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# Advances in Enhancing Bioavailability of Poorly Water-Soluble Drugs: A Comprehensive Review of Techniques and Formulations

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**ABSTRACT**

**Enhancing the bioavailability of poorly water-soluble drugs is a significant challenge in pharmaceutical development. Traditional techniques like particle size reduction, salt formation, and solid dispersions, along with newer approaches such as nanosizing and microemulsion technology, have been developed to improve drug solubility and absorption. Lipid-based delivery systems (LBDDS) offer promising solutions, and eutectic mixtures and solid solutions are emerging as innovative approaches. This review provides an overview of these bioavailability enhancement techniques, emphasizing their importance in improving the therapeutic efficacy of poorly water-soluble drugs.**

**Keywords: Bioavailability, Poorly water-soluble drugs, Lipid-based formulations, Lipid suspensions, Emulsions, Self-emulsifying drug delivery systems (SEDDS), Solid lipid nanoparticles (SLNs), Formulation optimization, Intestinal lymphatic transport, Permeability.**

## INTRODUCTION

One of the most important pharmacokinetic parameters, bioavailability describes the percentage of a given pharmacological dosage that enters the systemic circulation unaltered. When a medication is injected, its bioavailability is usually 100%; however, when it is taken orally, insufficient absorption or first-pass metabolism may cause a drop in bioavailability.[1]

More and more pharmacological compounds with larger molecular weights, worse water solubility, and increased lipophilicity have been developed in recent years.[2] Improvements in combinatorial chemistry and drug design are major drivers of this trend.[3–4]. It's interesting to note that 90% of compounds in the drug research pipeline and 40% of medicines with market approval are categorised as weakly water-soluble pharmaceuticals.[5–6] This frequency emphasises how urgent it is to solve problems with these chemicals' bioavailability.[7].

Poor water solubility has a significant influence on drug development and is blamed for a significant portion of new drug development failures.[8] Due to their restricted solubility and sluggish dissolving rates, poorly soluble medicines often show inadequate bioavailability, which ultimately leads to subpar drug delivery and therapeutic results.[9–10]

To ameliorate the dissolution rate and thus the bioavailability of poorly water-soluble drugs, a myriad of approaches have been explored. These encompass nanoparticlebased formulations,[11-12] lipid-based drug delivery systems,[13-14] pro-drugs,[15] amorphous solid dispersions,16 salt formation,17 co-crystals,18 and cyclodextrin complexes, among others.[19] Over the course of the last 15 years, lipid-based delivery systems, or LBDDS, have attracted a lot of interest in pharmaceutical research. Improved drug solubility, better gastrointestinal absorption, and preservation of medications against gastrointestinal tract degradation are only a few benefits of using LBDDS.[20–21]

This comprehensive review aims to delve into the diverse approaches of LBDDS in enhancing the bioavailability of drugs with low aqueous solubility. By providing an in-depth exploration Considering LBDDS, this study aims to further knowledge of lipid-based formulations as a potentially effective method of enhancing the therapeutic effectiveness and bioavailability of poorly water-soluble medications.[22]

**Bioavailability Enhancement Techniques for Poorly Water-Soluble Drugs:**
Due to their restricted solubility and sluggish dissolving rates, poorly water-soluble medicines often display low bioavailability, which presents a substantial barrier in pharmaceutical research. Improving these medications'

bioavailability is essential to raising their therapeutic effectiveness. To overcome this difficulty, a number A multitude of techniques have been developed to improve the solubility, dissolution, and ultimately the bioavailability of medicines that exhibit low water solubility. Here, we go over a couple of the most prominent strategies for enhancing bioavailability in detail:

**Traditional Bioavailability Enhancement Techniques**
For many years, standard ways of improving bioavailability have been employed to enhance the solubility and absorption of drugs that are not particularly soluble in water. Among these approaches are the following:

**Particle Size Reduction:** Reducing the size of the drug particles to a smaller size in order to maximise the surface area available for dissolution is known as particle size reduction, and it includes methods like micronization. Faster dissolution and increased bioavailability result from this.[23]

**Salt Formation:** The drug's solubility in water may be increased by transforming it into a salt form. This method is often used to increase the bioavailability of basic or acidic medications.

