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Review Article

Recent progress in pharmaceutical excipients as P-glycoprotein inhibitors for potential improvement of oral drug bioavailability: A comprehensive overview

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Abstract

Pharmaceutical excipients such as P-glycoprotein inhibitors can also increase the solubility and affinity of drugs to the intestinal membrane, enhance paracellular pathways and endocyte uptake, and activate lymph transport pathways, thereby increasing the bioavailability of oral drugs. This review aims to review and assess the performance of pharmaceutical excipients as P-glycoprotein permeability inhibitors in improving oral drug bioavailability in drug formulations by evaluating meta data from P-glycoprotein efflux in permeability and pharmacokinetics studies. The review results are pharmaceutical excipients that have proven effective as P-glycoprotein inhibitors from the surfactant and polymer groups, namely TPGS and Poloxamer 188, respectively. All nanosystems incorporating pharmaceutical excipients as P-gp inhibitors show potential in enhancing the permeability and bioavailability of oral drugs when compared to conventional formulations. The effectiveness of these systems has been evaluated through in vitro (Caco-2 cells), ex vivo (everted gut sac), in situ (SPIP), and in vivo (AUC) methods.

Keywords

bioavailability, excipient, inhibitors, permeability, P-glycoprotein

Introduction

Oral drug delivery is the most common method for administering medications because it is non-invasive and convenient for patients. However, before a drug can have a therapeutic effect, it must go through several biopharmaceutical processes. Despite this, certain drugs have limited therapeutic effectiveness due to the physicochemical properties of the active ingredients and the physiological conditions of the gastrointestinal tract, which hinder drug absorption and lower oral bioavailability. Factors such as the pKa of the drug, gastrointestinal pH, intestinal wall metabolism, and active transport mechanisms like P-glycoprotein efflux, which reduces drug permeability, all contribute to reduced bioavailability (Shah et al. 2021).

P-glycoprotein (P-gp) is a membrane-forming protein, sub-family B1 of the ATP-binding cassette (ABCB1) transporter, or so-called multidrug resistance (MDR), functioning to pump transmembrane efflux (Mealey et al. 2010; Hashimoto et al. 2017). P-gp is mainly found on epithelial cells that have an excretory role (Cherniakov et al. 2015). For example, P-gp is present on the apical surface of epithelial cells in areas such as the small intestine, colon, pancreatic duct, bile duct, proximal kidney tubule, and adrenal gland. Additionally, P-gp can be found on the endothelial cells of the blood-brain barrier (Cherniakov et al. 2015). Conversely, P-gp functions as a protective mechanism for these organs by restricting the cellular uptake of toxic substances or xenobiotics, preventing them from entering the cytosol, and actively removing them from the cell (Fortuna et al. 2011; Amin 2013).

P-gp activity can be suppressed by administering P-gp inhibitors (Rahman et al. 2011). These inhibitors are typically hydrophobic substrates of P-gp that can traverse the cell membrane through passive diffusion. Administration of P-gp inhibitors together with drugs can increase the permeability and absorption of oral drugs, resulting in increased bioavailability and therapeutic effects (Amin 2013). P-gp inhibitors are classified into three generations based on their specificity, affinity, and toxicity, namely small molecules, which include active pharmaceutical ingredients and new chemical entities, natural constituents, and inert pharmaceutical excipients (Leopoldo et al. 2019; Zhao et al. 2021).

Pharmaceutical excipients are commonly used as P-gp inhibitors because they are safe and not absorbed by the gut. Excipients as P-gp inhibitors have been shown to increase intestinal epithelial permeability, increase tight junction permeability, and decrease or inhibit drug efflux by P-gp, thereby increasing drug absorption (Tejeswari and Yalavarthi 2014). Excipients in drug formulations indirectly inhibit P-gp by affecting lipid membranes (Abdallah et al. 2015; Kesharwani et al. 2018). Apart from being a P-gp inhibitor, excipients can increase drug solubility and affinity to intestinal membranes, increase paracellular pathways and endocyte uptake, and activate lymph transport pathways, thereby increasing oral drug bioavailability (Ni et al. 2016; Shah et al. 2021).

