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# Breaking Barriers: Next-Generation Strategies For Enhancing Solubility And Permeability Of Poorly Bioavailable Drugs

**Made Prem Kumar[1], Chirravuri S Phani Kumar[2*]**
[1,2]Faculty of Pharmacy, Bir Tikendrajit University, Canchipur, Imphal West, Manipur-795003, India.
**Corresponding Author**: chsphanikumar@gmail.com

***Abstract***
*The bioavailability of numerous active pharmaceutical ingredients (APIs) is limited by poor aqueous solubility and low permeability, posing significant challenges in drug development. This review examines cutting – edge techniques to overcome these obstacles, focusing on the interplay between solubility and permeability in oral absorption and systemic exposure. We assess ten innovative solubility-enhancement strategies, including solid dispersions, amorphous formulations, co-crystals, lipid-based systems, and cyclodextrin inclusion complexes, as well as ten advanced permeability - boosting approaches. Such as prodrugs, absorption enhancers, nanocarriers, and mucoadhesive systems. Each technique is illustrated with examples, highlighting its mechanistic rationale, formulation considerations, and recent successes. The concludes by discussing hybrid systems that combine solubility and permeability improvement and recommends future research directions. By providing a unified framework for diverse innovations, this review aims to guide researchers toward next-generation solutions that effectively overcome drug bioavailability barriers.*
***Keywords:*** *Solubility enhancement, permeability improvement, bioavailability optimization, drug delivery strategies, and pharmaceutical formulation techniques.*

## 1. INTRODUCTION

### The Development of Orally Administered Pharmaceuticals

The development of orally administered pharmaceuticals often confronts a pervasive obstacle: inadequate bioavailability due to poor aqueous solubility and limited gastrointestinal membrane permeability. According to the Biopharmaceutics Classification System (BCS), Class II (low solubility, high permeability) and class IV (low solubility, low permeability) compounds comprise a majority of newly discovered drug candidates. These shortcomings can lead to subtherapeutic plasma concentrations, variable absorption, and ultimately compromised efficacy – posing serious risks in translation from bench to beside[1,2].

### Interconnected Barriers to Oral Bioavailability

Solubility and permeability are interdependent parameters in determining oral absorption. an API must first dissolve in the gastrointestinal fluids before it can permeate the intestinal epithelium. even when a drug is highly permeable, if its solubility is insufficient, it cannot reach adequate concentrations to drive absorption. Conversely, a soluble compound may still underperform if it lacks the physicochemical or biochemical attributes necessary for efficient membrane transport. Therefore, tackling one barrier without addressing the other can yield sub-optimal results[3,4].

### Why New Strategies Are Needed?

Traditional techniques – such as salt formation or micronization – have long been employed to improve solubility or permeability. while effective in some instances, they often fall short when dealing with high lipophilic, large-molecule, or chemically unstable APIs. Furthermore, escalating regulatory scrutiny and patient safety concerns demand that formulation approaches be both innovative and biocompatible. This imperative has galvanized research into next- generation strategies that harness advances in materials science, nanotechnology, molecular prodrug design, and formulation engineering[5,6].

### Scope of This Review

This review will:

a) Illuminate the latest solubility – enhancement techniques, discussing how each method manipulates molecular interactions, physical states, or deliver vehicles to increase apparent or intrinsic solubility.

b) Examine advanced permeability – improvement tactics, including both chemical and formulation – driven approaches to bolster transcellular and paracellular transport across the gut wall.

c) Provide real-world examples that illustrate successes and learning points for each technique, drawn from recent literature (within the past ~5 years where possible).

d) Synthesize an integrated framework for dual-barrier solutions – strategies that simultaneously elevate solubility and permeability, representing the true "next generation" of formulation science. By weaving together mechanistic insights, practical examples, and forward-looking perspectives, this review aims to equip pharmaceutical scientists and formulators with a robust knowledge base for advancing poorly bioavailable drugs toward clinical success[7,8].

e)

## 2. LITERATURE REVIEW

### 2.1 Solubility Enhancement Strategies

The solubility enhancement strategies are as follows [9-13]

**a) Solid Dispersion (Hot Melt and Spray Drying):** Solid dispersion enhances drug dissolution by dispersing the active ingredient in a hydrophilic carrier -often a polymer -either via hot-melt extrusion or spray – drying. This process transforms the crystalline API into an amorphous or finely dispersed form, significantly improving wettability and dissolute rate. Example: Itraconazole-HPMC spray -dried dispersion (Sporanox). This formulation markedly increases itraconazole's solubility and bioavailability by promoting rapid drug release in the aqueous environment of the gastrointestinal tract.

**b) Amorphous Formulations:** Amorphous drug forms exhibit higher free energy than their crystalline counterparts, resulting in superior solubility. Stabilization with polymers like polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC) prevents re-crystallization and preserves solubility gains. Example: Atorvastatin -PVP amorphous formulation. Atorvastatin in an amorphous state stabilized by PVP shows a significantly enhanced dissolution profile, making the drug more readily absorbable.

**c) Co- crystal Engineering:** In co- crystals, the API forms a crystalline lattice with a co- former though non- covalent bonds – such as hydrogen bonds – without modifying the drug`s molecule structure. This arrangement ca lower lattice energy, improve hydration, and enhance solubility. Example: Carbamazepine- saccharin co- crystals. Manufactured via anti -solvent crystallization, it achieves high solid yield and exhibits significantly increased solubility-2 to 10 times higher carbamazepine dihydrate, depending on pH – enhancing dissolution potential bioavailability.

