

Review Article

MIXED SOLVENCY APPROACH FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS: A COMPREHENSIVE REVIEW

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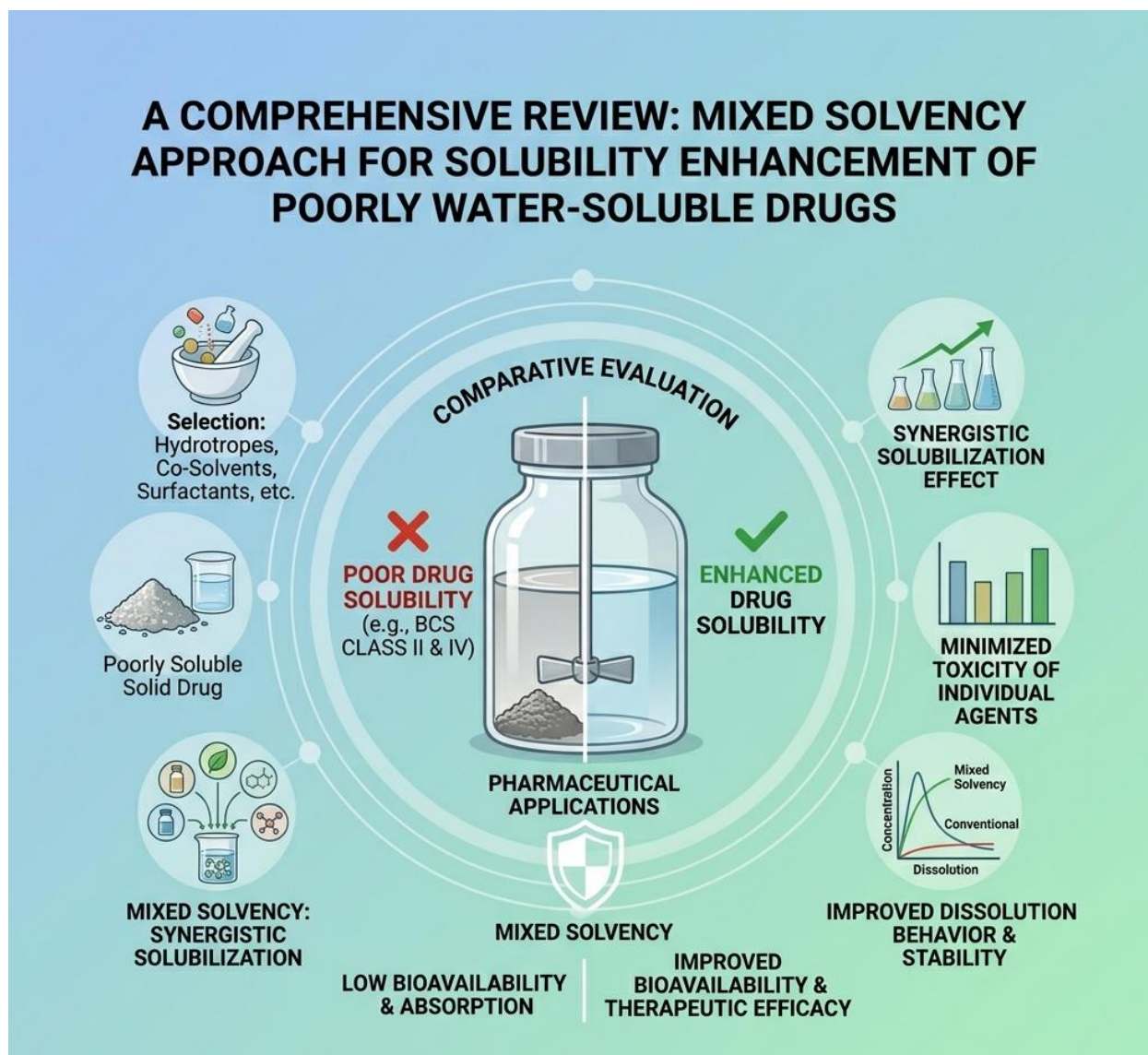
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ABSTRACT

