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A Comprehensive Review on Polymeric Novel Excipients for Enhancing Solubility and Oral Bioavailability of BCS Class II and IV Drugs

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Abstract: *The oral route remains the most preferred and patient-compliant mode of drug administration; however, poor aqueous solubility and low permeability continue to limit the therapeutic effectiveness of many newly developed drug molecules. According to the Biopharmaceutics Classification System, Class II drugs are characterized by low solubility and high permeability, whereas Class IV drugs exhibit both low solubility and low permeability, making them particularly challenging for formulation scientists. The present comprehensive review critically examines the role of polymeric novel excipients in enhancing the solubility and oral bioavailability of BCS Class II and IV drugs. Additionally, certain functional polymers enhance intestinal permeability by modulating membrane fluidity, opening tight junctions, or promoting mucoadhesion, thereby prolonging gastrointestinal residence time. Advanced polymer-based systems such as self-emulsifying drug delivery systems, nanosponges, polymeric micelles, hydrogels, and lipid–polymer hybrid nanoparticles further contribute to improved absorption and systemic exposure.*

The review also discusses critical formulation considerations, polymer drug compatibility, physicochemical characterization, scalability challenges, and regulatory perspectives associated with the use of novel excipients. Emphasis is placed on rational polymer selection based on drug properties, target release profile, and stability requirements. Overall, polymeric novel excipients represent a promising and adaptable strategy to overcome solubility and permeability barriers, offering significant potential to enhance the clinical performance of poorly water-soluble and low-permeability drugs.

Keywords: Polymeric excipients, Novel excipients, BCS Class II drugs

I. INTRODUCTION

The oral route remains the most preferred and widely accepted method of drug administration due to its convenience, patient compliance, cost-effectiveness, and suitability for chronic therapy. However, the therapeutic success of orally administered drugs largely depends on their aqueous solubility and permeability across the gastrointestinal membrane. A major challenge in contemporary pharmaceutical development is the increasing number of poorly water-soluble drug candidates emerging from modern drug discovery programs. The Biopharmaceutics Classification System categorizes drugs into four classes based on solubility and intestinal permeability. Among these, BCS Class II drugs (low solubility, high permeability) and BCS Class IV drugs (low solubility, low permeability) present significant formulation challenges due to limited dissolution in gastrointestinal fluids and, in the case of Class IV, restricted membrane transport. Consequently, improving solubility and oral bioavailability has become a central focus in pharmaceutical research, particularly through the development of polymeric novel excipients.

Solubility is a prerequisite for drug absorption because only dissolved drug molecules can permeate biological membranes. Inadequate aqueous solubility results in slow dissolution rates, erratic absorption, high inter-subject variability, and poor therapeutic outcomes. BCS Class II drugs typically exhibit dissolution rate-limited absorption, meaning that enhancing their solubility directly improves bioavailability. In contrast, BCS Class IV drugs suffer from

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both dissolution and permeability limitations, making formulation strategies more complex. Traditional approaches such as particle size reduction, salt formation, and use of conventional surfactants often provide limited improvement. Therefore, innovative polymeric excipients have emerged as promising tools to address these limitations through advanced drug delivery systems.

Polymeric novel excipients refer to newly developed or modified polymer-based materials that enhance drug solubility, stability, permeability, and overall bioavailability. These polymers may be synthetic, semi-synthetic, or natural in origin and are designed with functional groups that interact with drug molecules through hydrogen bonding, hydrophobic interactions, or ionic forces. Their multifunctional nature enables them to act not only as solubilizers but also as precipitation inhibitors, permeability enhancers, and stabilizers in supersaturated systems. Unlike traditional excipients that primarily serve as inert carriers, modern polymeric excipients play an active role in modulating drug release and absorption.

