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Surface Activation Strategies to Enhance Oral Bioavailability of Poorly Biopharmaceutical Drugs: A Narrative Review

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ABSTRACT

Surface activation has emerged as a promising strategy for improving the oral performance of drugs with poor biopharmaceutical properties. Many oral drugs face limitations in solubility, permeability, and stability in the gastrointestinal environment, which restrict their absorption and reduce therapeutic effectiveness. This review aims to summarize current approaches used to enhance oral bioavailability through surface modification of drug particles and delivery systems. A narrative methodology was used to examine studies involving conventional additives as well as advanced nanotechnology platforms. The findings show that surfactants, polymers, lipid-based excipients, and permeation enhancers can significantly increase solubility, dissolution rate, and epithelial transport. Nanotechnology approaches, including polymeric nanoparticles, nanocrystals, lipid nanocarriers, and stimuli-responsive systems, offer more precise control over particle behavior and demonstrate consistent improvements in permeability and gastrointestinal stability. Despite these advantages, challenges related to safety, long-term toxicity, and regulatory evaluation remain. Overall, the reviewed evidence indicates that surface activation represents an effective and adaptable approach for enhancing oral bioavailability and holds strong potential for future development of more efficient oral drug delivery systems.

Keywords: *surface activation, oral bioavailability, nanotechnology, solubility enhancement, permeability improvement.*

INTRODUCTION

Oral drug administration remains the most favored and practical approach for delivering medications, offering exceptional stability, minimal volume, accurate dosing, and straightforward manufacturing processes (Irwanto, 2025). In this method, drugs first dissolve in gastric or intestinal fluids before crossing the gastrointestinal membrane to reach systemic circulation. However, compounds with poor water solubility typically show restricted absorption linked to slow dissolution rates, while those with low membrane permeability face limitations in permeation speed. Despite its advantages in patient adherence and economic efficiency, oral delivery encounters significant challenges, particularly low bioavailability influenced by factors such as solubility, permeability, dissolution rate, and first-pass metabolism (Husni, 2017).

The Biopharmaceutics Classification System categorizes drugs into four classes based on these properties: class I with high solubility and permeability, class II with low solubility but high permeability, class III with high solubility but low permeability, and class IV with both low solubility and permeability. For class II drugs, bioavailability can be improved by boosting solubility and dissolution in gastrointestinal fluids, as their primary barriers involve drug release from formulations and solubilization in stomach fluids.

Biopharmaceutics serves as a core discipline in pharmacy, connecting a drug's physicochemical attributes in its formulation to observed pharmacological, toxicological, or clinical responses (Sopian et al., 2024). It examines how bioavailability relates to physical and chemical characteristics, determining the speed and extent of active ingredients entering systemic circulation to achieve optimal clinical results. Absorption depends on

physiological and physicochemical factors at the site, which biopharmaceutics aims to control through tailored pharmaceutical products (Salman et al., 2024).

Surface activation defined as modifying particle surface properties to enhance solubility and bioavailability, employs techniques like particle size reduction, crystallization, salt formation, solid dispersions, nanosuspensions, and cryogenic methods (Husni, 2017). This strategy plays a vital role in developing efficient oral drug delivery systems by improving interactions with biological environments, such as digestive fluids, to accelerate absorption into the bloodstream (Spleis et al., 2023). Modern biopharmaceutical approaches utilize surface activation (surface modification) as an engineering method in drug delivery systems. Surface modification aims to enhance the interaction between the drug carrier and the biological environment through changes in electrical charge, addition of functional groups, or coating with hydrophilic polymers such as polyethylene glycol (PEG).

Surface activation has emerged as a transformative technological advancement capable of reshaping oral drug formulation, particularly for compounds with inherently poor biopharmaceutical characteristics. By strategically modifying the physicochemical properties at the particle or carrier interface, this approach directly addresses key limitations in oral bioavailability such as inadequate solubility, limited permeability, and susceptibility to degradation while simultaneously supporting improved therapeutic performance and a more favorable safety profile. Accordingly, this review examines surface activation as a cutting-edge strategy for optimizing the bioavailability of orally administered drugs.

