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Bioavailability Enhancement Techniques For Poorly Soluble Drug

Published by MANSI. NARAYAN. BHUTEKAR ,DR.SUNIL.S.JAYBHAYE

ABSTRACT

Poor aqueous solubility remains one of the major challenges in the development of orally administered drug molecules, particularly those falling under BCS Class II and IV. Low solubility leads to inadequate dissolution, poor absorption, and ultimately reduced bioavailability, limiting therapeutic efficacy. Therefore, enhancing the solubility and bioavailability of such drugs has become a key focus in modern pharmaceutics. Various formulation and technological approached—including particle size reduction, solid dispersions, lipid-based systems, complexation, nanotechnology-based carriers, and supersaturation-enhancing systems—have been developd to address these limitations. Each technique offers unique advantages in improving dissolution rate, permeability, and stability of poorly soluble drugs. This review summarizes the principles, mechanisms, benefits, and applications of the major bioavailability enhancement strategies, highlighting their potential to optimize drug performance and support successful pharmaceutical development.

Defination

Bioavailability is the quantitative measure of the systemic availability of a drug from its dosage form. It describes both the rate of absorption (how quickly a drug enters the bloodstream) and the extent of absorption (the amount of drug absorbed). It is influenced by drug physicochemical properties, formulation factors, route of administration, and physiological condition.

Keywords: Bioavailability, poorly soluble drugs, Low aqueous solubility, Dissolution rate, solubility enhancement, permeability enhancement, micronization, Nanonization, Nanosuspensions, Solid dispersion, spray drying, PH modification, Salt formation

Aim: A review Article on Bioavailability Enhancement Techniques For Poorly Soluble Drugs.

Objectives:

1. **To understand the concept of bioavailability and** its importance in oral drug delivery, especially for BCS Class II and IV drugs**.**

2. **To identify the major challenges associated with poorly soluble drugs,** including low dissolution rate, poor absorption, and variable therapeutic response.

3. **To review and compare different bioavailability enhancement techniques,** such as particle size reduction, solid dispersions, lipid-based systems, surfactants, cyclodextrin complexes, and nanotechnology-based approaches.

4. **To study the mechanism of each enhancement technique** and how it improves solubility, dissolution, permeability, or overall absorption.

5. **To analyze formulation factors and excipients** used in different enhancement methods and their impact on drug performance.

6. **To evaluate the advantages, limitations, and suitability** of each technique for specific drug molecules or therapeutic categories.

Introduction

Bioavailability is a critical parameter in oral drug delivery, as it determines the rate and extent to which an administered drug reaches the systemic circulation. However, a large proportion of newly developed drug molecules—especially those categorized under Biopharmaceutical Classification System (BCS) Class II and Class IV—suffer from poor aqueous solubility, which becomes the primary barrier to achieving optimal therapeutic levels. Low solubility often results in inadequate dissolution in gastrointestinal fluids, reduced absorption across biological membranes, variable pharmacological response, and the need for higher doses, ultimately affecting patient compliance and treatment outcomes.

With advances in drug discovery, many new chemical entities (NCEs) are highly lipophilic and exhibit excellent potency but fail during development due to poor bioavailability. Therefore, enhancing the solubility and dissolution rate of such drugs has become a major challenge for formulation scientists. To overcome these limitations, a wide range of bioavailability enhancement techniques has been developed, encompassing physical modifications, chemical approaches, and novel drug delivery systems. These include particle size reduction, solid dispersions, lipid-based formulations, cyclodextrin complexes, nanotechnology-driven systems, and supersaturation strategies.

The Challenge: Why Poor Solubility Matters in Drug Development

Approximately 40% of new chemical entities exhibit poor water solubility, creating a significant barrier to effective drug delivery. When active pharmaceutical ingredients cannot dissolve adequately in gastrointestinal fluids, bioavailability suffers dramatically, reducing therapeutic efficacy and forcing patients to take higher doses with potential adverse effects.

Poor solubility leads to erratic absorption patterns, variable plasma concentrations, and inconsistent clinical outcomes. This challenge impacts drug development timelines, increases costs, and may render otherwise promising candidates clinically unusable. For Indian pharmaceutical manufacturers competing globally, developing robust bioavailability enhancement strategies is essential for creating differentiated products and improving patient outcomes across diverse populations.

Dissolution Problem

Drug remains undissolved in GI fluids, limiting absorption from the intestinal lumen.

Absorption Barrier

Reduced concentration gradient prevents efficient permeation across intestinal epithelium.

Clinical Impact

Unpredictable plasma levels compromise therapeutic efficacy and patient safety.