Poor aqueous solubility remains one of the most significant challenges in pharmaceutical formulation development, affecting the dissolution, absorption, and bioavailability of numerous therapeutic agents. The present review comprehensively discusses the mixed solvency approach as an innovative and effective strategy for enhancing the solubility of poorly water-soluble drugs. Mixed solvency is based on the principle that a combination of various water-soluble additives, such as hydrotropes, co-solvents, surfactants, polymers, and buffering agents, can collectively produce a synergistic solubilization effect while minimizing the concentration-related toxicity associated with individual solubilizers. The review highlights the concept of drug solubility, factors affecting solubility, and the challenges posed by poorly water-soluble drugs, particularly those belonging to Biopharmaceutics Classification System (BCS) Classes II and IV. The mechanism, theoretical basis, advantages, limitations, and pharmaceutical applications of mixed solvency are also discussed in detail. Furthermore, a comparative evaluation of mixed solvency with conventional solubility enhancement techniques demonstrates its superiority in terms of simplicity, cost-effectiveness, safety, and versatility. The approach has shown promising results in the formulation of tablets, capsules, oral liquids, injectables, and topical preparations. Overall, mixed solvency represents a practical and economically viable tool for improving drug solubility, dissolution behavior, bioavailability, and therapeutic efficacy in modern pharmaceutical development.

GRAPHICAL ABSTRACT



INTRODUCTION

Solubility refers to the capacity of a solute to dissolve in a specific solvent, producing a homogeneous mixture known as a solution. The solubility of a substance is primarily influenced by factors such as the nature of the solvent, temperature, and pressure. The degree to which a solute dissolves in a given solvent is generally expressed in terms of its saturation concentration. ⁽¹⁾

Researchers have long focused on developing effective methods to enhance drug solubility, as improved solubility can significantly increase drug bioavailability. Poor aqueous solubility remains a major challenge in pharmaceutical development and affects the bioavailability of more than 40% of newly

identified drug candidates. For a drug to be absorbed through the epithelial membrane via passive diffusion, it must first be dissolved in the aqueous environment of the gastrointestinal tract. Consequently, inadequate solubility can limit drug absorption and therapeutic effectiveness.⁽²⁾

Drug absorption is largely governed by two key properties: solubility and permeability. Based on these characteristics, drugs are categorized using the Biopharmaceutical Classification System (BCS).⁽³⁾ The BCS classifies drugs into four categories according to their solubility and permeability profiles. While low solubility is a common feature of both Class II and Class IV drugs, Class IV compounds additionally exhibit poor permeability. A drug is considered highly soluble if its highest therapeutic dose can dissolve in 250 mL or less of aqueous medium across a pH range of 1.0–7.5 at 37°C.⁽⁴⁾

CONCEPT OF DRUG SOLUBILITY

Definition of Solubility

Solubility is defined as the maximum amount of a solute that can dissolve in a specified quantity of solvent under equilibrium conditions to form a homogeneous solution. It is one of the most important physicochemical properties of pharmaceutical compounds because it directly influences drug dissolution, absorption, and therapeutic effectiveness. Drug molecules must dissolve in biological fluids before they can be absorbed into systemic circulation. Therefore, adequate solubility is essential for achieving the desired pharmacological response. However, a significant number of newly developed drug candidates exhibit poor aqueous solubility, which poses challenges in formulation development and limits their clinical utility.⁽⁵⁾

Factors Affecting Drug Solubility

Several factors influence the solubility of pharmaceutical compounds. The chemical nature and molecular structure of the drug play a vital role in determining its interaction with a solvent. Drugs having polar functional groups generally exhibit higher aqueous solubility, whereas non-polar compounds tend to be poorly soluble in water. The principle of “like dissolves like” is commonly used to explain solvent–solute compatibility.