One of the most important mechanisms by which polymeric excipients enhance solubility is through the formation of solid dispersions. In such systems, the poorly soluble drug is molecularly dispersed or amorphously embedded within a polymer matrix. The amorphous form of a drug possesses higher free energy and improved apparent solubility compared to its crystalline counterpart. Polymers such as polyvinylpyrrolidone, hydroxypropyl methylcellulose, polyethylene glycol, and methacrylate-based copolymers are widely utilized for this purpose. These polymers inhibit drug recrystallization, stabilize supersaturated solutions, and prolong the time available for absorption in the GI tract.

In addition to solid dispersions, polymeric micelles and nanocarriers represent another innovative strategy. Amphiphilic block copolymers can self-assemble in aqueous media to form micelles with hydrophobic cores and hydrophilic shells. The poorly soluble drug is incorporated into the hydrophobic core, thereby improving its apparent solubility and protecting it from degradation. Such systems are particularly useful for BCS Class II drugs with high lipophilicity. For BCS Class IV drugs, polymeric excipients may also incorporate permeability-enhancing functionalities that modulate tight junctions or inhibit efflux transporters such as P-glycoprotein, thereby increasing intestinal absorption.

The design of novel polymeric excipients also considers physicochemical compatibility, safety, regulatory acceptance, and scalability. Biocompatibility and non-toxicity are essential, especially for chronic oral administration. Polymers must exhibit minimal irritation to the GI mucosa and should not interfere adversely with normal physiological processes. Advances in polymer chemistry have enabled the development of tailor-made excipients with controlled molecular weight, functional substitution, and biodegradability. Stimuli-responsive polymers that alter their solubility or swelling behavior in response to pH changes in the GI tract further enhance site-specific drug release and absorption.

Another critical aspect in the application of polymeric excipients is their role in maintaining supersaturation. After dissolution, poorly soluble drugs may rapidly precipitate in the intestinal environment, reducing bioavailability. Polymers can act as precipitation inhibitors by forming drug–polymer complexes or by increasing solution viscosity, thereby maintaining a metastable supersaturated state for prolonged periods. This “parachute effect” ensures sustained availability of dissolved drug molecules for absorption. Such mechanisms are particularly beneficial for drugs with narrow absorption windows or those prone to rapid crystallization.

From a formulation perspective, polymeric novel excipients support diverse manufacturing technologies such as hot-melt extrusion, spray drying, freeze drying, and solvent evaporation. These advanced techniques enable uniform dispersion of drug within polymer matrices and scalable production. The compatibility of polymers with these processes is crucial for industrial feasibility. Furthermore, the integration of Quality by Design principles allows systematic optimization of polymer type, concentration, and processing parameters to achieve consistent performance.

For BCS Class IV drugs, where both solubility and permeability are compromised, multifunctional polymers that combine solubilization and permeability enhancement are of particular interest. Certain polymers can transiently open tight junctions or inhibit enzymatic degradation in the GI tract. Others may facilitate lymphatic transport, thereby bypassing first-pass metabolism. Such comprehensive approaches are essential to improve systemic exposure and therapeutic efficacy of challenging drug molecules.

In recent years, the pharmaceutical industry has increasingly shifted toward the co-development of drug substances and enabling excipients. Polymeric novel excipients are no longer considered passive ingredients but strategic components of formulation design. Their ability to address multiple barriers simultaneously makes them indispensable in modern

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oral drug delivery. Moreover, the rising number of poorly soluble new chemical entities in the drug development pipeline underscores the need for continuous innovation in excipient science.

Polymeric novel excipients represent a transformative approach in enhancing solubility and oral bioavailability of BCS Class II and IV drugs. Through mechanisms such as amorphous solid dispersion formation, micellization, precipitation inhibition, permeability enhancement, and controlled drug release, these polymers overcome fundamental limitations associated with poor aqueous solubility. A comprehensive review of their physicochemical properties, mechanisms of action, formulation strategies, and future prospects is essential to guide the development of effective and patient-friendly oral dosage forms. As pharmaceutical research advances, the rational design and application of polymeric excipients will remain central to improving therapeutic outcomes and expanding the range of orally deliverable drug candidates.