Fundamentals of Bioavailability: Absorption, Distribution, Metabolism, Excretion

Bioavailability represents the fraction of an administered dose reaching systemic circulation in unchanged form. This critical parameter depends on four interconnected processes that determine drug destiny within the body.

Absorption

Drug movement from administration site into systemic circulation, heavily dependent on solubility and permeability characteristics.

Distribution

Drug dispersal throughout body tissues and organs, determined by lipophilicity, protein binding, and tissue affinity.

Metabolism

Enzymatic transformation of drug into metabolites, primarily occurring in liver through Phase I, II, and III processes.

Excretion

Elimination of drug and metabolites via kidneys, bile, lungs, or other routes, completing the pharmacokinetic cycle.

For poorly soluble drugs, enhancement strategies primarily focus on improving the absorption phase by maximizing dissolution in gastrointestinal fluids and permeation across intestinal membranes, thereby increasing bioavailability and achieving therapeutic concentrations reliably.

Conventional Approaches and Their Limitations

Traditional methods for enhancing bioavailability of poorly soluble drugs include particle size reduction, salt formation, and pH adjustment. Micronization reduces particle size to increase surface area and dissolution rate, yet particle aggregation often reverses benefits. Salt forms enhance solubility through ionisation but require careful pH considerations and may cause gastrointestinal irritation.

Micronization

Reduced particle size increases surface area, but particles aggregate, reducing effectiveness and shelf-life stability remains problematic.

Salt Formation

Improves solubility through ionisation, yet pH-dependent dissolution causes variable absorption and potential GI side effects.

pH Adjustment

Buffering systems enhance dissolution but are complex to formulate, expensive, and may not provide sustained benefits throughout GI transit.

Surfactant Solutions

High surfactant concentrations needed for adequate solubility risk gastrointestinal toxicity and regulatory scrutiny regarding safety profiles.

These conventional approaches often prove insufficient for highly lipophilic compounds, prompting pharmaceutical scientists to develop innovative formulation technologies that provide robust, reproducible bioavailability enhancement.

Novel Formulations: Amorphous Solid Dispersions and Co-crystals

Amorphous Solid Dispersions (ASDs) represent a revolutionary approach, dispersing poorly soluble drugs within hydrophilic polymer matrices. This molecular-level mixing prevents drug crystallisation, dramatically enhancing dissolution rates and maintaining supersaturation—a metastable state where drug concentration exceeds saturation solubility, enabling enhanced absorption.

- Amorphous Solid Dispersions
- Drug dispersed at molecular level in polymer carrier
- Prevents crystallisation and recrystallisation
- Maintains supersaturation in GI tract
- Enhanced dissolution rates up to 100-fold
- Requires stabiliser and processing control

Co-crystals

•Multicomponent crystals with drug and co-former

•Modified crystal lattice improves solubility

•Single-phase material with defined stoichiometry

•Enhanced stability compared to salt forms

•Requires regulatory classification clarity

Co-crystals involve molecular association between drug and co-crystal former, creating new crystal forms with improved solubility profiles. Unlike salts, co-crystals maintain neutral species stability, offering advantages for weakly acidic or basic compounds. Indian pharmaceutical companies increasingly utilise these technologies for developing differentiated formulations, particularly for challenging candidates in pain management, antiretroviral, and cardiovascular domains.

Nanotechnology in Action: Nanosuspensions and Lipid Nanoparticles

Nanosuspensions reduce drug particles to nanometer scale (50-500 nm), maximising surface area and dissolution kinetics. These colloidal dispersions comprise drug nanoparticles stabilised by surfactants or polymers, effectively bypassing traditional solubility limitations through sheer surface area advantage and particle size-dependent enhanced absorption through lymphatic uptake and epithelial penetration.

Nanosuspensions

Ultra-fine drug particles achieve rapid dissolution and improved bioavailability through enhanced surface area and permeation via M-cells in Peyer's patches.

Lipid Nanoparticles (LNPs)

Lipid-based carriers encapsulate poorly soluble drugs, protecting from degradation, enhancing absorption through lymphatic pathway, and enabling targeted delivery to specific tissues.

Advantages in India

Cost-effective manufacturing scale-up, compatibility with existing pharmaceutical infrastructure, and proven safety profiles make these technologies attractive for Indian manufacturers developing affordable yet effective formulations.

Lipid nanoparticles offer additional advantages through hepatic uptake avoidance or facilitation, lymphatic absorption, and reduced first-pass metabolism. These nanotechnologies address bioavailability challenges whilst meeting stringent regulatory requirements for pharmaceutical quality and safety.