**d) Lipid- Based System (SMEDDS, SNEEDDS):** Self- emulsifying formulations spontaneously form oil-in-Water emulsion in the GI tract, enhancing dissolution and absorption of] lipophilic drugs. These nano- or micro-emulsion offer uniform and fast drug release. Example: Cyclosporine A SMEDDS (Neoral) this commercial formulation enables hydration and absorption of the highly lipophilic drug, reducing inter- and intra- patient variability.

**e) Cyclodextrin Inclusion Complexes:** Cyclodextrins possess a hydrophobic central cavity capable of encasing hydrophobic drug molecules, while their outer surface remains hydrophilic- improving drug solubility and stability without altering chemical structure. Example: itraconazole – hydroxypropyl-ß -cyclodextrin (HP-ß -CD) complex (Onmel). This complex significantly enhancing aqueous solubility and dissolution of itraconazole, improving bioavailability.

**f) pH-modulated Formulations:** Incorporating pH – modifying excipients creates a local; micro – environment that favors dissolution of pH – sensitive drugs. This strategy ensure that the drug remains in its soluble form in the GI tract. Example Disatinib tablets with acidic excipients (e.g., citric acid). These excipients lower local pH, enhancing dasatinib`s solubility and dissolution in the stomach.

**g) Nanocrystals / Nanosuspensions:** Reducing drug particle size to the nanometer scale drastically increases surface area and saturation solubility, leading to accelerated dissolution and improved drug absorption. Example: Fenofibrate nanosuspension formulations (Tricor and Triglide™). These products eliminate the food effect seen demonstrating enhanced solubility and bioavailability.

**h) Polymer Micelles:** Amphiphilic polymers self- assemble into micelle in aqueous media, sequestering hydrophobic drugs in their cores. This configuration improves solubility and avoids the use of toxic solubilizers. Example: Paclitaxel- loaded polymeric micelles (Genxol-PM). These micelles improve solubility and eliminate the need for Cremophor EL, a surfactant associated with hypersensitivity reactions.

**i) Co- amorphous Systems:** Co-amorphous systems combine an API with a small conformer (such as an amino acid), forming a single amorphous phase that enhances solubility and physical stability by reducing molecular mobility and minimizing re-crystallization. Example: Indomethacin- arginine co-

amorphous mixture. This system exhibits significantly improved dissolution and enhanced long – term stability compared to the pure API in its crystalline form.

**j) Inclusion of Solubilizing Excipients:** Adding surfactants (e.g., Tween80), polyethylene glycols (PEGs), or poloxamers improve wettability, forms micelles, and promotes drug dissolution in aqueous media. Example: Griseofulvin with Tween 80. Inclusion of this surfactant enhances dissolution and absorption efficiency, aiding its therapeutic effectiveness.

**2.2 Permeability Enhancement Strategies**

The permeability enhancement strategies are as follows[14-17]

**a) Prodrugs:** Prodrugs are chemically modified derivatives of active drugs designed to enhance properties like lipophilicity or transport affinity to improve permeability across biological membranes. Once absorbed, enzymatic or chemical conversion regenerates the parent drug in vivo. Example: Valacyclovir, a prodrug of acyclovir, is modified with an L-valyl ester to utilize peptide transporters (PEPT1), resulting in significantly improved intestinal absorption and bioavailability compared to acyclovir alone.

**b) Absorption Enhancers:** Absorption enhancers, such as surfactants, bile salts, and fatty acids, transiently alter membrane fluidity of open tight junctions, enabling paracellular or transcellular transport of poorly permeable drugs. Their effect is typically. Example: Sodium caprate is widely used as an absorption enhancer to increase the permeability of macromolecules like peptides across intestinal epithelium.

**c) Nanocarriers:** Nanocarriers, including liposomes, solid-lipid nanoparticles (SLNs), and polymeric nanoparticles, encapsulate drugs to protect them from degradation for targeted delivery and controlled release. Example: Insulin-loaded liposomes improve intestinal uptake of insulin by protecting it from enzymatic degradation and enhancing permeability across the intestinal mucosa.

**d) Mucoadhesive System:** Mucoadhesive system utilize polymers that adhere to mucosa surfaces, prolonging the drug`s residence time in the gastrointestinal tract and with narrow absorption sites. Example: Chitosan-based mucoadhesive nanoparticle have been used to improve the intestinal permeability and absorption of peptide like calcitonin.

**e) Permeation-Enhancing Excipients:** Excipients such as cyclodextrins, thiolated polymers (thiomers), and surfactants facilitate drug permeation by enhancing drug solubility or modulating epithelial transport pathways. These agents often act synergistically with formulation techniques. Example: Hydroxypropyl- - cyclodextrin improves the permeability of itraconazole by enhancing its solubility and enabling better interaction with biological membranes.

**f) Cell-Penetrating peptide (CPPs):** CPPs are short, often positively charged peptides that can transport drugs, proteins, or nucleic acids across cell membranes without significant toxicity. They work by interacting with cell membrane components, facilitating internalization via endocytosis or direct penetration. Example: TAT peptide – conjugated nanoparticles have been developed for the delivery of anticancer agents, enhancing intracellular uptake and therapeutic efficacy.

**g) Enzyme Inhibitor Co-formulation:** Co-formulation drugs with enzyme inhibitors reduce presystemic metabolism in the gastrointestinal tract, allowing more of the drug to permeate intact into systemic circulation. This approach is particularly valuable for peptides and other labile molecules. Example: Ritonavir is co-formulated with lopinavir in antiretroviral therapy to inhibit CYP3A4-mediated metabolism, thereby improving lopinavir`s permeability and bioavailability.