Temperature is another important factor affecting solubility. For most solid drugs, an increase in temperature enhances solubility by increasing molecular movement and reducing intermolecular forces. The pH of the medium significantly influences the solubility of ionizable drugs. Weak acids become more soluble in alkaline conditions, while weak bases show greater solubility in acidic environments. Particle size also affects dissolution behavior, as smaller particles provide a larger surface area for solvent interaction.

Other factors such as crystal form, polymorphism, salt formation, dielectric constant of the solvent, and the presence of solubilizing agents like surfactants, hydrotropes, and co-solvents can substantially alter the solubility characteristics of a drug. Understanding these variables is essential for developing effective strategies to improve drug dissolution and bioavailability.^(6,7)

Importance of Solubility in Drug Absorption and Bioavailability

Drug solubility plays a crucial role in determining the rate and extent of drug absorption following oral administration. Before a drug can permeate the gastrointestinal membrane and reach systemic circulation, it must first dissolve in the gastrointestinal fluids. Poorly soluble drugs often exhibit slow dissolution rates,

resulting in incomplete absorption and reduced bioavailability. Consequently, insufficient solubility may lead to therapeutic failure, increased dose requirements, and variability in patient response.

The significance of solubility is reflected in the Biopharmaceutics Classification System (BCS), which classifies drugs according to their solubility and permeability characteristics. Drugs belonging to BCS Class II possess high permeability but low solubility, making dissolution the rate-limiting step in absorption. Many clinically important drugs fall into this category and require formulation approaches to enhance their aqueous solubility. In contrast, BCS Class IV drugs exhibit both poor solubility and poor permeability, making them particularly challenging to formulate.

To address these issues, pharmaceutical scientists employ various solubility enhancement techniques such as particle size reduction, solid dispersion, complexation, hydrotropy, co-solvency, and mixed solvency approaches. Enhancement of drug solubility improves dissolution rate, facilitates gastrointestinal absorption, increases bioavailability, and ultimately enhances therapeutic efficacy. Therefore, solubility remains a critical parameter in the successful development of safe and effective pharmaceutical dosage forms. ⁽⁸⁾

POORLY WATER-SOLUBLE DRUGS

Challenges Associated with Poor Solubility

Poor aqueous solubility is a major concern in modern pharmaceutical development, as a large proportion of newly discovered drug candidates exhibit limited solubility in water. Since most drugs are administered orally, they must dissolve in gastrointestinal fluids before they can be absorbed into systemic circulation. Drugs with poor water solubility often show slow dissolution rates, resulting in delayed absorption and reduced bioavailability. The increasing use of combinatorial chemistry and advanced drug discovery techniques has led to the development of many lipophilic molecules with excellent pharmacological activity but inadequate aqueous solubility. Consequently, formulation scientists face significant challenges in developing effective dosage forms for such compounds.

Poorly soluble drugs frequently exhibit low wettability, incomplete dissolution, instability in biological fluids, and high variability in absorption. Their performance may also be influenced by physiological factors such as gastric pH, gastrointestinal transit time, food intake, and intestinal fluid composition. These factors can produce unpredictable drug absorption patterns and inconsistent therapeutic outcomes among patients. Furthermore, poor solubility often necessitates the administration of larger doses to achieve therapeutic plasma concentrations, which may increase the risk of side effects and reduce patient compliance. Therefore, improving the solubility characteristics of drug molecules remains a critical objective in pharmaceutical formulation research. ⁽⁸⁾

Impact on Therapeutic Efficacy

The therapeutic efficacy of a drug is closely linked to its ability to dissolve and become available for absorption. Only drug molecules present in dissolved form can permeate biological membranes and enter systemic circulation. Consequently, poor aqueous solubility can significantly limit the amount of drug absorbed, resulting in reduced bioavailability and inadequate therapeutic response. In many cases, potentially effective drug candidates fail during development because their poor solubility prevents the achievement of sufficient plasma concentrations.

