of excipients and packages that are capable of preventing the drug from turning into an amorphous state over the desired shelf life.
- High-Dose Formulation Optimization: Further work is required to optimize formulation parameters for high-dose drugs with the aim of preventing the "liquid squeezing out" effect and optimizing the excipient blend to yield smaller, more patient-friendly tablets. Expansion of Applications: This success with furosemide is likely to be applicable to a vast array of other poorly soluble BCS Class II and Class IV drugs. Its application in the future should be investigated with drugs with varying physicochemical properties as well as therapeutic implications, even in the case of immediate- or sustained-release formulations.
- The liquisolid technique, when integrated with the novel mixed solvency idea, is likely to be a pillar of tomorrow's oral drug delivery systems. By solving the basic issues of poor solubility and restricted dosing, this integrated mechanism provides a straightforward, economical, and very efficient route toward converting problem drug candidates into therapeutically effective products.

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