Drugs that are P-gp substrates usually show poor bioavailability or MDR activity due to low permeability. Drugs in the biopharmaceutics classification system (BCS) class III and IV that have low permeability will limit drug absorption in the gut. Examples of drugs in BCS class III are linagliptin (Shah et al. 2021) and metformin hydrochloride (Mady et al. 2021), while BCS class IV are etoposide (Zhao et al. 2013) and paclitaxel (PTX) (Zhao et al. 2021). However, some drugs in BCS class II with low solubility and high permeability can still be combined with P-gp inhibitors such as irinotecan (Negi et al. 2013) and candesartan (Gurunath et al. 2015). Meanwhile, drugs in BCS class I do not require the addition of P-gp inhibitors because they already have high solubility and permeability.

The previous review thoroughly discussed various pharmaceutical formulations with P-glycoprotein-inhibiting effects as a promising approach to improve oral drug absorption and bioavailability (Nguyen et al. 2021). Whereas this review includes detailed meta-data comparing the permeability and pharmacokinetic outcomes between conventional preparations (e.g., solutions, suspensions, etc.) and nanosystem preparations (NPs, NEs, SMEDDS, SNEDDS, SLNs, NLCs, etc.) so that the effect of excipients as P-gp inhibitors on the oral delivery of drugs with low solubility and low permeability (BCS class II, III, and IV) can be clearly seen. This review also comprehensively describes the mechanism of drug absorption across the intestinal membrane as a basis for evaluating the process of intestinal permeability to drugs, which is presented through figures and tables on various permeability absorption models and methods that were gaps in previous reviews. Therefore, this review aims to describe and assess the performance of pharmaceutical excipients as P-gp inhibitors on permeability in improving the bioavailability of oral drugs in nanosystems.

Drug absorption across the intestinal membrane

The effective absorption of oral drugs through biological membranes is a critical step in the creation of new drug formulations. The process of drug absorption across the intestinal membrane is complex and involves multiple pathways (Figure 1). Passive absorption primarily occurs through the cell membranes of enterocytes (transcellular route) or via the tight junctions between enterocytes (paracellular route). Carrier-mediated absorption can happen through active or secondary active processes, as well as facilitated diffusion. Efflux transporters like P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-related protein 2 (MRP2) may also be involved, potentially reducing drug absorption. Additionally, intestinal enzymes may metabolize drugs into alternative forms that could be absorbed, and receptor-mediated endocytosis may also contribute to the absorption process.

Because of the multivariate processes involved in the intestinal absorption of drugs, it is often difficult to use a single model to accurately predict the in vivo permeability characteristics. Therefore, evaluating the process of intestinal permeability to drugs can be done from physicochemical, in vitro, ex vivo, in situ, in silico, and in vivo methods. Table 1 lists the various models or methods to evaluate the drug permeability process.

ATP-binding cassette (ABC) transporters

ATP-binding cassette (ABC) is one of the largest protein pools consisting of functionally distinct protein groups. In humans, there are 48 different ABC transporters that are divided into 7 families based on sequence homology, namely ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, and ABCG (Klepsch et al. 2014). Among the seven families, the ABCB and ABCC families contain the most investigated transporters that affect human intestinal absorption. ABC transporters play a role in transporting chemicals across the