Low solubility can also contribute to delayed onset of action, inconsistent drug levels in the bloodstream, and substantial inter-patient variability. These issues are particularly critical for drugs requiring rapid absorption or precise maintenance of therapeutic concentrations. Moreover, poor bioavailability often necessitates higher or more frequent dosing, increasing treatment costs and the likelihood of adverse effects. As a result, considerable research efforts have focused on developing innovative approaches to improve drug solubility and dissolution. Various techniques, including particle size reduction, solid dispersion systems, complexation, nanotechnology-based formulations, and solubilization methods, have been successfully employed to enhance the therapeutic performance of poorly soluble drugs. ⁽⁹⁾

BCS Classification and Solubility Issues

The Biopharmaceutics Classification System (BCS) is widely used to classify drugs based on their aqueous solubility and intestinal permeability characteristics. This system provides valuable guidance for predicting oral drug absorption and selecting appropriate formulation strategies. According to the BCS, drugs are divided into four classes. Class I drugs possess high solubility and high permeability and generally exhibit excellent oral absorption. Class II drugs are characterized by low solubility but high permeability, making dissolution the rate-limiting step for absorption. Many important therapeutic agents, including several anti-inflammatory, antifungal, and cardiovascular drugs, belong to this category. Class III drugs exhibit high solubility but low permeability, whereas Class IV drugs possess both poor solubility and poor permeability, making them the most challenging compounds to formulate successfully. For Class II and Class IV drugs, improving solubility is essential to enhance dissolution rate and bioavailability. Various formulation approaches have therefore been developed to address solubility limitations and optimize therapeutic outcomes. The BCS framework has become an indispensable tool in pharmaceutical research because it helps scientists understand drug absorption behavior and design suitable strategies for overcoming solubility-related challenges. ⁽¹⁰⁾

MIXED SOLVENCY CONCEPT

Definition and Principle

The mixed solvency concept is an innovative pharmaceutical approach used to enhance the aqueous solubility of poorly water-soluble drugs. The concept is based on the observation that all substances possess some degree of solubilizing potential and that a combination of different water-soluble additives can significantly improve the solubility of a drug beyond what can be achieved by a single solubilizer alone. Instead of employing a high concentration of one solubilizing agent, mixed solvency utilizes multiple agents in lower concentrations to achieve the desired solubilization effect while minimizing toxicity and adverse effects.

The principle of mixed solvency involves the synergistic action of various solubilizers such as hydrotropes, co-solvents, water-soluble polymers, and surfactants. When these agents are combined, they modify the solvent environment and enhance drug-solvent interactions, resulting in increased drug solubility. The approach is particularly beneficial for poorly water-soluble drugs because it allows substantial solubility enhancement without the need for complex manufacturing processes or expensive formulation technologies. Moreover, mixed solvency can improve drug dissolution, absorption, and

bioavailability while maintaining formulation stability and safety. The simplicity, cost-effectiveness, and versatility of this technique have made it increasingly attractive for pharmaceutical applications. ⁽¹¹⁾

Historical Development

The concept of solubility enhancement has evolved considerably over the past several decades. Initially, pharmaceutical scientists relied on traditional methods such as pH adjustment, salt formation, co-solvency, and surfactant-based solubilization to improve drug solubility. Although these techniques proved effective for certain compounds, they often required large quantities of additives, which could lead to toxicity concerns, incompatibility issues, or formulation instability.

A significant advancement occurred when researchers recognized that multiple solubilizing agents could be combined to produce greater solubility enhancement than individual agents used alone. This observation led to the development of the mixed solvency concept. The approach was systematically introduced and popularized through the work of Maheshwari and coworkers, who demonstrated that the combined use of various hydrotropic agents, co-solvents, and other water-soluble substances could substantially increase the aqueous solubility of poorly soluble drugs. Their studies established that the cumulative solubilizing effect of multiple additives could be utilized safely and efficiently in pharmaceutical formulations.