METHODS

This article was developed through a narrative literature review, involving the collection, selection, and analysis of pertinent scientific publications addressing surface activation and modification strategies to enhance the oral bioavailability of pharmaceutical compounds. A comprehensive literature search was conducted using prominent scientific databases, including PubMed, ScienceDirect, MDPI, and Google Scholar, encompassing publications from the period of 2015–2025. The search strategy incorporated various combinations of keywords, such as "surface activation," "surface modification," "oral drug delivery," and "biopharmaceutical performance."

DISCUSSION

Poor oral bioavailability presents a critical limitation for many orally administered drugs, particularly those classified as BCS Class II and IV. These drugs often exhibit low aqueous solubility, slow dissolution kinetics, and limited permeability across the gastrointestinal epithelium. Formulation studies indicate that compounds such as atorvastatin calcium, ravuconazole, baicalein, irbesartan, simvastatin, and zaleplon are primarily dissolution-limited, necessitating formulation-based interventions to enhance absorption (Ghanem et al., 2025; Liu et al., 2022; Spósito et al., 2017; Yin et al., 2017).

In addition to inherent solubility limitations, oral drug absorption is often impeded by instability within the gastrointestinal tract. Factors such as pH-dependent precipitation, enzymatic degradation, and chemical instability diminish the fraction of drug available for absorption, particularly for weakly soluble or chemically labile compounds. These challenges are further amplified in macromolecular therapeutics, such as insulin and exenatide, which exhibit both limited epithelial permeability and poor stability within the mucosal environment (Barbari et al., 2017; Schmidt et al., 2025a).

Systemic drug uptake is limited by physicochemical properties and biological barriers, including mucus entrapment, efflux transporter activity, and restricted paracellular transport. These combined barriers suggest that poor oral bioavailability is rarely attributable to a single factor but rather to the complex interplay between dissolution behavior, interfacial interactions, and epithelial transport limitations. This multifactorial nature strongly supports the development of surface activation strategies to simultaneously enhance drug dissolution, stabilize drug particles, and improve epithelial transport efficiency. Mechanistically, surface activation primarily enhances oral bioavailability by modulating drug–interface interactions, rather than altering intrinsic drug chemistry, thereby improving dissolution, prolonging mucosal contact, and facilitating epithelial transport.

Surface-Active Additives and Their Role in Enhancing Oral Biopharmaceutical Performance

Surface activation strategies rely on the selection of appropriate additives that can modify interfacial properties at both the particle and epithelial levels. Surfactant-based systems consistently demonstrate marked improvements in oral performance by reducing interfacial tension, enhancing wettability, and facilitating the formation of finely dispersed drug domains. Self-emulsifying and nanoemulsion-based systems developed for drugs such as ravuconazole, ciprofloxacin, zaleplon, and lovastatin exemplify how surfactants, including Labrasol, lavender oil components, and hyaluronic acid coatings, promote improved dispersion, increased apparent solubility, and enhanced mucus permeation (Ali et al., 2022; Beg et al., 2015; Spósito et al., 2017). The incorporation of co-surfactants and lipid carriers further stabilizes these systems and expands their solubilization

capacity, particularly for dissolution-limited compounds. These systems are particularly effective for BCS Class II drugs, where dissolution is the primary rate-limiting step, but may offer limited benefit for macromolecules unless combined with additional permeation-enhancing or mucoadhesive components.

Surfactants primarily address solubility and dispersion limitations; however, permeation enhancers are critical for overcoming epithelial transport barriers. For example, L-tryptophan significantly enhances the intestinal absorption of insulin and other peptide drugs by modulating mucosal structure without compromising membrane integrity or inducing cytotoxicity (Kamei et al., 2018). This mechanism highlights that surface activation can extend beyond particulate modification to include reversible alterations in epithelial permeability, which is particularly relevant for macromolecules with inherently poor transcellular transport.

Polymer-based surface modification improves oral drug performance by increasing residence time at the absorption site. Cationic polymers, such as chitosan and its derivatives, interact electrostatically with the negatively charged mucosal surface, enhancing mucoadhesion, improving gastrointestinal stability, and prolonging epithelial contact. For example, chitosan-coated solid lipid nanoparticles and PLGA nanoparticles exhibit improved adhesion and sustained drug release, leading to enhanced therapeutic effectiveness (Öztürk et al., 2019; Parvez et al., 2020). Similarly, hydrophilic and thiolated polymers, such as Carbopol, HPMC, and thiolated xanthan gum, improve wettability and structural stability, as demonstrated by simvastatin thiolated nanocrystals, which exhibit extended release and improved mucoadhesive behavior (Bakhaidar et al., 2022). However, excessive surface modification or high polymer density may hinder drug diffusion and should therefore be carefully optimized to balance mucoadhesion and drug release.