**h) Efflux Pumo Modulators:** Many drugs are substrates for efflux transporters like p-glycoprotein (P-gp), which pump drugs back into the intestinal lumen, reducing absorption. Efflux pump modulators inhibit these transporters there by increasing intracellular drug retention Example: Quercetin has been studied as a P-gp inhibitor to enhance the permeability and oral bioavailability of drugs like paclitaxel.

**i) Lipid-Based Vehicles with surface ligand:** Surface-functionalized lipid-based carriers exploit receptor-mediated uptake pathways to enhance permeability and achieve targeted delivery. These systems combine the advantages of lipid-based solubilization with specific tissue targeting. Example: Folate-conjugated lipid nanoparticles have been used for targeted delivery of anticancer drugs to tumor cells overexpressing folate receptors, improving both permeability and therapeutic index.

**j) Permeability-Enhancing Prodrugs:** This strategy combines prodrug design with permeability enhancement by attaching chemical groups that not only improve transporter affinity but also evade efflux mechanisms. These prodrugs are converted back to the active parent compound once absorbed. Example: Valganciclovir, a prodrug of ganciclovir, is engineered to utilize PEPT1 transporters and bypass efflux, leading to markedly higher oral bioavailability compared to ganciclovir itself.

## 3. SOLUBILITY ENHANCEMENT TECHNIQUES

### 3.1 Solid Dispersions

The drug is dispersed in a hydrophilic polymer matrix, typically via hot -melt extrusion or spray drying, maintaining the API in a dispersed or amorphous state to enhance dissolution rate and apparent solubility[18-20].

**a) Nifedipine-PVP Solid Dispersion Improving Dissolution Rate:** Nifedipine, a poorly water-soluble calcium channel blocker, has shown significantly improved dissolution when formulated as a solid dispersion with polyvinylpyrrolidone (PVP). The hydrophilic nature of PVP enhances the wettability of the drug particles, reduces crystallinity, and stabilizes the amorphous form of nifedipine. This combination leads to a faster dissolution rate, which translates to improved bioavailability. Such dispersions are usually prepared using solvent evaporation or hot-melt methods, making them practical and scalable for industrial applications.

**b) Griseofulvin Dispersion in PEG 6000:** Griseofulvin, an antifungal drug with low aqueous solubility. Has been successfully incorporated into polyethylene glycol (PEG) 6000 dispersions to enhance solubility and dissolution. PEG 6000, being a hydrophilic carrier, improves the wettability and dispersibility of griseofulvin particles in the gastrointestinal tract. Additionally, the molecular interaction between PEG and griseofulvin reduces the drug`s crystallinity, enhancing its dissolution profile and ensuring a more rapid onset of therapeutic activity.

**c) Itraconazole Solid Dispersion via Hot-Melt Extrusion:** Itraconazole, a triazole antifungal agent with poor water solubility, benefits from hot-melt extrusion (HME) solid dispersion techniques using polymers such as PVP or HPMC. This method creates a stable amorphous solid dispersion where the drug is uniformly distributed within the polymer matrix. The amorphous form enhances dissolution and ensures consistent release in the gastrointestinal tract. Moreover, HME is a solvent-free, continuous process suitable for larger-scale production, making it highly advantageous for commercial formulations.

**d) Celecoxib Spray-Dried Dispersion with HPMC-AS:** Celecoxib, a selective COX-2 inhibitor with limited solubility, achieves improved dissolution when processed into a spray-dried solid dispersion with hydroxypropyl methylcellulose acetate succinate (HPMC-AS) The polymer acts as a stabilizer for the amorphous form of celecoxib and provides pH – dependent release, protecting the drug in acidic environments and releasing it in the intestine. This results in enhanced bioavailability and reduced variability in drug absorption, making this approach particularly suitable for oral dosage forms targeting improved therapeutic efficacy.

**e) Ritonavir -Copovidone Solid Dispersion:** Ritonavir, an antiretroviral drug with poor aqueous solubility, shows significant enhancement in solubility and bioavailability when formulated with copovidone (a copolymer of vinylpyrrolidone and vinyl acetate). The copovidone matrix stabilizer ritonavir in its amorphous form and increases drug wettability, enabling rapid dissolution. Additionally, this formulation overcomes polymorphic transitions of ritonavir that often reduce its solubility, ensuring consistent drug release and therapeutic activity. This technique has been successfully used in marketed formulations, demonstrating its practical utility.

### 3.2 Amorphous Formulations

Preparing the drug in a non-crystalline amorphous state increases its free energy and solubility relative to the crystalline form, often stabilized by polymers or surfactants[21-23].

**a) Amorphous Indomethacin with PVP:** Indomethacin, a poorly water-soluble nonsteroidal anti-inflammatory drug (NSAID), shows enhanced dissolution when formulated as an amorphous solid dispersion with polyvinylpyrrolidone (PVP). PVP stabilizes the amorphous form by inhibiting recrystallization and improving wettability. This results in faster dissolution and enhanced bioavailability, making the formulation suitable for improved therapeutic effectiveness in pain and inflammation management.