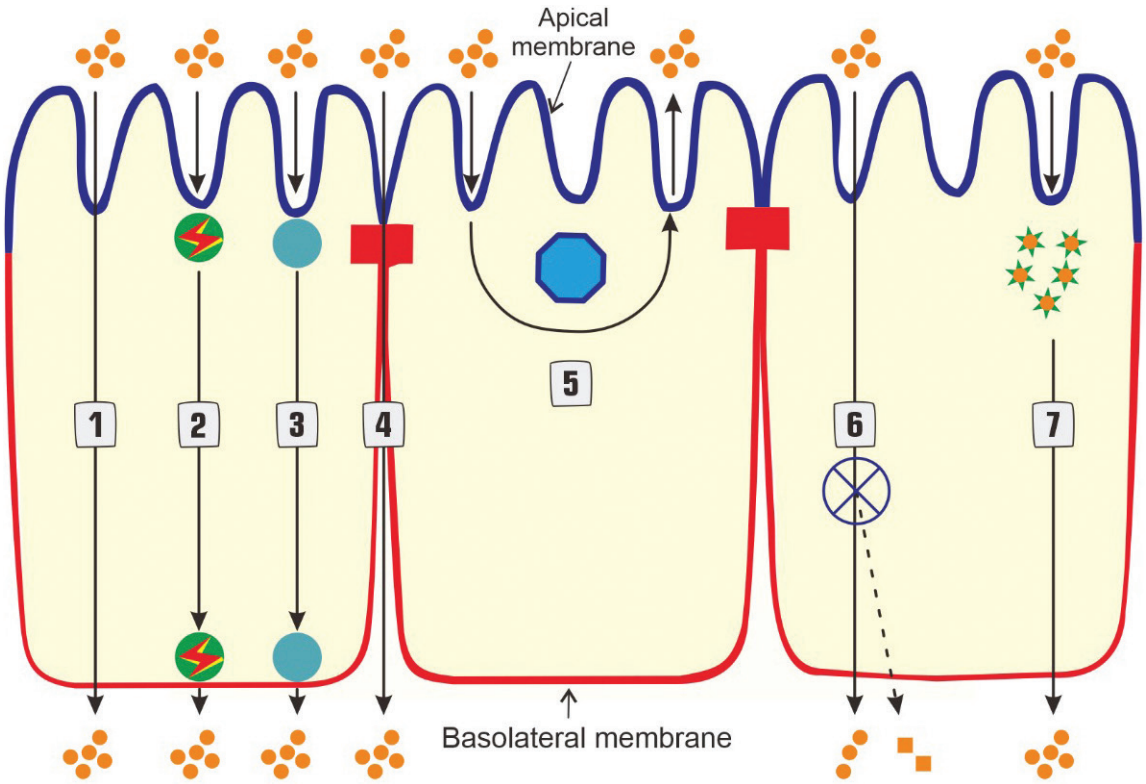

Figure 1. Multiple pathways for intestinal absorption of a compound: (1) passive, transcellular; (2) active or secondary active; (3) facilitated diffusion; (4) passive, paracellular; (5) absorption limited by P-gp and/or other efflux transporters; (6) intestinal first-pass metabolism followed by absorption of parent and metabolite; (7) receptor-mediated transport.

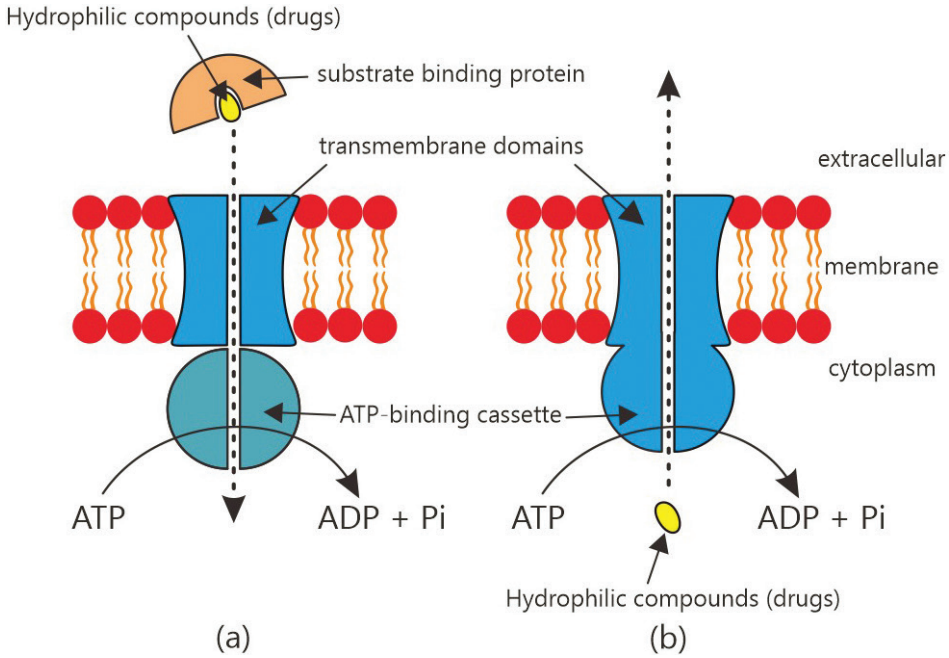

Figure 2. Schematic of ABC transporter function: (**a**) ABC importers, (**b**) ABC exporters, in the cell membrane.

cell membrane (Klepsch et al. 2014). Broadly, ABC transporters are categorized as importers or exporters, depending on the direction of transport relative to the cytoplasm. Several subfamilies of highly polyspecific ABC transporters have the ability to export a wide variety of chemical compounds that are hydrophilic out of the cell (efflux), including P-gp or ABCB1, multidrug resistance-related protein 1 (MRP1) or ABCC1, and breast cancer resistance protein (BCRP) or ABCG2 (Klepsch et al. 2014). Figure 2 describes the working scheme of the ABC transporter, which consists of ABC importers that require a substrate-binding protein that feeds the hydrophilic substrates into the translocation pathway formed by the transmembrane domain. The ABC are separate subunits with the transmembrane domain, as well as ABC exporters, which typically have their transmembrane domain fused to the ABC (Locher 2009).