At the molecular level, surface activation can also be achieved through complexation. Cyclodextrin-based systems, particularly those combining hydroxypropyl-β-cyclodextrin with L-arginine, significantly enhance drug solubility and promote amorphization, resulting in markedly improved dissolution performance for aripiprazole (Awais et al., 2023). Concurrently, lipid-based excipients such as phosphatidylcholine, cholesterol, and bile salts, when incorporated into bilosomal systems, provide enhanced interfacial stability and facilitate intestinal uptake. The improved bioavailability observed in irbesartan-loaded nano-bilosomes underscores the importance of lipid-mediated surface activation in protecting drugs from gastrointestinal degradation while promoting epithelial transport (Ghanem et al., 2025). These observations highlight that effective surface activation necessitates a formulation-specific approach, wherein excipient selection is guided by the dominant biopharmaceutical limitation of each drug.

Table 1. Representative Studies on Surface-Active Additives and Their Biopharmaceutical Outcomes Across BCS Classes

Active Compound	BCS	Materials	Test subject	Study Outcome	References
Miconazole base	BCS Class II	Oleic acid, tween 20, PEG 400, water, and other excipients used in characterization	In-vitro	The developed miconazole microemulsion has been proven to be stable, nano-sized, and have good surface adhesion. The optimal formula increases the solubility and diffusion of miconazole, making its release more effective than commercial gels, making it a strong candidate for buccal drug delivery.	(Talianu et al., 2024)
Irbesartan	BCS Class II	Nano-bilosomes consist of: Soybean phosphatidylcholine (SPC), Cholesterol, Bile salts (SDC/STGC), Span 60, Edge activators (Capryol PGMC / Cremophor RH40)	In-vitro & In-vivo (Wistar albino rats)	The optimal formulation showed a particle size of 109.99 nm, a zeta potential of –30.999 mV, and an entrapment efficiency of 94.54%. The characterization results showed amorphization of Irbesartan without chemical interaction with excipients and a homogeneous spherical bilosomal morphology. The release profile was biphasic and controlled up to 95.5% in 24 hours, following the Higuchi model (R^2 = 0.987). Pharmacokinetic tests showed a 1.3-fold increase in relative bioavailability compared to IRB suspension and 1.4-fold compared to commercial products, with a Cmax of 12.4 ± 1.2 µg/mL and a significant increase in AUC0–24h. The nano-bilosomes system was shown to improve the absorption, stability, and oral effectiveness of Irbesartan as a hypertension therapy.	(Ghanem et al., 2025)