**b) Amorphous Ezetimibe with HPMCAS:** Ezetimibe, a cholesterol absorption inhibitor with low solubility, exhibits significant improvement in dissolution when combined with Hydroxypropyl Methylcellulose Acetate succinate (HPMCAS). HPMCAS acts as a stabilizing polymer, preventing crystallization and improving supersaturation during gastrointestinal transit. This amorphous system enhancement drug absorption and ensures consistent plasma levels, providing better lipid-lowering efficacy.

**c) Rivaroxaban Amorphous Formulation using Soluplus:** Rivaroxaban, an anticoagulant with limited aqueous solubility, demonstrates improved dissolution and bioavailability in amorphous formulations prepared with Soluplus. Soluplus. An amphiphilic polymer, enhances solubilization, maintains drug supersaturation, and offers physical stability against crystallization. This approach results in improved therapeutic outcomes in thromboembolic disorder treatments.

**d) Ketoconazole Amorphous Solid Dispersion:** Ketoconazole, a broad-spectrum antifungal drug with poor solubility, benefits from amorphous solid dispersion technique using suitable polymers such as PVP or HPMC. The amorphous state increases surface area and wettability, promoting rapid dissolution and enhanced oral absorption. This improves its bioavailability ensures more effective systemic antifungal therapy.

**e) Amorphous Lacidipine with Lipids/polymers:** Lacidipine, a calcium channel blocker used for hypertension, shows significant dissolution enhancement when converted into an amorphous system with lipids or hydrophilic polymers. Lipid-based carriers or polymers prevent recrystallization and improve solubility through better dispersion and micellar solubilization. This leads to higher absorption and improved therapeutic performance for blood pressure control.

**3.3 Co-crystals**

API molecules form a crystalline complex with suitable through non-covalent interactions, improving solubility without chemical modification[24-26].

**a) Carbamazepine-Nicotinamide Co-crystals:** Carbamazepine, an antiepileptic drug, suffers from low aqueous solubility, which limits its bioavailability. The formation of a co-crystal with nicotinamide significantly enhances its solubility and dissolution profile. Nicotinamide acts as a co-former that interacts via hydrogen bonding with carbamazepine, stabilizing the crystalline lattice while improving wettability. This system result in better drug adsorption and potentially more consistent therapeutic effects.

**b) Theophylline-Succinic Acid Co-crystal:** Theophylline, a bronchodilator, forms a stable co-crystal with succinic acid, enhancing its physicochemical properties. This co-crystal improves solubility and dissolution rate due to the presence of the hydrophilic succinic acid moiety. It also helps reduce the hygroscopic nature of theophylline, thereby improving its stability storage. These advantages make this co-crystal promising for developing more efficient oral formulations.

**c) Lopinavir-Maleic Acid Co-crystal:** Lopinavir, a poorly soluble antiretroviral drug, benefits from co-crystallization with maleic acid. This interaction improves its aqueous solubility and dissolution profile, leading to enhanced bioavailability. The co-crystal structure and modifies the drug`s crystal lattice and reduces lattice energy, making it easier to dissolve. This strategy valuable in fixed-dose combination therapies for HIV treatment where bioavailability is critical.

**d) Furosemide-Pyridine-2,5-Dicarboxylic Acid Co-crystal:** Furosemide, a loop diuretic, exhibits poor solubility and variable bioavailability. Co-crystallization with pyridine-2,5-dicarboxylic acid result in a stable solid form with markedly improved dissolution characteristics. The hydrogen bonding between the functional groups of furosemides and the co-former enhancing wettability and drug release, offering better therapeutic consistency in clinical use.

**e) Acetaminophen-Isonicotinamide Co-crystal:** Acetaminophen (paracetamol), a widely used analgesic and antipyretic, forms a co-crystal with isonocotinamide to improve its mechanical and dissolution properties. The co-crystal enhances tablet ability, reducing issues like capping or lamination during compression.

Additionally, the modified crystal structure promotes faster dissolution, which can lead to quicker onset of therapeutic action. This makes it suitable for developing more efficient and robust dosage forms.

**3.4 Lipid-Based Systems (SMEDDS/SNEDDS)**

Self -emulsifying drug delivery systems (SMEDDS or SNEDDS) from fine oil-in-water emulsion upon contact with GI fluids, thus solubilizing lipophilic drugs and improving absorption[27-29].

**a) Cyclosporine SMEDDS (e.g., Neoral):** cyclosporine is a poorly water-soluble immunosuppressant, and its bioavailability was significantly enhanced through the development of a self-micro emulsifying drug delivery system (SMEDDS), marketed as Neoral. This formulation uses a mixture of oils, surfactants, and co-solvents to spontaneously form microemulsion in the gastrointestinal tract. The improved solubilization and absorption resulted in plasma concentration, enhanced bioavailability, and reduced variability compared to earlier formulations like Sandimmune.

**b) Fenofibrate SNEEDS formulation:** Fenofibrate, a BCS Class II drug with low aqueous solubility, has been successfully formulation into a self – nanoemulsifying drug delivery system (SNEDDS) to enhance oral absorption. The system uses lipids, surfactants, and co-solvents that produce nano-sized droplets upon contact with gastrointestinal fluids, improving drug dissolution and intestinal absorption. This approach leads to improved therapeutic efficacy and consistent pharmacokinetics.

**c) Efavirenz-loaded SMEDDS:** Efavirenz, an antiretroviral drug with poor aqueous solubility, benefits from SMEDDS technology to enhance its bioavailability. The formulation incorporates a suitable oil phase, surfactant, and co-surfactant to create a fine microemulsion in the GI tract. This leads to improved solubilization, reduced food effect, and enhanced drug absorption, making it a promising strategy for consistent therapeutic plasma levels in HIV treatment.