**Complexation:** The solubility and stability of the medicine may be improved by complexing it with cyclodextrins or other complexing agents. This method works especially well for medications that are not very soluble in water.[24]

**Solid Dispersions:** To improve a drug's solubility, solid dispersions include distributing it inside a solid matrix, such a polymer. Drugs that dissolve slowly in water may have their bioavailability increased by solid dispersions.

**Emulsions:** Emulsions are used to increase lipophilic medication solubility and absorption. By increasing the amount of surface area accessible for absorption, they may improve medication solubility and bioavailability.

**Co-solvents:** Co-solvents are often used to solubilize medications that are not very soluble in water. They may boost a drug's bioavailability by making it more soluble in aqueous solutions.

**Complex Formulation:** To improve the bioavailability of medications that are poorly soluble in water, several conventional formulations combine several methods, such as complexation or solid dispersions with emulsions.[25]

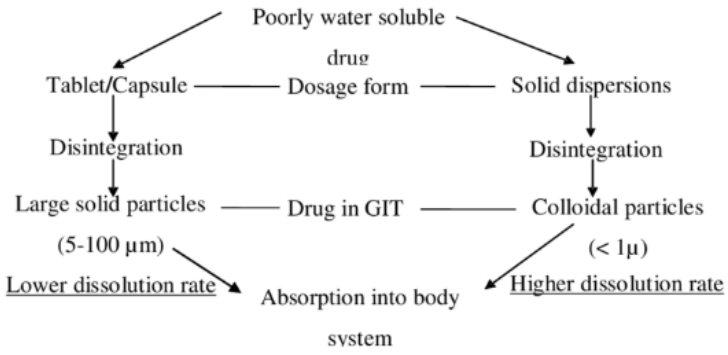


**Figure: 1. A diagram illustrating the improved absorption of a medication with low water solubility by the use of solid dispersion.**

**Newer Technique**
Using a state-of-the-art method called nanosizing, medicines with low water solubility may have their bioavailability increased by lowering their particle size to the nanometer range. This method increases the absorption and solubility of drugs, which increases therapeutic effectiveness.

**A number of techniques may be used to accomplish nanosizing, such as the:**
**Top-Down Approach:** entails using mechanical techniques like high-pressurehomogenization or milling to reduce the size of medication particles. Although this technique is good at lowering particle size, it might lead to crystal structural alterations or aggregation.

**Bottom-Up Approach:** involves creating drug nanoparticles by synthesising a drug suspension or solution. Nanoparticles of regulated size and shape are created using methods such supercritical fluid technology, emulsification, solvent evaporation, andnanoprecipitation.

**Combination Approach:** achieves the best particle size reduction and control by combining top-down and bottom-up methods.[26]

**Nanosizing offers several advantages for enhancing bioavailability, including:**

- Increased surface area for drug dissolution
- Enhanced drug solubility and dissolution rate
- Improved drug stability
- Controlled drug release
- Potential for targeted drug delivery

**Technology of Microemulsions:** Microemulsions are isotropic mixes of water, oil, surfactant, and cosurfactant that are thermodynamically stable. By increasing solubility and permeability, they may solubilize both hydrophilic and hydrophobic medications, increasing their bioavailability. Other benefits of microemulsions are their simplicity of manufacture and possibility for controlled medication release.

**Size Reduction Technology:** Drug particles are made smaller by size reduction methods including micronization and nanosizing, which increase surface area and speed up dissolution. Through the facilitation of quicker and more thorough medication absorption, this results in increased bioavailability.