Simvastatin	BCS Class II	Thiolated Xanthan Gum–Based Mucoadhesive Nanocrystals (TXG-SIM-NC)	In-vitro & In-vivo (Wistar albino rats)	The nanocrystal formulation enhanced simvastatin's biopharmaceutical performance by increasing entrapment efficiency (88.87%), improving mucoadhesion through thiolated xanthan gum, and providing sustained drug release for up to 96 hours. Cytotoxicity assays showed higher anticancer activity compared to free simvastatin, while in vivo pharmacokinetic studies in Wistar albino rats demonstrated an approximate 21.82% increase in oral bioavailability. Overall, the TXG-SIM nanocrystals improved stability, mucoadhesion, and therapeutic potential.	(Bakhaidar et al., 2022)
Aripiprazole	BCS Class II	Hydroxypropyl -β-cyclodextrin (HPβCD), L-Arginine (LA)	In-vitro	The study demonstrated that aripiprazole (ARP) complexes with hydroxypropyl-β-cyclodextrin (HPβCD) and L-arginine (LA) significantly improved the drug's in-vitro solubility and dissolution. The ternary lyophilized complex (ARP–HPβCD–LA, 1:1:0.27) provided the highest enhancement, increasing solubility up to 82-fold and showing the fastest dissolution rate in PBS pH 6.8. Solid-state analysis confirmed complete amorphization and improved surface interactions, explaining the superior performance.	(Awais et al., 2023)
Amphotericin B & Paromomycin	BCS Class IV & BCS Class III	Chitosan-coated Solid Lipid Nanoparticles (Cs-SLN)	In-vitro	Chitosan-coated SLN showed high cell internalization, was stable in gastrointestinal fluids, had a gradual drug release profile up to 72 hours, increased mucoadhesion, and significantly reduced the number of intracellular amastigotes with greater antileishmanial potency compared to the free drug.	(Parvez et al., 2020)
Insulin	-	L-Tryptophan (hydrophobic amino acid used as absorption-enhancing material)	In-situ & In-vivo (mice)	L-Tryptophan significantly increased intestinal absorption of insulin (dose-dependent). Enhanced absorption of GLP-1 & Exendin-4. Increased uptake of dextrans (4–70 kDa). No cytotoxicity: membrane integrity & viability preserved (LDH & TEER). Mechanism: modulation of intestinal mucosal structure, not by direct drug interaction. Reversible effect; safe as absorption-enhancing material.	(Kamei et al., 2018)
Clarithromycin	BCS Class II	Chitosan (CS)-coated PLGA NPs	In-vitro	This study developed chitosan coating shifted the zeta potential to strongly positive values (around +75 mV), indicating successful surface modification and improved adhesion to negatively charged epithelial membranes. The nanoparticles demonstrated good stability under simulated gastrointestinal conditions and provided a sustained drug-release profile. In-vitro antimicrobial assays confirmed clear inhibitory effects against pathogenic microorganisms, showing that the chitosan layer contributed functional biological activity.	(Öztürk et al., 2019)
Doxorubicin	BCS Class III	Cu_2S/Tween-20 nanocom-posites	In-vitro and In-vivo (Balb/c nude mice)	Doxorubicin-loaded copper sulfide nanoparticles coated with Tween-20 exhibited good stability, low toxicity, strong tumor inhibition, and complete tumor eradication	(Liu et al., 2022)

				when combined with photothermal therapy	
All-trans Retinoic Acid (ATRA)	BCS Class IV	Fish oil	In-vitro	The microemulsion system demonstrated markedly improved in-vitro performance compared with ATRA in fish oil. ATRA showed the highest solubility in oleth-5, which enabled the formation of a stable microemulsion with droplet sizes below 200 nm and a negative zeta potential. In-vitro intestinal absorption studies using Franz diffusion cells with porcine intestine showed that the ME4 formulation achieved significantly higher apparent permeability than the ATRA fish-oil solution. Confocal microscopy confirmed deeper and more intense penetration of the fluorescent probe delivered by the microemulsion. LDH release and histological analysis showed no intestinal damage, indicating good biocompatibility of the ME4 formulation.	(Subongkot & Ngawhirunpat, 2017)

Nanotechnology Approaches for Surface Activation

Nanotechnology-based delivery systems represent a significant advancement in surface activation strategies for improving oral biopharmaceutical performance (Beg et al., 2015; Liu et al., 2022). The reviewed studies consistently demonstrate the ability of nanoscale carriers to modulate drug–interface interactions, resulting in enhanced dissolution, improved stability under gastrointestinal conditions, and increased epithelial transport (Spósito et al., 2017; Yin et al., 2017). In this context, nanotechnology facilitates surface activation by engineering particle size, surface composition, and interfacial properties, rather than altering the intrinsic chemical structure of the drug (Beg et al., 2015). Polymeric nanoparticle systems, particularly PLGA-based carriers and polymer–lipid hybrid nanoparticles, effectively enhance the oral absorption of dissolution-limited compounds. For atorvastatin calcium, both PLGA nanoparticles and PLGA–DSPE–PEG hybrid systems exhibited small particle sizes, high drug entrapment efficiency, and sustained-release profiles. Notably, the hybrid formulation achieved superior systemic exposure and pharmacodynamic outcomes in vivo, suggesting that combining polymeric matrices with lipid components provides synergistic benefits by improving both surface wettability and biological interaction. These polymeric and hybrid systems exemplify how surface activation can be achieved through controlled surface composition, enhancing wettability and biological interaction while maintaining sustained drug release (Liu et al., 2022).