POLYMERIC SOLID DISPERSIONS

Solid dispersion technology is one of the most widely utilized strategies for BCS Class II/IV drugs. In this system, drug molecules are molecularly dispersed within a polymeric matrix, often in an amorphous state, thereby improving dissolution rate and super saturation generation.

Extensively employed polymeric carriers include:

Polyvinylpyrrolidone (PVP)
Copovidone
Polyethylene glycol (PEG)
Hydroxypropyl methylcellulose (HPMC)
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)
Soluplus®

These polymers enhance drug solubility through hydrogen bonding, inhibition of crystallization, and maintenance of supersaturation.

Soluplus®, an amphiphilic graft copolymer, has demonstrated remarkable ability to form stable amorphous solid dispersions. Studies report significant solubility and bioavailability enhancement of BCS Class II drugs using Soluplus®-based systems. Additionally, Soluplus® nanomicelles have been shown to improve solubility of BCS II drugs by incorporating hydrophobic molecules within micellar cores.

Hot-melt extrusion and spray drying are commonly used preparation techniques, with HME often yielding more stable amorphous dispersions due to stronger drug–polymer interactions.

POLYMERIC MICELLES AND NANOMICELLES

Polymeric micelles are self-assembled core–shell nanostructures formed from amphiphilic block copolymers. Their hydrophobic core solubilizes poorly soluble drugs, while the hydrophilic shell enhances aqueous stability .

Recent reviews highlight that polymeric micelles improve solubility, stability, and permeability of hydrophobic drugs, addressing key barriers in oral delivery . A 2026 review emphasizes innovations in preclinical development of oral polymeric micelles, particularly for enhancing dissolution and intestinal transport .

For example:

PEG-PPG-PEG triblock copolymer micelles increased tamoxifen solubility approximately 60-fold and improved dissolution performance .

Soluplus® nanomicelles improved solubility of BCS Class II drugs in liquid dosage forms .

Polymeric micelles also provide protection from gastrointestinal degradation and physiological stress, enhancing oral stability .

POLYMERIC NANOPARTICLES AND AMORPHOUS SYSTEMS

Amorphous drug/polymer nanoparticles increase surface area and dissolution rate. Studies on celecoxib nanoparticles demonstrated faster Tmax and improved systemic exposure compared to crystalline capsules .

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Mesoporous silica combined with polymer matrices can stabilize amorphous dispersions and enhance dissolution by confining drug molecules within nanoscale pores .

Furthermore, PEGylated polymers enhance stability and circulation time, demonstrating the potential of polymer engineering in drug delivery systems .

Mechanisms of Solubility and Bioavailability Enhancement

Polymeric excipients enhance solubility and bioavailability through multiple mechanisms:

Amorphization and crystallization inhibition

Hydrogen bonding and intermolecular interactions

Micellar solubilization

Improved wettability and dissolution rate

Permeability enhancement and protection from degradation

Hydrogen bonding and electrostatic interactions between polymers and active compounds play a critical role in encapsulation efficiency and stabilization .

COMPARATIVE OVERVIEW OF MAJOR POLYMERIC EXCIPIENTS

Table 1: Major Polymeric Novel Excipients for Solubility and Bioavailability Enhancement

Polymer	Type	Mechanism	Suitable BCS Class	Key Advantages	Supporting Evidence
PVP	Hydrophilic polymer	Amorphization, hydrogen bonding	II, IV	Crystallization inhibition	
HPMC	Cellulosic polymer	Supersaturation stabilization	II, IV	Strong drug–polymer interactions	
HPMCAS	Enteric polymer	pH-dependent release	II, IV	Enhanced intestinal targeting	
Soluplus®	Amphiphilic graft copolymer	Solid dispersion + micellization	II	High solubilization capacity	
PEG-PPG-PEG	Triblock copolymer	Polymeric micelle formation	II	60-fold solubility increase	
Ethyl cellulose (nanoparticles)	Hydrophobic polymer	Nanoparticle dispersion	II	Faster Tmax, improved exposure	