**Molecular Encapsulation with Cyclodextrin:** Cyclodextrins are cyclic oligosaccharides that may increase the solubility and bioavailability of poorly water-soluble medicines by forming inclusion complexes with them. Enhancing bioavailability and therapeutic effectiveness, cyclodextrin molecular encapsulation increases medication stability, solubility, and release properties.[27]

A formulation method called solid dispersion is used to improve the solubility and bioavailability of medications that are not very soluble in water. In a solid dispersion, the medication is either crystalline or amorphous and is distributed in a hydrophilic carrier matrix, either a polymer or a surfactant. The drug's dissolving rate may be accelerated by this dispersion, increasing absorption and bioavailability.[28]

**There are several methods for preparing solid dispersions, including:**
**Melting Process:** To create a solid dispersion, the medication and carrier are melted together and then allowed to cool. Drugs with low melting points may be used using this technique.

**Method of Solvent Evaporation:** A common solvent is used to dissolve the medication and carrier. The solvent is then evaporated to produce a solid dispersion. Drugs and carriers that are soluble in the same solvent may be used using this technique.

**Melt extrusion:** Melt extrusion involves mixing the medication with the carrier and heating the mixture over the carrier's melting point. To create a solid dispersion, the mixture is then extruded and solidified. Drugs and carriers that can be processed at high temperatures may be used using this approach.

**Spray drying**: Spray drying involves dispersing or dissolving the medication and carrier in a solvent, then spraying the combination into a heated chamber to evaporate the solvent and create a solid dispersion. Drugs and carriers that are stable at high temperatures may be used using this technique.[29]

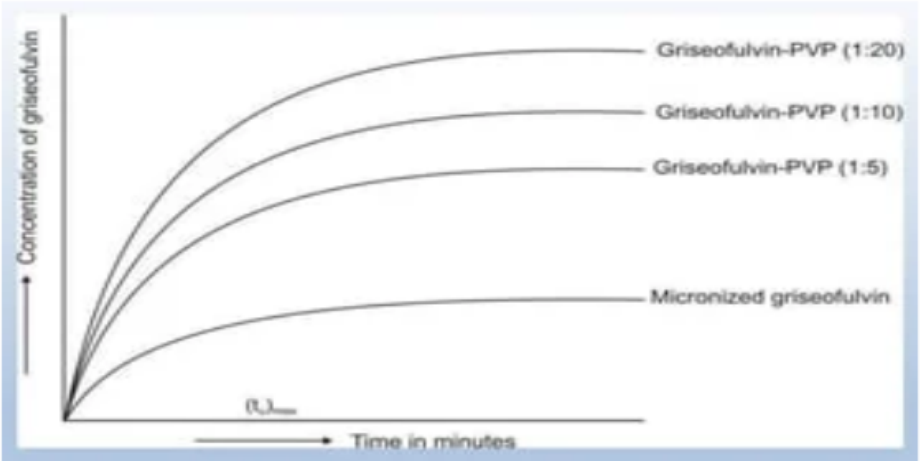


**Figure: 2 Improving the rate at which griseofulvin dissolves using solid dispersion technology**

**Eutectic Mixture: A Unique Approach to Enhancing Bioavailability**

Eutectic mixes are brand-new formulations designed to take advantage of the special qualities of certain medication pairings. These combinations include two or more components that melt together at a temperature lower than any of the components melting separately, creating a eutectic system. Eutectic mixes are used in the pharmaceutical industry to increase the bioavailability and solubility of medications that are not very soluble in water.

The physical and chemical characteristics of the constituent components may be dramatically changed by the development of a eutectic system, which can increase the solubility and rate of dissolution of the medicine. This may enhance the absorption and bioavailability of medications that have restricted aqueous solubility.[30]

The capacity of eutectic mixes to improve medication distribution without the need for intricate formulation procedures is one of their main benefits. The medicine may be made far more soluble and bioavailable by simply mixing it with another appropriate chemical to create a eutectic combination.

Eutectic mixes are adaptable and may be used in liquid formulations, pills, and capsules, among other dosage forms. They provide a simple but efficient way to increase the bioavailability of poorly water-soluble medicines, so offering a possible solution to the problems they present.