Nanoemulsions and self-emulsifying drug delivery systems are established nanotechnological strategies for surface activation, particularly beneficial for Biopharmaceutics Classification System (BCS) Class II and IV drugs (Beg et al., 2015; Spósito et al., 2017). Formulations developed for ravuconazole, baicalein, ciprofloxacin, zaleplon, and lovastatin consistently produced nanometric droplets, maintaining drugs in a solubilized state and facilitating controlled release (Arshad et al., 2021; Spósito et al., 2017; Yin et al., 2017). These systems significantly enhanced intestinal permeability and oral bioavailability, as evidenced by substantial increases in systemic exposure and therapeutic efficacy across multiple in vivo models. Furthermore, modifications such as hyaluronic acid coating improved mucus penetration and biological targeting, underscoring the importance of surface functionalization beyond particle size reduction (Arshad et al., 2021). Mechanistically, these systems enhance oral absorption by maintaining drugs in a supersaturated or solubilized state, while simultaneously reducing interfacial energy barriers to dissolution and epithelial transport (Beg et al., 2015).

Lipid-based nanocarriers, including solid lipid nanoparticles, self-nanoemulsifying drug delivery systems (SNEDDS), solid SNEDDS, bilosomes, and lipid nanoparticles, offer significant advantages by protecting drugs from gastrointestinal degradation and facilitating epithelial uptake (Guada et al., 2015; Kenechukwu et al., 2025). These systems have demonstrated particular efficacy with chemically unstable or poorly permeable compounds such as cyclosporine A, artemether, amphotericin B, and paromomycin, where enhanced stability and prolonged release have translated into improved pharmacological outcomes.

Advanced surface-engineered nanocarriers augment the capabilities of nanotechnology-based surface activation. Nanoparticles modified with cell-penetrating peptides significantly increased the intestinal permeability of macromolecules such as insulin, while peptide-modified liposomal systems enhanced the oral absorption of vancomycin derivatives without compromising biological activity (Barbari et al., 2017; Werner et al., 2024). Similarly, chitosan-coated lipid nanoparticles exhibited strong mucoadhesive properties, improved

gastrointestinal stability, and enhanced therapeutic efficacy in antimalarial and antiparasitic applications (Kenechukwu et al., 2025). Collectively, these findings indicate that nanotechnology facilitates precise surface engineering strategies that simultaneously address solubility, stability, and epithelial transport barriers in oral drug delivery.

Table 2. Representative Nanotechnology-Based Surface Activation Strategies and Their Biopharmaceutical Outcomes Across BCS Classes

Active Compound	BCS	Method	Test subject	Study Outcome	References
Atorvastatin Calcium	BCS Class II	PLGA nanoparticles (polymeric) and PLGA-DSPE-PEG-nanoparticles (polymer-lipid hybrid)	In-vitro & In-vivo (Wistar rat)	Both polymeric and lipid–polymer hybrid nanoparticles showed small particle sizes, high entrapment efficiency, and sustained drug release in vitro, with polymeric nanoparticles releasing the drug more slowly. In vivo, both systems enhanced the oral absorption of atorvastatin, and the hybrid nanoparticles achieved the highest Cmax and AUC. Pharmacodynamic studies in hyperlipidemic rats also confirmed stronger lipid-lowering effects, particularly with the hybrid formulation.	(Liu et al., 2022)
Ravuconazole	BCS Class II	Self-emulsifying drug delivery systems (SEDDSs) type III A	In-vitro & In-vivo (Swiss mice)	The type IIIA SEDDS maintained ravuconazole in a dissolved, stable state with droplet sizes under 250 nm and zeta potentials of –45 to –57 mV. All formulations were polydisperse without large aggregates. Ravuconazole dissolution reached 20% in 6 hours, compared to only 3% for the free drug. Toxicity tests showed dose-dependent Labrasol toxicity, while the low-surfactant (10% v/v) formulation was safe during 20-day treatment in *T. cruzi*-infected mice. SEDDS delivery significantly enhanced anti-*T. cruzi* activity, indicating strong potential for further in vivo preclinical development.	(Spósito et al., 2017)
Cyclosporine A (CsA)	BCS Class IV	Lipid nanoparticles (LN) were prepared using hot homogenizatio n followed by ultrasonication	In-vitro	This study produced stable lipid nanoparticles (LN) for oral cyclosporine A delivery, achieving nearly 100% entrapment using hot homogenization and ultrasonication. The particles were 121–202 nm fresh and 163–270 nm after freeze-drying, with negative charges and confirmed structural integrity. The formulations were stable for three months at 4°C, and dual-surfactant LNs also remained stable at room temperature. CsA-LN demonstrated dose-dependent immunosuppressive activity by lowering IL-2 levels, indicating strong potential as an oral CsA delivery system.	(Guada et al., 2015)
Insulin	-	Nano-emulsion–based method to produce ultra-small insulin-loaded nanoparticles	In-vitro	The optimization process produced nanoparticles measuring about 12 nm in their dry state and around 100 nm when dispersed in water, with a smooth and spherical morphology. After CPP conjugation and insulin loading, the particle size increased to approximately 234–367 nm while maintaining good stability. In vitro release studies showed a controlled release pattern, with 85% insulin released over 24 hours at pH 7.4 and 77% at pH 6.8. Tests on Caco-2 cells confirmed that the nanoparticles were safe, maintaining nearly	(Barbari et al., 2017)