**d)Ritonavir SNEDDS with improved bioavailability:** Ritonavir, a poorly soluble antiretroviral drug, has been formulated into SNEDDS to overcome solubility and bioavailability limitations. The nano emulsion formed upon dispersion in gastrointestinal fluids enhances surface area and dissolution, promoting higher absorption rates. This approach not only improves systemic exposure but also reduces inter-patient variability and enhances therapeutic performance.

**e) Curcumin SMEDDS to enhance oral absorption:** Curcumin, a natural compound with potent anti-inflammatory and anticancer properties, suffer from poor aqueous solubility and bioavailability. A SMEDDS formulation enables curcumin to form fine microemulsions in gastrointestinal fluids, improving solubilization and lymphatic uptake. This results in significantly higher oral absorption, improved systemic bioavailability, and enhanced pharmacological activity compared to conventional formulations.

**3.5 Cyclodexrtin Inclusion Complexes**

Cyclodextrins (e.g., ß -cyclodextrin) encapsulate the lipophilic portion of API molecules within their hydrophobic cavity, enhancing aqueous solubility and stability[30-32].

**a) Itraconazole-ß - cyclodextrin complex:** Itraconazole, a poorly water-soluble antifungal drug, forms an inclusion complex with – cyclodextrin to significantly improve its aqueous solubility and dissolution rate. This complexation enhances bioavailability and ensures more consistent therapeutic levels. It is particularly useful in oral formulation to increase absorption and reduce variability in systemic availability.

**b) Ketoconazole-HP-ß-cyclodextrin inclusion:** Ketoconazole, another poorly soluble antifungal, benefits from inclusion with hydroxypropyl-ß-cyclodextrin (HO-ß-CD). This derivative offers better water solubility compared to plain ß-CD, forming a stable complex that improves drug dissolution and absorption. It also minimizes gastric irritation, making it more suitable for oral dosing.

**c) Fenoprofen -ß-cyclodextrin complex:** Fenoprofen, a nonsteroidal anti – inflammatory drug (NSAID), forms a host -guest complex with ß-cyclodextrin that improves its solubility and dissolution rate. This leads to faster onset of analgesic and anti-inflammatory action and can reduce gastrointestinal irritation associated with unmodified Fenoprofen, enhancing patient tolerability.

**d) Praziquantel with sulfobutyl ether -ß-cyclodextrin:** Praziquantel, used to treat parasitic infections, has limited water solubility. Complexing it with sulfobutyl ether-ß-cyclodextrin (SBE-ß-CD) significantly improves its solubility and oral bioavailability. This inclusion allows for better absorption in the gastrointestinal tract, potentially enabling dose reduction while maintaining therapeutic efficacy.

**e) Naproxen- cyclodextrin complex:** Naproxen, another NSAID with low water solubility, forms a stable complex with cyclodextrins to enhance its dissolution and onset of action. This complexation can also help minimize gastrointestinal side effects and improve patient compliance, especially in fast-dissolving oral formulations.

**Table 1: Solubility enhance formulations**

| S. No. | Marketed Formulation | Drug Name | Purpose of Enhancement | Formulation Type |
|---|---|---|---|---|
| 1 | Sporanox ® | Itraconazole | Improve aqueous solubility | Cyclodextrin – based dispersion |
| 2 | Rapamune ® | Sirolimus | Enhance dissolution and absorption | Nanocrystal formulation |
| 3 | Tricor ® | Fenofibrate | Improve solubility and bioavailability | Nanocrystal/ nanosuspension |

| | | | | |
|---|---|---|---|---|
| 4 | Emend ® | Aprepitant | Accelerate dissolution rate | Nanocrystal Formulation |
| 5 | Fortovase ® | Saquinavir | Boost dissolution and absorption | SMEDDS (liquid) |
| 6 | Norvir ® | Ritonavir | Enhance solubility and bioavailability | SMEDDS (liquid) |
| 7 | Sandimmune ® Neoral ® | Cyclosporine A | Improve solubility and absorption | SMEDDS (liquid) |
| 8 | Cabenuva ® | Cabotegravir + Rilpivirine | Enhance solubility in extended- release Suspension | Injectable nanosuspension |

## 4. PERMEABILITY ENHANCEMENT TECHNIQUES

### 4.1 Prodrugs

APIs are chemically modified to more lipophilic or transporter-recognized forms; they are metabolized in vivo back to the active parent compound, improving absorption[33-35].

**a) Enalapril (prodrug of enalaprilat):** Enalapril is an orally active prodrug that is converted in the liver to its active form, enalaprilat, by hepatic esterases. Enalaprilat is an angiotensin-converting enzyme (ACE) inhibitor that effectively lowers blood pressure and is used for the treatment of hypertension, heart failure, and left ventricular dysfunction. The prodrug form, enalapril, has improved oral bioavailability compared to enalaprilat, which is poorly absorbed in the gastrointestinal tract. This modification allows for convenient oral administration and consistent therapeutic effects.

**b) Lisdexamfetamine (psycho-stimulant prodrug of dextroamphetamine):** Lisdexamfetamine is a prodrug of dextroamphetamine, primarily used for the treatment of attention-deficit/hyperactivity disorder (ADHD) and binge eating disorder. It is pharmacologically inactive until enzymatically hydrolyzed in the blood to release active dextroamphetamine. This design provides controlled release of the active drug, reducing the potential for abuse and improving the duration of action. It also minimizes the rapid spikes in drug concentration associated with immediate-release stimulants, thereby improving safety and compliance.