Since its introduction, mixed solvency has been applied to numerous drug molecules including non-steroidal anti-inflammatory drugs, antimicrobial agents, antihistamines, and other poorly soluble therapeutic compounds. Continuous research has expanded its applications in tablet formulations, oral liquids, parenteral preparations, and analytical methods. The growing acceptance of mixed solvency reflects its effectiveness as a practical and economical strategy for addressing solubility-related challenges in drug development. ⁽¹²⁾

Theoretical Basis of Mixed Solvency

The theoretical foundation of mixed solvency is based on the synergistic interaction of multiple solubilizing agents within an aqueous system. Each solubilizer contributes to the overall enhancement of drug solubility through different mechanisms. Hydrotropes increase solubility by disrupting water structure and improving drug-solvent interactions. Co-solvents reduce the polarity of the solvent system, making it more favorable for dissolving lipophilic drug molecules. Surfactants facilitate micelle formation, which can encapsulate poorly soluble drugs and increase their apparent solubility. Water-soluble polymers may further stabilize the dissolved drug and prevent precipitation.

When these agents are used together, their combined effects often exceed the sum of their individual contributions. This synergistic phenomenon forms the basis of mixed solvency. The approach enables substantial enhancement of drug solubility while reducing the concentration of each individual solubilizer, thereby minimizing potential toxicity and formulation-related problems. The concept is supported by intermolecular interaction theories, which suggest that the presence of multiple solubilizers creates a more favorable microenvironment for drug dissolution.

Another important theoretical aspect is the reduction of limitations associated with single-solubilizer systems. High concentrations of individual hydrotropes or co-solvents may cause irritation, instability, or incompatibility. Mixed solvency overcomes these issues by distributing the solubilization burden among several agents. Consequently, the technique provides an effective balance between solubility enhancement, safety, formulation stability, and economic feasibility. Owing to these advantages, mixed solvency has emerged as a scientifically sound and widely accepted strategy for improving the performance of poorly water-soluble drugs in modern pharmaceutical formulations. ^(13,14)

MECHANISM OF SOLUBILITY ENHANCEMENT BY MIXED SOLVENCY

The mixed solvency approach enhances the solubility of poorly water-soluble drugs through the combined action of multiple water-soluble substances known as solubilizers. These solubilizers may include hydrotropic agents, co-solvents, surfactants, water-soluble polymers, and other pharmaceutical additives. Rather than relying on a single solubilizing agent at a high concentration, mixed solvency utilizes several agents at lower concentrations to achieve a significant increase in drug solubility while minimizing potential toxicity and formulation-related issues.

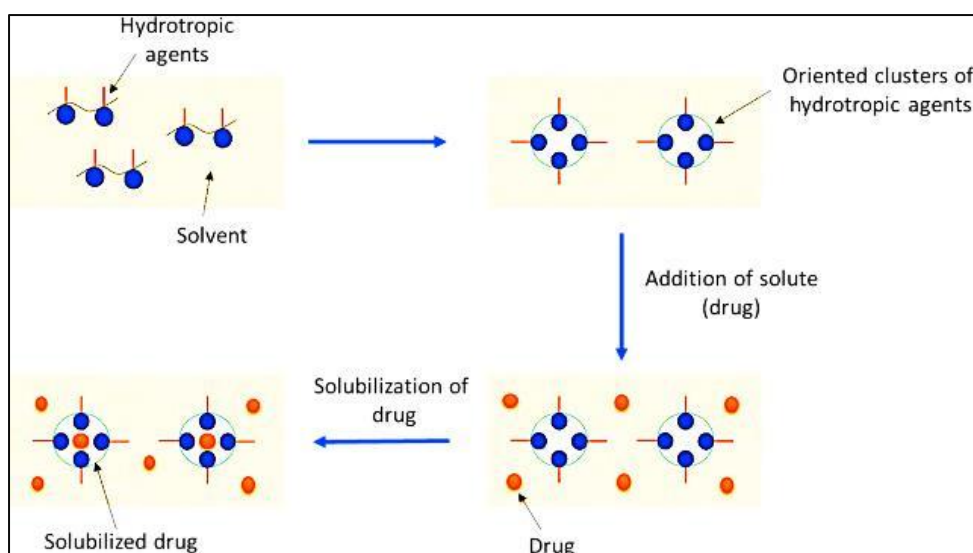


Figure 1: Mechanism of Solubility Enhancement by Mixed Solvency Approach^[15]