CHALLENGES AND FUTURE PERSPECTIVES

Despite promising outcomes, challenges remain:

Physical instability of amorphous systems

Scale-up complexities

Regulatory evaluation of novel excipients

Long-term safety considerations

Future research focuses on stimuli-responsive polymers, hybrid nanocarriers, and personalized oral drug delivery systems. Rational polymer design targeting hydrophilic–hydrophobic balance is expected to further optimize drug loading and release behavior.

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II. CONCLUSION

The comprehensive review on polymeric novel excipients for enhancing the solubility and oral bioavailability of Biopharmaceutics Classification System (BCS) Class II and Class IV drugs underscores the pivotal role of advanced polymer science in overcoming one of the most persistent challenges in pharmaceutical development poor aqueous solubility and limited gastrointestinal absorption. BCS Class II drugs are characterized by low solubility and high permeability, whereas Class IV drugs exhibit both low solubility and low permeability, making their formulation particularly complex. In both categories, dissolution rate and solubility become critical determinants of systemic drug exposure and therapeutic efficacy. Polymeric novel excipients have emerged as transformative tools that address these limitations through multifaceted mechanisms including solubilization, precipitation inhibition, permeability enhancement, stabilization of amorphous forms, and controlled drug release.

The integration of hydrophilic polymers such as polyvinylpyrrolidone, hydroxypropyl methylcellulose, polyethylene glycol, and copolymers like Soluplus® and poloxamers has significantly advanced the formulation of poorly soluble drugs. These polymers function by forming solid dispersions, micellar systems, nanosuspensions, and polymer drug conjugates that enhance wettability, reduce crystallinity, and maintain supersaturation in gastrointestinal fluids. Particularly, amorphous solid dispersions prepared using polymeric carriers have demonstrated consistent improvement in dissolution profiles by inhibiting drug recrystallization and promoting molecular-level dispersion. This stabilization of the amorphous state is critical for maintaining enhanced bioavailability during storage and after administration.

For BCS Class II drugs, polymeric excipients primarily enhance dissolution rate, leading to improved plasma concentration and therapeutic response. In contrast, for BCS Class IV drugs, the challenge extends beyond solubility to permeability limitations. In such cases, functional polymers with bioadhesive or permeability-enhancing properties contribute to improved intestinal residence time and transport across epithelial barriers. Certain polymers interact with mucosal membranes, modulate tight junctions, or reduce efflux transporter activity, thereby supporting improved absorption. The synergistic use of polymers with surfactants and lipid-based systems further strengthens formulation strategies for highly problematic molecules.

Another critical advantage of polymeric novel excipients lies in their versatility and adaptability across different drug delivery platforms. Techniques such as hot-melt extrusion, spray drying, electrospinning, and nanoprecipitation have enabled scalable production of polymer-based formulations. Advances in polymer chemistry have also facilitated the design of stimuli-responsive and biodegradable excipients that respond to pH or enzymatic conditions within the gastrointestinal tract, ensuring site-specific drug release and enhanced therapeutic precision.

Despite these significant advancements, challenges remain. Physical stability of amorphous systems, moisture sensitivity, scale-up complexities, and regulatory considerations related to novel excipient approval continue to demand focused research. Additionally, understanding polymer–drug intermolecular interactions at the molecular level remains essential for rational formulation design. Future perspectives emphasize the integration of computational modeling, quality-by-design (QbD) approaches, and nanotechnology-driven polymer systems to predict performance and optimize formulation parameters. The development of multifunctional polymers capable of simultaneously enhancing solubility, permeability, and stability represents a promising direction for next-generation oral drug delivery systems.

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