**c) Valacyclovir (prodrug of acyclovir):** Valacyclovir is the L-valyl ester prodrug of acyclovir, an antiviral drug used in the treatment of herpes simplex virus (HSV) and varicella – zoster virus (VZV) infections. The prodrug form significantly enhances oral bioavailability (approximately 3-5 times higher) compared to acyclovir. After administration, valacyclovir is rapidly converted by first-pass intestinal and hepatic metabolism into acyclovir and L-valine. This conversion results in higher systemic levels of the active drug, allowing foe reduced dosing frequency and better patient adherence.

**d) Oseltamir (prodrug):** Oseltamivir is an ethyl ester prodrug that is converted in the liver esterases into its active metabolite, oseltamivir carboxylate. It is widely known under the brand name Tamiflu and is used for the treatment and prophylaxis of influenza A and B infections. The prodrug design improves oral absorption, while the active metabolite inhibits neuraminidase enzymes, preventing the release of viral particles and limiting the spread of the virus in the body.

**e) Prednisolone palmitate:** Prednisolone palmitate is a lipophilic prodrug of prednisolone used in sustained anti-inflammatory and immunosuppressive therapy. The palmitate ester modified enhances lipid solubility, enabling formulations for long-acting injections or suspensions. Once administered, esterases hydrolyze prednisolone palmitate to release active prednisolone, providing prolonged therapeutic effects useful in managing chronic conditions such as asthma, autoimmune disorders, and certain types of inflammatory diseases.

### 4.2 Absorption Enhancers (Surfactants, Bile Salts)

Excipients additive (e.g., medium -chain fatty acids, bile salts, polysorbate 80) modulate membrane fluidity or open tight junctions temporarily to boost absorption[36-38].

**a) Sodium Caprate Enhancing Peptide Absorption:** Sodium caprate, a medium chain fatty acid derivative, is widely used as a permeation enhancer for peptide and protein drugs. It primarily works by opening tight junctions in the intestinal epithelium, thereby improving the paracellular transport of hydrophilic macromolecules. Additionally, sodium caprate can increase membrane fluidity, facilitating

better transcellular drug uptake. This property makes it particularly valuable in oral peptide formulations, where the intestinal barrier typically limits bioavailability.

**b) Labrasol in Formulations to Improve Peptide Uptake:** Labrasol, a non-ionic surfactant composed mainly of caprylocaproyl macrogol-8 glycerides, serves as a bioavailability enhancer for peptide -based drugs. It enhances absorption by increasing membrane permeability and facilitating the solubilization of lipophilic compounds. Labrasol also promotes lymphatic transport and may inhibit efflux transporters, thereby improving systemic exposure. Its biocompatibility and proven safety profile make it a preferred excipient in lipid-based formulations for oral and mucosal peptide delivery systems.

**c) Bile Salts (Sodium Deoxycholate) Enhancing Peptide Permeation:** Sodium deoxycholate, a bile salt, plays a significant role in enhancing the intestinal permeation of peptide and protein drugs. It disrupts the integrity of the epithelial cell membrane and loosens tight junctions, promoting both paracellular and transcellular transport. Additionally, bile salts aid in solubilizing hydrophobic molecules and improving drug stability in gastrointestinal fluids. Their natural occurrence and surfactant properties make them highly effective in boosting the absorption of poorly permeable therapeutic peptides.

**d) Tween 80 to Facilitate Drug Transport:** Tween 80 (Polysorbate 80) is a non-ionic surfactant commonly used to enhance the absorption and transport of both small-molecule drugs and biologics like peptides. It acts by increasing membrane fluidity, reducing surface tension, and inhibiting efflux pumps such as P-glycoprotein, thereby improving drug permeation across biological barriers. Tween 80 is frequently employed in oral, injectable, and nanoparticulate formulations to improve the bioavailability and therapeutic efficacy of challenging drug molecules.

**e) Sodium Lauryl Surfacte Increasing Paracellular Uptake:** Sodium lauryl sulfate (SLS), an anionic surfactant, is used in low concentrations to enhance the paracellular transport of peptide drugs. It works by transiently opening tight junctions and increasing membrane fluidity, enabling larger molecules to pass through the intestinal epithelium more efficiently. Moreover, SLS can improve drug solubility and dissolution, which further contributes to enhanced absorption. However, its concentration must be carefully optimized to avoid irritation or mucosal damage while maintaining its permeation – enhancing benefits.

**4.3 Nanocarriers (Liposomes, SLNs, Polymeric NPs)**

Encapsulation of APIs into nano-sized carriers that protect against degradation and exploit cellular uptake pathways such as endocytosis to improve permeability[39-41].

**a) Doxorubicin Liposomes (e.g., Doxil):** Doxil is a liposomal prolongs its circulation time, enhances tumor targeting through the enhanced permeability and retention (EPR) effect, and minimizes cardiotoxicity commonly with conventional doxorubicin. The PEGylation of the liposome surface further increases stability and avoids rapid clearance by the reticuloendothelial system, allowing for controlled and sustained drug release at the tumor site.

**b) Insulin -Loaded Solid Lipid Nanoparticles (SLNs):** Insulin-loaded SLNs are advanced carriers developed to enhance oral or pulmonary delivery of insulin. These nanoparticles protect insulin from enzymatic degradation in the gastrointestinal tract, improve absorption across biological membrane, and provide a sustained release profile. The lipid matrix in SLNs allows improved stability and biocompatibility while enhancing patient compliance by reducing the frequency of administration compared to conventional insulin therapy.