				100% cell viability. CPP-modified nanoparticles reduced TEER values almost twice as much as non-CPP nanoparticles and increased insulin transport across the cell layer from about 5% to 18%, demonstrating a significant enhancement in intestinal permeability and delivery efficiency.	
Baicalein (BCL)	BCS Class II	Nanoemulsion (NEs) was made by High-Pressure Homogenization (HPH) using hemp oil & low surfactant	In-vitro, In-situ, and In-vivo (Sprague–Dawley rats)	Nanoemulsion size ~90 nm, EE 99.31%. Increases oral bioavailability by 524.7% compared to suspension. Increases intestinal permeability (duodenum, jejunum, ileum). Increases transcellular transport (Caco-2 uptake ↑). Stable, biocompatible (cell viability >90%), low toxicity.	(Yin et al., 2017)
Exenatide	BCS Class III	Hydrophobic ion pairing and dry reverse micelles.	In-vitro & In-vivo (Sprague–Dawley rats)	Both HIP and dRM in SEDDS improved oral exenatide delivery, with HIP showing slightly higher bioavailability and longer release, while dRM showed better safety; both produced stable nanoemulsions and effectively lowered glucose in vivo.	(Schmidt et al., 2025b)
Artemether	BCS Class II	High-shear melt homogenization based on SRMS (Solidified Reverse Micellar Solution).	In-vitro & In-vivo (Albino (BALB/c) mice)	The study developed stable SRMS-based artemether-loaded chitosan-coated SLNs that produced nanometric particles (~293 nm) with a positive zeta potential (+32.5 mV) and high encapsulation efficiency (82%). The nanoparticles showed smooth morphology with a clear chitosan layer, enhanced drug amorphization, and good component compatibility. They were minimally toxic to Caco-2 cells and provided controlled drug release compared to the rapid release of artemether suspension. In vivo, the formulation demonstrated significantly stronger antimalarial activity ($p < 0.05$), indicating its promise as an improved oral delivery system for malaria treatment.	(Kenechukwu et al., 2025)
Vancomycin-hexa-arginine derivative	BCS Class III	Surface-modified liposomal nanocarrier	In-vitro & In-vivo (Wistar rats)	CPP-GCTE liposomes increased FU002 oral absorption, improved cellular uptake, preserved antimicrobial activity, and produced effective oral therapy.	(Werner et al., 2024)
Zaleplon	BCS Class II	Self-nanoemulsifying drug delivery system (SNEDDS) & Lyophilized self-nanoemulsifying tablets (SNELTs)	In-vitro & In-vivo (Rabbit)	This study developed a lavender-oil–based self-nanoemulsifying formulation of zaleplon with a droplet size of ±87 nm and high drug-loading capacity. The lyophilized SNELTs showed rapid disintegration (±30 seconds) and a 17-fold faster dissolution rate compared to the commercial tablet. In vivo testing demonstrated a 1.6-fold increase in bioavailability and a shorter Tmax, indicating faster transmucosal absorption.	(Ali et al., 2022)
Lovastatin	BCS Class II	Solid self-nanoemulsifying drug delivery system (S-SNEDDS)	In-vitro, In-vivo (Rats)	This study developed optimized solid SNEDDS using a QbD approach. The formulation produced nano-sized droplets (69–231 nm), rapid emulsification and liquefaction, and fast drug release (>85% within 30 minutes). In situ intestinal perfusion showed significant increases in intrinsic, effective, and wall permeability, while in vivo pharmacodynamic evaluation demonstrated improved lipid-	(Beg et al., 2015)