Permeation Enhancers: Strategies for Improved GI Absorptionn

Permeation enhancers represent chemical strategies to improve drug transport across intestinal epithelium, particularly valuable for polar or hydrophilic compounds with poor membrane permeability. These agents modulate tight junction proteins, enhance transcellular pathways, or inhibit efflux transporters, thereby increasing absorption independent of solubility improvements.

1 **Tight Junction Modulators**

Reversibly alter tight junction proteins (claudins, occludin, ZO-1), increasing paracellular transport without causing permanent damage to intestinal barrier integrity.

2 **Transcellular Enhancers**

Increase cell membrane fluidity and drug partitioning, facilitating passive diffusion across enterocyte membranes for lipophilic compounds.

3 **Efflux Inhibitors**

Block P-glycoprotein and other transport proteins that actively pump drugs back into intestinal lumen, significantly improving bioavailability for substrate compounds.

4 **Enzymatic Inhibitors**

Suppress intestinal metabolising enzymes (CYP3A4, UGT1A1), preventing first-pass metabolism and maintaining higher systemic drug concentrations.

Careful selection and dosing of permeation enhancers is essential to maintain intestinal barrier function whilst improving drug bioavailability. Indian researchers are actively investigating natural permeation enhancers from traditional medicinal plants, offering sustainable and culturally relevant innovation pathways.

Case Studies: Successful Bioavailability Enhancement in Indian Pharma

Indian pharmaceutical companies have successfully implemented bioavailability enhancement technologies across multiple therapeutic areas, creating commercially viable and clinically effective formulations that compete globally whilst serving diverse patient populations.

1. **Ritonavir Formulation**

ASD technology improved bioavailability of this protease inhibitor through polymer-based formulation, enabling more effective antiretroviral therapy with improved patient compliance and reduced pill burden.

2. **Curcumin Enhancement**

Lipid-based nanoformulations of curcumin increased bioavailability 100-fold, enabling traditional compound to achieve therapeutic efficacy in inflammation and cancer research through novel delivery systems.

Bioavailability enhancement through enhancement of drug solubility or dissolution rate.

•*Micronization*

•*Nanonization*

•*Supercritical Fluid Recrystallization*

•*Spray Freezing into Liquid*

•*Evaporative Precipitation into Aqueous solution(EPAS)*

•*Use of Surfactants*

•*Use of Salt Forms*

1. **Micronization**: The process involves reducing the size of solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (Fluid energy or jet mill). This process is called as **micromilling** . **Example**: Griseofulvin

2. **Nanonization:** A process whereby the drug powder is convertrd to nanocrystals of sizes 200-600 nm. Example: Amphotericin. B. The main production technologies currently in use to produce drug nanocrystals in a liquid typically water (Called Nanosuspension) . There are three basic technologies currently use to prepare nanoparticles?

3. **Supercritical Fluid Recrystallization:** Another novel nanonising and solubilization technology application has increased in recent years is particles size reduction via supercritical fluid (SCF) process

4. **Spray Freezing into Liquid (SFL) :** The techniques involves atomizing an aqueous organic, aqueous-organic sosolvent solution, aqueous – organic emulsion or suspension containing a drug or pharmaceutical excipients directly into a comoressed gas(i.e nitrogen, argon or hydro fluro ethers)

5. **Evaporative Precipitation into Aqueous Solution(EPAS) :**This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution.

6. **Use of surfactants :** Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug.

   •They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drugs entrapped in the micelle structure fails to partition in the dissolution fluid.

   •They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

7. **Use of salt forms:** Salts have improved solubility and dissolution characteristicsin comparison to the original drug.

   • It is generally accepted that the a minimum difference that a minimum difference of3 units between the pKa value of the group and that of its counter ion is required to form stable salts.

   • Alkali metal salts of avidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than the parent drug.

2.1. Physical Modifications

2.1.1. Particle Size Reduction

The drug solubility depends on its particle size. Large particles provide a low surface area, which results in less interaction of particles with the solvent. One of the methods to increase the drug's surface area is to reduce its particle size, which improves its dissolution property.

Micronization:

The process of producing drug particles in micron size by using the physical method. The methods widely used for increasing BCS class II drugs' solubility are freeze-drying, crystallization, spray drying, and milling [58].

Size reduction in the conventional time is achieved through mechanical methods, i.e., grinding, milling, and crushing of heavier particles to reduce their size by applying fric-tion, pressure, attrition, shearing or impact. For mechanical micronization, ball mills, jet mills and high-pressure homogenizers are utilized. Dry milling is the most preferred mi-cronization method. [59].

Micronization raises the dissolution speed rather than the drug's equilibrium solu-bility. In various studies, it has been reported these that methods for the reduction in size are used to increase the dissolution and bioavailability through decreasing dimension and increasing the surface area of poorly aqueously soluble drugs.