Eutectic mixes are made via fusion, in which the solvent and solute exhibit perfect miscibility when melted. They aren't the same as solid solutions, however, since they are basically physical combinations of two crystalline substances. The soluble carrier in a eutectic combination dissolve when it comes into contact with water, leaving the medication in a microcrystalline form that solubilizes quickly.[31]

Notable instances of eutectic production include two medicinal products. First, an aspirin and acetaminophen eutectic mixture, which dissolves more quickly and melts at a lower temperature than previous combinations probably because of weaker binding forces and finer particle size. Compared to a straightforward mixing of the two chemicals, this eutectic dissolves more rapidly. In the second case, urea and acetaminophen combine to create a eutectic that melts in the 1100–1150 range, including around 46% urea and 54% acetaminophen.[32]

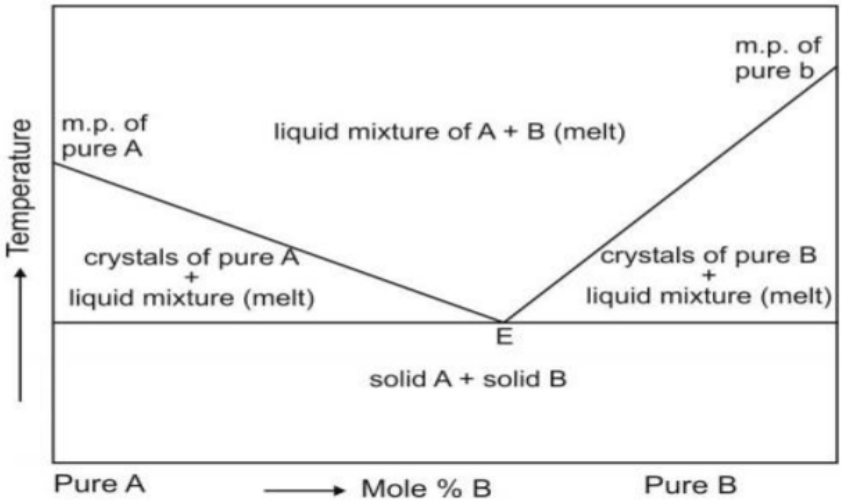


**Figure: 3 E represents the eutectic point in a basic binary phase diagram. The substance with the dose melting point is the one with eutectic content at point E of substances A and B. Pure A and pure B have melting points TA and TB.**

A solid solution refers to a binary system consisting of a solid solute that is dispersed molecularly inside a solid solvent. A solid solution, also known as a mixed crystal, is a uniform and single-phase system that forms when two components crystallise together. Due to the lower size of particles at the molecular level in solid solutions compared to eutectics and solid dispersions, solid solutions dissolve more rapidly and have higher solubility in water.[33]

The fusion process, which involves melting a physical combination of solute and solvent and quickly solidifying it, is often used to make solid solutions. These fusion-prepared systems, such the solid solution of griseofulvin and succinic acid, are often referred to as melts. In this instance, the solid solution of griseofulvin dissolves six to seven times quicker than pure griseofulvin. [34]

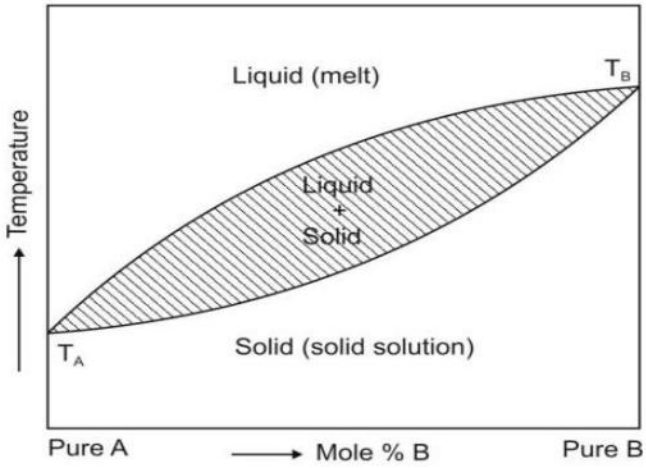


**Figure: 4 Binary phase diagram for continuous solid solution of A and B. TA and TB are melting points of pure A and pure B respectively**