The primary mechanism involved in mixed solvency is the modification of the solvent environment surrounding the drug molecules. Hydrotropic agents increase solubility by weakening the intermolecular forces between drug molecules and improving their interaction with water molecules. Co-solvents such as polyethylene glycol, propylene glycol, and glycerol reduce the polarity of the aqueous medium, making it more suitable for dissolving lipophilic drugs. Surfactants contribute by forming micelles that encapsulate poorly soluble drug molecules within their hydrophobic core, thereby increasing the apparent solubility of the drug.

Another important mechanism is the synergistic effect produced when multiple solubilizers are combined. Each solubilizer enhances drug solubility through a different pathway, and their collective action often results in greater solubility enhancement than that achieved by individual agents alone. The combined system creates a favorable microenvironment that promotes drug dissolution, improves wettability, and prevents drug precipitation. This synergistic interaction allows substantial solubility enhancement while maintaining lower concentrations of individual additives.⁽¹⁶⁾

SOLUBILIZING AGENTS USED IN MIXED SOLVENCY

Mixed solvency technology employs a combination of different water-soluble substances to enhance the solubility of poorly water-soluble drugs. These agents work through various mechanisms and collectively produce a synergistic solubilizing effect. The selection of appropriate solubilizers is crucial for achieving maximum drug solubility while maintaining formulation safety and stability. The major categories of solubilizing agents used in mixed solvency systems include hydrotropes, co-solvents, water-soluble polymers, surfactants, and buffering agents.⁽¹⁷⁾

Hydrotropes are compounds that improve the aqueous solubility of poorly soluble drugs by increasing drug–solvent interactions. Common hydrotropic agents include urea, sodium benzoate, sodium citrate, and sodium acetate. These agents are widely used because of their effectiveness and low toxicity. Co-solvents such as polyethylene glycol (PEG), propylene glycol, glycerol, and ethanol reduce the polarity of the solvent system, thereby enhancing the solubility of lipophilic drugs.⁽¹⁸⁾

Water-soluble polymers also contribute significantly to solubility enhancement. Polymers such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene oxide improve drug wettability and help maintain drugs in a solubilized state. Surfactants enhance solubility through micelle formation, where poorly soluble drug molecules become entrapped within the hydrophobic core of micelles. Common pharmaceutical surfactants include Tween 80, Sodium Lauryl Sulfate (SLS), and Poloxamers. Buffering agents are utilized to maintain an optimal pH environment that favors drug ionization and solubility. Examples include phosphate buffers, citrate buffers, and acetate buffers. The combined use of these agents forms the basis of the mixed solvency concept and provides an effective strategy for improving drug dissolution and bioavailability.⁽¹⁹⁾

Table 1. Common Solubilizing Agents Used in Mixed Solvency

Category	Examples	Mechanism of Solubility Enhancement
Hydrotropes	Urea, Sodium Benzoate, Sodium Citrate, Sodium Acetate	Increase drug–solvent interactions and disrupt water structure
Co-solvents	PEG 400, Propylene Glycol, Ethanol, Glycerol	Reduce solvent polarity and improve dissolution of lipophilic drugs
Water-Soluble Polymers	PVP K-30, HPMC, Polyethylene Oxide	Improve wettability and stabilize dissolved drug molecules
Surfactants	Tween 80, SLS, Poloxamer 188	Enhance solubility through micelle formation
Buffering Agents	Phosphate Buffer, Citrate Buffer, Acetate Buffer	Maintain favorable pH conditions for drug ionization and dissolution