**c) Paclitaxel-Loaded Polymeric Nanoparticles (PLGA):** Poly (lactic-co-glycolic acid) (PLGA) nanoparticles are widely used for delivering poorly soluble drugs like paclitaxel. The encapsulation of paclitaxel in PLGA nanoparticles improves its solubility, stability, and controlled release, resulting in enhanced therapeutic efficacy against various cancers. These nanoparticles also reduce systemic toxicity and improve bioavailability while enabling passive tumor targeting through the EPR effect, making them a promising approach for safer and more efficient chemotherapy.

**d) Amphotericin B Liposomes (Ambisome):** Ambisome is a liposomal formulation of amphotericin B, primarily used for the treatment of systemic fungal infections and leishmaniasis. The liposomal encapsulation reduces the drug's nephrotoxicity and other systemic side effects while maintaining potent antifungal activity. But targeting infected tissues and ensuring controlled drug release, AmBisome improves patient safety and therapeutic outcomes compared to conventional amphotericin B formulations.

**e) Crcumin-Loaded Nanoliposomes for Enhanced Uptake:** Curcumin-loaded nanoliposomes are developed to overcome the poor solubility and low bioavailability of curcumin. Encapsulated in nanoliposomes enhances its stability, absorption, and cellular uptake, allowing for improved therapeutic efficacy in managing inflammatory disorders, cancer, and neurodegenerative diseases. |These nanocarriers also protect curcumin from rapid metabolism and degradation, facilitating sustained release and targeted delivery to specific tissues.

**4.4 Mucoadhesive Systems**

Polymers such as chitosan or Carbopol that adhere to mucosal surfaces, increasing residence time and creating a concentration gradient that enhances absorption[42-44].

**a) Chitosan-Coated Nanoparticles for Nasal Delivery:** Chitosan-coated nanoparticles are widely explored foe nasal delivery of peptides, proteins, and small molecules due to their mucoadhesive and permeation-enhancing properties. Chitosan interacts with negatively charged mucins in the nasal mucosa, prolonging residence time and improving drug absorption. Additionally, chitosan transiently opens tight junctions, enabling enhanced paracellular transport. This system is particularly useful for drugs that require rapid systemic absorption or direct nose-to-brain delivery, such as peptides, neurotherapeutics, or vaccines.

**b) Carbopol Mucoadhesive Gel for Buccal Delivery:** Carbopol-based mucoadhesive gels are used in buccal delivery to achieve prolonged retention and localized adheres to mucosal surface and hydrates upon application, forming a gel matrix that allows sustained release of the drug. This formulation is especially beneficial for drugs with poor oral bioavailability, such as peptides or drugs that undergo extensive first-pass metabolism, thereby improving therapeutic efficacy.

**c) HPMC-Based Mucoadhesive Buccal Patch:** Hydroxypropyl methylcellulose (HPMC)-based buccal patches and designed for controlled drug release and strong mucosal adhesion. HPMC swells upon hydration, forming a thin, flexible film that adheres to the buccal mucosa, ensuring prolonged contact tine and improved absorption. These patches are particularly useful for drug requiring consistent plasma levels or localized treatment, offering advantages like reduced dosing frequency and patient compliance.

**d) Thiolated Chitosan Nanoparticles for enhanced uptake:** Thiolated Chitosan nanoparticles are an advanced version of chitosan systems, incorporating thiol groups that improve mucoadshesion and permeation. The thiol groups form disulfide bonds with cysteine- rich domains of mucin, significantly increasing the residence time and drug uptake. These nanoparticles also enhance paracellular transport by opening tight junctions more effectively. They are especially promising for the delivery of poorly permeable biomolecules like peptides, proteins, and oligonucleotides.

**e) Mucoadhesive in situ nasal gel with poloxamers: poloxamers**-based in situ nasal gels combine temperature-sensitive gelling and mucoadhesion for efficient drug delivery. The formulations remain liquid at room temperature for easy administration and undergo gelation upon contact with nasal mucosa due to body temperature. The mucoadhesive properties help prolong nasal residence time, while the gel matrix provides controlled drug release. This approach is highly effective for drugs requiring rapid onset, brain targeting, or improve bioavailability, such as peptides, antiviral, and CNS agents.

**4.5 Efflux Pump Modulators**

Co-formulation with inhibitors of efflux transporters (e.g., P-glycoprotein, BCRP) to reduce drug extrusion from epithelial cell and boost net absorption[45-47].

**a) Verapamil (P-gp inhibitor) co-formulated with digoxin:** Verapamil, a well know p-glycoprotein (P-gp) inhibitor, is often co-formulated with digoxin to enhance the drug`s oral bioavailability. Digoxin, a cardiac glycoside, is a P-gp substrate, and its absorption is significantly limited by efflux mechanisms in the intestine. The inclusion of verapamil inhibits P-gp activity, reducing the efflux of digoxin back into the intestinal lumen, thereby improving systemic absorption and therapeutic efficacy. This strategy ensures more consistent plasma levels, enhancing the drug`s effectiveness in managing condition like heart failure and atrial fibrillation.

**b) Cyclosporin A inhibiting P-gp uptake of Paclitaxel:** Cyclosporine A acts as both an immunosuppressant and a potent P-gp inhibitor, making it valuable in combination with chemotherapeutic agent like paclitaxel. Paclitaxel is a P-gp substrate, and its therapeutic levels are often reduced due to active efflux from tumor cells. By co-administering cyclosporine A, the efflux mechanism is inhibited, allowing higher intracellular concentrations of paclitaxel. This leads to improved cytotoxicity against cancer cell and enhanced treatment outcomes, particularly in drug-resistant tumors.