Nanosuspension:

Nanosuspension is well-defined as a colloidal dispersion of sub-micron drug elements, stabilized by using a surfactant. To produce a nanosuspension, wet milling and homogenization are used. Milling defragments the active compound in the

presence of a surfactant.

•Advantages of nanosuspension [60]

• Enhancement of drug solubility and its bioavailability

•Higher drug loading

• Suitable for hydrophobic drugs

•Passive drug targeting

•Reduction in dosage

• Increase in drug's physical and chemical stability.

Methods for the Preparation of a Nanosuspension:

•A nanosuspension is primed via two main methods—"bottom-up" and "top-down" technology [61].

•Bottom-up technology—This is an assembling technique for the formation of nano-particles, such as precipitation, melt emulsification, and microemulsion.

•Top-down technology—Includes the decomposition of heavier particles into small particles, such as the high-pressure homogenization method and the grinding techniques.

Factors influencing bioavailability

Bioavailability of a drug is affected by multiple factors related to the drug, the formulation, and the patient. These factors determine how much and how fast the drug reaches systemic circulation.

1. **Physicochemical Factors** (Drug-related factors)
2. **Solubility**: Poorly soluble drugs show slow dissolution and low absorption.
3. **Particle size:** Smaller particles dissolve faster, increasing bioavailability.
4. **Polymorphism**: Different crystalline forms have different dissolution rates.
5. **pKa and ionization:** Unionized forms absorb better across membranes.
6. **Partition coefficient (lipophilicity):** Affects membrane permeability.
7. **Stability in GI tract:** Drugs degraded by pH or enzymes show reduced bioavailability.

Formulation Factors (Dosage form-related factors)

1.**Disintegration time:** Tablets that break apart faster dissolve quicker.

2.**Excipients**: Wetting agents, disintegrants, and surfactants improve dissolution.

3.**Manufacturing process:** Compression force, granulation method affect dissolution.

4.**Drug release mechanism:** Immediate release vs controlled release formulations.

5.**Interactions with excipients:** Example: complexation or binding reduces absorption.

2. **Physiological Factors (Patient-related factors)**

1. **Gastrointestinal pH:** Affects ionization and solubility.
2. **Gastric emptying time:** Faster emptying → quicker absorption.
3. **Intestinal motility:** High motility can reduce absorption time.
4. **Presence of food:** May increase or decrease absorption depending on drug
5. **First-pass metabolism:** Liver metabolism reduces systemic drug availability.
6. **dissolution**: GI diseases, liver disease, malabsorption disorders alter bioavailability.
7. **Age and gender**: Influence metabolic enzymes and GI function.

4.Route of Administration Factors

1. **Oral**: Most affected by first-pass effect and GI conditions.
2. **IV**: 100% bioavailability.
3. **IM/SC:** Depends on blood flow, muscle mass, and injection site.
4. **Transdermal**: Affected by skin thickness, hydration, and lipid content.

5. Drug–Drug and Drug–Food Interactions

1.**Enzyme inhibitors:** Increase bioavailability (e.g., ketoconazole).

2.**Enzyme inducers:** Decrease bioavailability (e.g., rifampicin).

3.**Food components:** Fat-rich meals may enhance absorption of lipophilic drugs.

Challenges of Poorly Soluble Drugs

Poorly soluble drugs—especially those belonging to BCS Class II and IV—face multiple formulation and biological barriers that limit their effectiveness. These challenges affect absorption, onset of action, dosing, and overall therapeutic success.

1.Low Oral Bioavailability

•Poor aqueous solubility reduces dissolution in gastrointestinal (GI) fluids.

•Since only dissolved drug can be absorbed, the absorbed fraction fraction becomes very small.

2.**High Dose Requirements**

•To achieve therapeutic plasma levels, large doses may be required.

•This increases the risk of side effects and patient non-compliance.

3.**Variable or Incomplete Absorption**

•Dissolution becomes the rate-limiting step.

•Small changes in GI pH, food intake, or motility cause large variations in absorption.

4.**Slow Onset of Action**

•Poorly soluble drugs dissolve slowly → delayed absorption → slow pharmacological response.

5.**Poor Reproducibility & Bio-variability**

•Batch-to-batch variability in formulation affects dissolution behaviour.

•Leads to inconsistent therapeutic outcomes.

6. **Formulation Difficulties**

•Difficult to develop stable, uniform dosage forms.

•Techniques like nanoparticles, solid dispersions, cyclodextrins, lipid-based systems require complex equipment and high cost.