ADVANTAGES OF THE MIXED SOLVENCY APPROACH

The mixed solvency approach has emerged as a promising and effective technique for enhancing the

solubility of poorly water-soluble drugs. Unlike conventional methods that rely heavily on a single solubilizing agent, mixed solvency utilizes a combination of different water-soluble additives at lower concentrations to achieve substantial solubility enhancement. One of the primary advantages of this approach is its ability to significantly increase the aqueous solubility of poorly soluble drugs without requiring sophisticated equipment or complex manufacturing processes. This makes the technique economical and suitable for large-scale pharmaceutical production. ⁽²⁰⁾

Another major advantage is the reduction of toxicity associated with high concentrations of individual solubilizers. Since multiple agents share the solubilization burden, each component can be used at a lower and safer concentration. The approach also provides synergistic solubilization effects, often resulting in greater enhancement than the sum of individual contributions. Mixed solvency improves dissolution rate, bioavailability, and therapeutic efficacy while maintaining formulation stability. Furthermore, it is applicable to a wide variety of drug molecules and dosage forms, making it a versatile tool in pharmaceutical formulation development. ⁽²¹⁾

The technique is also environmentally friendly because it reduces dependence on organic solvents and other potentially hazardous chemicals. Its simplicity, cost-effectiveness, safety, and compatibility with existing manufacturing methods have contributed to its growing acceptance in pharmaceutical research and industry. ⁽²²⁾

LIMITATIONS AND CHALLENGES OF MIXED SOLVENCY

Despite its numerous advantages, mixed solvency also presents certain limitations and challenges. The selection of appropriate combinations of solubilizing agents requires extensive experimentation and optimization. Different drugs may respond differently to the same solvent system, making formulation development a time-consuming process. In some cases, incompatibilities may arise between solubilizers and drug molecules, leading to instability or precipitation during storage. ⁽²³⁾

Another challenge is maintaining the long-term stability of the solubilized drug. Changes in temperature, pH, or storage conditions may affect drug solubility and lead to crystallization or degradation. Regulatory concerns regarding the safety of multiple excipients in a single formulation may also require additional toxicological evaluation. Furthermore, excessive use of certain hydrotropes or co-solvents can affect organoleptic properties, patient acceptability, and formulation performance. Therefore, careful selection and optimization of solubilizing agents are essential for successful application of mixed solvency technology. ⁽²⁴⁾

APPLICATIONS OF MIXED SOLVENCY IN PHARMACEUTICAL FORMULATIONS

The mixed solvency approach has found wide application in various pharmaceutical dosage forms due to its effectiveness in enhancing drug solubility and dissolution characteristics.

Tablets

Mixed solvency is extensively used in tablet formulations, particularly for poorly water-soluble drugs. Enhanced solubility improves drug dissolution, resulting in faster onset of action and improved bioavailability. Immediate-release tablets of drugs such as indomethacin, ibuprofen, and aceclofenac have demonstrated improved performance using mixed solvency systems.

Capsules

In capsule formulations, mixed solvency helps maintain the drug in a solubilized state, thereby improving dissolution upon administration. The technique is especially useful for hard gelatin and soft gelatin capsules containing poorly soluble active pharmaceutical ingredients.

Oral Liquids

Oral liquid formulations require drugs to remain dissolved throughout their shelf life. Mixed solvency enables the preparation of stable syrups, suspensions, and oral solutions containing poorly soluble drugs while reducing the need for excessive amounts of organic solvents.

Injectable Formulations

Parenteral preparations demand complete drug solubilization to ensure safety and therapeutic effectiveness. Mixed solvency can be utilized to formulate aqueous injectable solutions of poorly soluble drugs while minimizing irritation and toxicity associated with conventional solvents.