Solute molecules may fit between solvent molecules when their diameter is less than 60% of solvent molecules' diameter or when their volume is less than 20% of solvent molecules' volume. Digitoxin-PEG 6000 solid solution, which shows quicker dissolving, is an illustration of this.[35]

Glass solutions are defined as homogenous, transparent, and brittle solid solutions. To improve the solubility and quick dissolution of molecular dispersions: two methods are suggested. The soluble carrier rapidly dissolves when exposed to water, leaving the insoluble medication in a microcrystalline dispersion consisting of minuscule particles.[36] Upon contact with the dissolving fluid, the solid solution, consisting of solute and solvent molecules arranged randomly in the crystal lattice, rapidly dissolves the soluble carrier, while the insoluble drug remains trapped at a nearly molecular level.[37]

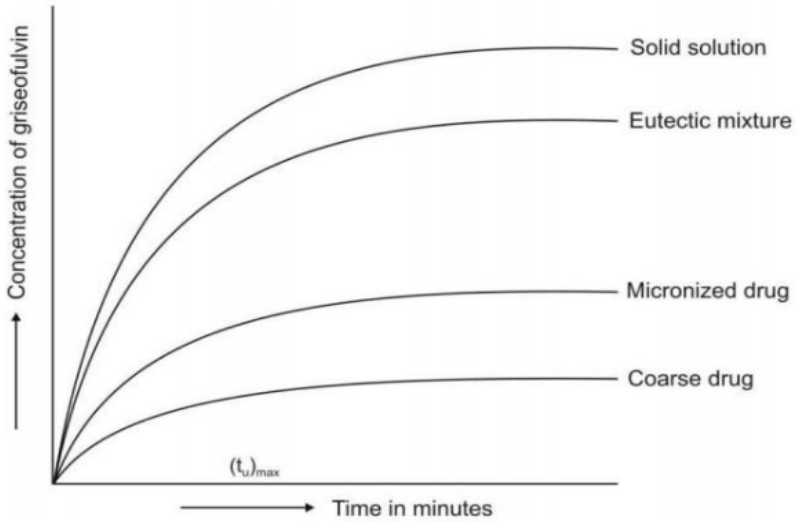


**Figure: 5 The rates at which griseofulvin dissolves were studied in several forms: as coarse particles, as micronized particles, and as a eutectic and solid solution with succinic acid. This graph illustrates the comparative dissolving rates of several types of griseofulvin.**

## CONCLUSION

Enhancing the bioavailability of poorly water-soluble drugs is a critical challenge in pharmaceutical development. The use of various techniques, including traditional methods like particle size reduction, salt formation, complexation, solid dispersions, emulsions, and co-solvents, as well as newer approaches like nanosizing and microemulsion technology, has significantly advanced the field. These techniques improve drug solubility, dissolution rate, and ultimately, bioavailability, leading to enhanced therapeutic outcomes.

Among these techniques, lipid-based delivery systems (LBDDS) have emerged as a promising strategy. LBDDS offer several advantages, including improved drug solubility, enhanced gastrointestinal absorption, and protection of drugs

from degradation in the gastrointestinal tract. Their versatility and effectiveness in enhancing the bioavailability of poorly water-soluble drugs make them a valuable tool in pharmaceutical research.

Eutectic mixtures and solid solutions are also innovative approaches that have shown promise in improving drug delivery and bioavailability. Eutectic mixtures, formed by combining two or more components that melt at a lower temperature than any individual component, offer a simple yet effective means of enhancing drug solubility and bioavailability. Solid solutions, on the other hand, are homogeneous mixtures of a solid solute molecularly dispersed in a solid solvent. They exhibit greater aqueous solubility and faster dissolution compared to eutectics and solid dispersions, making them valuable for enhancing drug delivery.

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