				lowering activity compared to marketed and inclusion complex formulations.	
Ciprofloxacin	BCS Class IV	Self-nanoemulsifying drug delivery system SNEDDS modified with hyaluronic acid to produce HA-CIP-SNEDDS	In-vitro, Ex-vivo, & In-vivo (Mice)	This study demonstrated that the HA-CIP-SNEDDS formulation significantly enhanced the performance of ciprofloxacin by producing small droplets (50 nm), a PDI of 0.3, and a zeta potential of −11.4 mV. The formulation improved intestinal mucus permeation by up to fourfold compared to free CIP and provided controlled drug release of up to 80% over 72 hours. HA-CIP-SNEDDS also exhibited stronger antibiofilm activity against *Salmonella typhi*, along with superior biocompatibility and oral pharmacokinetics. Overall, this system proved effective and promising for the treatment of *Salmonella typhi* infections.	(Arshad et al., 2021)

Impact of Surface Activation on Biopharmaceutical Parameters

Multiple studies show that surface activation improves key biopharmaceutical parameters such as dissolution rate, solubility, epithelial permeability, and oral bioavailability. Nanoemulsions and SEDDS or SNEDDS systems enhance dissolution and maintain drugs in a solubilized state. This effect is seen in ravuconazole, zaleplon, and ciprofloxacin formulations (Ali et al., 2022; Spósito et al., 2017). Nanoparticles and mucoadhesive formulations improve transcellular transport and reduce efflux activity as observed in insulin CPP nanoparticles and chitosan coated systems (Barbari et al., 2017; Öztürk et al., 2019).

Gastrointestinal stability is also improved with lipid carriers and polymer coated nanoparticles that protect drugs such as cyclosporine A, artemether, and amphotericin B with paromomycin from degradation while supporting controlled release (Guada et al., 2015; Kenechukwu et al., 2025; Parvez et al., 2020). The combination of enhanced solubility, permeability, and stability leads to significantly higher bioavailability. For example, baicalein nanoemulsions show an increase of more than five hundred percent and atorvastatin, irbesartan, and lovastatin also show substantial enhancement in SNEDDS formulations (Beg et al., 2015; Ghanem et al., 2025; Liu et al., 2022; Yin et al., 2017).

Challenges, Safety Concerns, and Future Directions

Despite promising improvements, safety concerns and regulatory limitations remain important obstacles. Some surfactants used in SEDDS show dose dependent toxicity, as reported for Labrasol in ravuconazole formulations (Spósito et al., 2017). Long term safety of various nanocarriers including chitosan coated SLNs, cell penetrating peptide modified systems, and hybrid nanoparticles still requires deeper investigation due to risks of accumulation, mucosal irritation, and potential effects on gut microbiota (Barbari et al., 2017; Parvez et al., 2020). Regulatory guidelines for oral nanotechnology based products are still limited. Many studies emphasize the need to evaluate characteristics such as surface charge, coating stability, and interactions with mucus especially in innovative systems that incorporate surface ligands, cell penetrating peptides, and thiolated polymers (Bakhaidar et al., 2022; Werner et al., 2024). Future research should focus on scalable production, long term toxicity evaluation, and standardized characterization methods to facilitate the clinical translation of surface activated nanocarriers.

CONCLUSION

Surface activation has become an important approach for improving the oral performance of drugs with poor biopharmaceutical characteristics. Based on the evidence reviewed in this paper, modifying the surface of drug particles or carriers can enhance key factors that determine oral absorption, including solubility, dissolution behavior, permeability, and stability in the gastrointestinal environment. Conventional excipients such as surfactants, polymers, permeation enhancers, and lipid-based materials help improve interactions with biological fluids and epithelial tissues, while more advanced nanotechnology approaches offer greater control over particle behavior and transport pathways. Together, these strategies show potential for increasing oral bioavailability, particularly for drugs in BCS class II and IV. Although challenges such as safety concerns and limited regulatory guidance still need attention, ongoing research continues to support the development of surface-activated formulations as a promising direction for creating more effective and patient-friendly oral therapies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest related to the preparation and publication of this manuscript.

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