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Impact of Therapeutic Efficacy

Therapeutic efficacy refers to the ability of a drug to produce the desired therapeutic effect at the target site. The impact of therapeutic efficacy is crucial in determining the overall success and clinical usefulness of a drug.

1. Determines Clinical Outcomes

A drug with high therapeutic efficacy produces a stronger and more reliable clinical response, leading to better disease control or cure. Low efficacy results in incomplete or inadequate treatment.

2. Influences Dosage Requirements

Poorly efficacious drugs require higher doses to achieve the desired effect, which may increase the risk of side effects and toxicity. Drugs with high efficacy achieve results at lower doses.

3. Affects Patient Compliance

If a drug shows good therapeutic benefit with minimal adverse effects, patients are more motivated to adhere to therapy. Low efficacy often discourages patients due to poor symptom relief.

4. Determines Market Success and Drug Development

Drugs with superior therapeutic efficacy gain wider acceptance, better clinical preference, and stronger market value. Poor efficacy leads to redesign of formulations or withdrawal.

5. Guides Selection of Drug Delivery Systems

Formulations are optimized (e.g., nanoparticles, liposomes, solubility enhancers) to improve therapeutic efficacy, especially !

Particle Size Reduction

Particle size reduction is a fundamental technique used to improve the dissolution rate, solubility, and bioavailability of poorly soluble drugs (especially BCS Class II). It involves breaking down coarse drug particles into smaller particles using mechanical or specialized methods.

Methods of Particle Size Reduction

1. Mechanical Methods (Conventional)

a. Milling / Comminution

- Uses mechanical energy to break down particles.
- **Ball mill**: Rotating cylinder containing balls.
- **Hammer mill**: Repeated impact of hammers.
- **Jet mill:** Particles collide at high velocity (suitable for thermolabile drugs).

2. Micronization

•Reduces particle size to 1–10 µm.

•Usually done using fluid energy mill (jet mill).

•Improves dissolution but may cause electrostatic charge or aggregation.

3. Nanosizing (Advanced Technique)

•Reduces size to 10–1000 nm.

Methods:

•Nanomilling (wet media milling)

•High-pressure homogenization

Advantages:

Dramatic increase in surface area

Enhances solubility and bioavailability

Used for drugs like fenofibrate, danazol, naproxen.

•Disadvantages

Increased surface area and dissolution

Improved bioavailability for poorly soluble drugs

Better mixing and uniform distribution

Can enhance stability in suspensions

•Limitations

Heat generation may degrade thermolabile drugs

Possible contamination from milling equipment

Aggregation of very fine particles

Not suitable for sticky or highly elastic materials

•Applications

Tablet and capsule formulation

Preparation of suspensions and emulsions

Enhancing solubility of BCS Class II drugs

Solid Dispersion Techniques

⬘ Introduction

Solid dispersion refers to the dispersion of one or more active pharmaceutical ingredients (API) in an inert carrier or polymer matrix in the solid state. It is one of the most effective techniques to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs (BCS Class II & IV).

⬘ Definition

Solid dispersion is a molecular or particulate dispersion of a poorly soluble drug in a solid hydrophilic carrier prepared by melting, solvent, or melting–solvent methods to enhance solubility and dissolution.

⬘ Purpose / Need

•To improve solubility & dissolution rate

•To enhance wetting and dispersibility

•To convert crystalline drug to amorphous form

•Classification of Solid Dispersions

1. Eutectic mixtures
2. Solid solutions (continuous, substitutional, interstitial)
3. Glass solutions
4. Glass suspension
5. Amorphous precipitations in crystalline carrier

• Carriers Used in Solid Dispersions

Hydrophilic polymers: PVP, PEGs, HPMC

Sugars: Mannitol, Lactose, Sorbitol

Surfactants: Poloxamers, Gelucire

Organic acids: Citric acid, Succinic acid

⬘ Solid Dispersion Techniques

1. Fusion (Melting) Method

• Drug and carrier are melted together and then cooled rapidly with stirring.

• Solid mass is pulverized to obtain dispersion.

Advantages: Simple, solvent-free

Disadvantages: Not suitable for heat-sensitive drugs

2. Solvent Evaporation Method

• Drug and carrier dissolved in a common volatile solvent.

• Solvent is evaporated under reduced pressure.

• Solid mass is ground to fine powder.

Advantages: Suitable for thermolabile drugs

Disadvantages: Residual solvent, costlier

3. Melt–Solvent Method (Mixed Method)

• Carrier is melted; drug is dissolved in a small amount of solvent.

• Drug solution is added to melt and solvent is evaporated.

• **Advantage**: Lower temperature required than fusion alone

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