**c) Elacridar co-delivered with anticancer drugs:** Elacridar (also known as GF120918) is a dual inhibitor of P-gp and breast cancer resistance protein (BCRP), making it an effective agent for overcoming for overcoming multidrug resistance. When co-delivered with anticancer drugs such as doxorubicin, paclitaxel, or topotecan, elacridar inhibits the efflux transporters that limit drug accumulation in cancer cells. This results in higher intracellular drug levels, improved tumor cytotoxicity, and better therapeutic response, especially in resistant cancer phenotypes.

**d) Quercetin to inhibit BCRP-mediate efflux:** Quercetin, a naturally occurring flavonoid, exhibits potent inhibitory activity against the breast cancer resistance protein (BCRP) efflux transporter. By inhibiting BCRP substrates, improving a valuable adjunct in formulations or combination therapies, particularly for improving the performance of chemotherapeutic and targeted drugs affected by BCRP-mediated efflux.

**e) Inhibiting P-gp in formulation:** TPGS is a derivative of vitamin E that functions as a non-ionic surfactant and a potent P-gp inhibitor. It is widely incorporated into drug delivery formulations, such as nanoparticles, solid dispersions, and micelles, to enhance the absorption of P-gp substrate drugs. By inhibiting P-gp medicated efflux, TPGS improves drug permeability and bioavailability, making it higher useful in oral and parenteral formulations of poorly soluble of P-gp-substrate drugs. Additionally, its surfactant properties aid in drug solubilization, contributing to enhanced overall therapeutic performance.

**Table 2: Permeability enhanced marketed formulations**

| S.No. | Marketed Formulation | Drug Name | Purpose of Enhancement | Formulation Type |
|---|---|---|---|---|
| 1 | Doxil® (Caelyx in EU) | Doxorubicin | Targeted delivery; Reduced Cardiotoxicity | PEGylated Liposomal formulation |
| 2 | AmBisome® | Amphotericin B | Lower toxicity; Improved tissue Penetration | Liposomal Formulation |
| 3 | DaunoXome® | Daunorubicin | Targeted delivery to tumors | Liposomal Formulation |
| 4 | Onivyde® | Irinotecan | Tumor uptake; Reduced side effects | Liposomal Formulation |
| 5 | Marqibo® | Vincristine Liposomal | Enhanced tumor delivery | Liposomal formulation |
| 6 | Myocet® | Doxorubicin | Lower cardiotoxicity | Liposomal formulation |
| 7 | Visudyne® | Verteporfin | Localized retinal delivery | Liposomal formulation |
| 8 | DepoDur® | Morphine | Sustained release | Liposomal depot formulation |
| 9 | Depocyt® | Cytarabine | Sustained intrathecal release | Liposomal formulation |
| 10 | Exparel® | Bupivacaine | Extended anesthetic release | Liposomal formulation |

**Table 3: Solubility and permeability enhanced marketed formulations**

| S. No. | Marketed Formulation | Drug Name | Purpose of Enhancement | Formulation Type |
|---|---|---|---|---|
| 1 | Neoral® | Cyclosporine A | Enhance solubility and oral absorption | SMEDDS (liquid) |
| 2 | Norvir® | Ritonavir | Improve solubility and bioavailability | SMEDDS (liquid) |

| | | | | |
|---|---|---|---|---|
| 3 | Ambisome ® | Amphotericin B | Improve solubility (IV) and tissue penetration | Liposomal formulation |
| 4 | Tricor® | Fenofibrate | Solubility and reduced food effect solubility and | Nanocrystal / nanosuspension |
| 5 | Rapamune ® | Sirolimus | Enhanced systemic exposure | Nanocrystal formulation |
| 6 | Emend ® | Aprepitant | Solubility and consistent absorption | Nanocrystal formulation |
| 7 | Cabenuva ® | Cabotegravir +Rilpivirine | Solubility in injectable form; controlled release | Injectable nanosuspension |
| 8 | Fortovase ® | Saquinavir | Solubility and bioavailability enhancement | SMEDDS (liquid) |
| 9 | Sandimmune ® Neoral ® | Cyclosporine A | Solubility + absorption improvement | SMEDDS (liquid) |
| 10 | Others (e.g., Telmisartan SMEDDS) | Telmisartan | Solubility +absorption enhancement | SMEDDS / SNEDDS |

## 5. CONCLUSION

This review, Breaking Barriers: Next-Generation Strategies for Enhancing Solubility and Permeability of poorly Bioavailable Drugs," explores the diverse landscape of formulation science, highlighting a robust array of tools to overcome bioavailability challenges. By examining ten advanced solubility-enhancement approaches and ten permeability-boosting tactics, each illustrated with practical examples, we emphasize that the next generation of drug delivery relies on integrated systems rather than isolated techniques. Hybrid technologies, such as nanocarriers the improve both dissolution and epithelial penetration, or prodrugs that optimize physicochemical and transporter-mediated uptake, exemplify this evolution. Moving forward, interdisciplinary convergence combining computational modeling, higher-throughput screening, smart excipients, and advanced carriers will be crucial. This synthesis advocates for holistic strategies that leverage synergistic enhancements in both solubility and permeability to accelerate the development of poorly bioavailable drugs into safe and effective therapeutics.

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