Topical Preparations

Creams, gels, lotions, and ointments often require enhanced drug solubility for optimal skin penetration and therapeutic activity. Mixed solvency improves drug dispersion and release from topical formulations, thereby enhancing local drug delivery and efficacy. ⁽²⁵⁾

COMPARISON OF MIXED SOLVENCY WITH OTHER SOLUBILITY ENHANCEMENT TECHNIQUES

Enhancement of drug solubility is a major objective in pharmaceutical formulation development, particularly for poorly water-soluble drugs. Over the years, various techniques such as micronization, solid dispersion, complexation, co-solvency, hydrotropy, and surfactant-based solubilization have been developed to improve drug dissolution and bioavailability. Among these methods, the mixed solvency approach has gained considerable attention because of its simplicity, cost-effectiveness, and ability to achieve significant solubility enhancement using safe concentrations of multiple solubilizers. ⁽²⁶⁾

Micronization is a widely used technique that reduces particle size and increases surface area, thereby improving the dissolution rate of drugs. However, it does not significantly alter the intrinsic solubility of a drug and may lead to particle aggregation during storage. Solid dispersion techniques can provide substantial improvements in solubility and dissolution, but they often require specialized manufacturing processes and may suffer from stability issues due to drug recrystallization. ⁽²⁷⁾

Complexation methods, particularly those involving cyclodextrins, improve drug solubility through the formation of inclusion complexes. Although effective, these techniques may be expensive and are

sometimes limited by the amount of complexing agent that can be incorporated into the formulation. Co-solvency and hydrotropy are simpler approaches, but high concentrations of individual solubilizing agents may result in toxicity, irritation, or formulation instability. Surfactant-based systems improve apparent solubility through micelle formation; however, excessive surfactant concentrations can affect product safety and patient acceptability.

In contrast, mixed solvency combines the advantages of several solubilization techniques by utilizing multiple water-soluble additives at lower concentrations. This approach minimizes toxicity concerns while producing synergistic solubilization effects. Additionally, mixed solvency does not require sophisticated equipment, making it suitable for large-scale manufacturing. The technique has demonstrated effectiveness in enhancing the solubility of numerous poorly water-soluble drugs while maintaining formulation stability and economic feasibility. Consequently, mixed solvency is increasingly regarded as a versatile and practical alternative to conventional solubility enhancement methods. ⁽²⁸⁾

Table 2. Comparison of Mixed Solvency with Other Solubility Enhancement Techniques

Technique	Principle	Advantages	Limitations
Micronization	Particle size reduction	Increased surface area and dissolution rate	Does not significantly improve intrinsic solubility; aggregation possible
Solid Dispersion	Drug dispersed in carrier matrix	High solubility enhancement	Stability and recrystallization issues
Complexation	Formation of inclusion complexes	Improved drug solubility and stability	Expensive and limited complexing capacity
Co-solvency	Use of water-miscible solvents	Simple and effective	High solvent concentration may cause toxicity
Hydrotropy	Use of hydrotropic agents	Significant solubility enhancement	Large amounts of hydrotropes may be required
Surfactant Solubilization	Micelle formation	Improved apparent solubility	Excess surfactant may affect safety and acceptability
Mixed Solvency	Combination of multiple solubilizers	Synergistic effect, lower toxicity, economical, versatile	Requires optimization of solubilizer combinations

CONCLUSION

Drug solubility plays a crucial role in determining the absorption, bioavailability, and therapeutic effectiveness of pharmaceutical products. Poor aqueous solubility continues to be a major challenge in the development of many modern drug molecules. The mixed solvency approach has emerged as a promising and efficient technique for overcoming these limitations by utilizing combinations of hydrotropes, co-

solvents, surfactants, polymers, and buffering agents to achieve enhanced drug solubilization. This strategy offers several advantages, including improved dissolution rate, reduced toxicity of individual solubilizers, cost-effectiveness, and applicability to a wide range of dosage forms. Although challenges related to formulation optimization, stability, and regulatory considerations remain, the benefits of mixed solvency outweigh its limitations. The successful application of this approach in tablets, capsules, oral liquids, injectable formulations, and topical preparations highlights its versatility. Therefore, mixed solvency represents a valuable and innovative solubility enhancement technique with significant potential in future pharmaceutical research and formulation development.

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