Table 1. Permeability absorption models or methods.

Model	Methods	Description
Physicochemical	Lipophilicity (Log P)	Lipophilicity (Log P) is one of the most important physicochemical parameters in predicting and interpreting membrane permeability. In most of the early studies, the oral drug absorption was demonstrated to be dependent on the lipophilicity. Historically, the octanol-water partition coefficient (Log P) was accepted as a surrogate to biological systems for predicting absorption.
	Absorption Potential (AP)	Absorption Potential (AP) incorporated the various basic physicochemical parameters in one single equation and was highly predictive of the extent of absorption in humans.
	Immobilized Artificial Membrane (IAM)	IAM is a chromatographic surface prepared by covalently immobilizing cell membrane phospholipids to solid surfaces at monolayer density.
		The IAM chromatography column emulates the lipid environment of cell membranes.
		The IAM methodology has been used to predict not only drug intestinal absorption but also solute partitioning into liposomes, brain uptake, and human skin permeability.
In vitro	Animal Tissue-Based:	
	– Everted gut sac (ex vivo)	The everted gut sac method is ideal for studying the absorption mechanism of drugs since both passive and active transport can be studied. This model may be used to evaluate the role of efflux transporters in the intestinal absorption of drugs by comparing the transport kinetics of drugs in the absence and presence of P-gp inhibitors or substrates.
	– Ussing Chamber	In this method, the permeability is measured based on the appearance of the drug in the serosal side rather than the disappearance of the drug in the mucosal side.
		Suitable for studying differences in drug absorption in intestinal tissues in different regions of the intestine.
	– Isolated Membrane Vesicles	An ideal system for mechanistic absorption tests, performed on small amounts of drug (mg), usually allows several experiments to be performed with vesicles prepared from a single experimental animal.
	Cell-Based:	
	– Caco-2: Human colon adenocarcinoma	Most well-established cell models differentiate and express some relevant efflux transporters; expression of influx transporters is variable (lab-to-lab).
	– MDCK: Mardin-Darby canine kidney epithelial cells	Polarized cells with low intrinsic expression of ABC transporters, ideal for transfections.
	– LLC-PK1: Pig kidney epithelial cells	Polarized cells with very low intrinsic transporter expression, ideal for transfections.
	– 2/4/A1: Rat fetal intestinal epithelial cells	Temperature-sensitive, ideal for paracellularly absorbed compounds (leakier pores).
	– TC-7: Caco-2 sub-clone	Similar to Caco-2 cells.
	– HT-29: Human colon	Contains mucus-producing goblet cells.
	– IEC-18: Rat small intestine cell line	Provides a size-selective barrier for paracellularly transported compounds.
In situ	*In situ* experiments for studying intestinal drug absorption involve perfusion of drug solution prepared in physiological buffer through isolated cannulated intestinal Segments, such as:	*In situ* perfusion of intestinal segments of rodents (rats or rabbits) is frequently used to study the permeability and absorption kinetics of drugs. The biggest advantage of the *in situ* system compared to the *in vitro* techniques discussed earlier is the presence of an intact blood and nerve supply in the experimental animals.
	– Single Pass Intestinal Perfusion (SPIP)	
	– Recirculating Intestinal Perfusion (RIP)	
	– Closed Loop (CL)	
In silico	– Molecular Dinamic (MD)	In silico models that can accurately predict the membrane permeability of test drugs based on lipophilicity, hydrogen bonding capacity, molecular size, polar surface area, and quantum properties without requiring chemical compound synthesis and direct experimental studies.
	– Quantitative structure property relationship (QSPR)	
In vivo	Comparison of AUC (plasma concentration vs. time curve) values after intravenous, oral, and intraportal (or intraperitoneal) administration can often indicate the absolute extent of in vivo absorption.	In vivo models are conducted on experimental animals to predict the absorption rate of drugs in humans.

P-glycoprotein (P-gp)

P-gp, also referred to as ATP-binding cassette sub-family B member 1 (ABCB1), is commonly known as a multi-drug resistance (MDR) protein (Nguyen et al. 2021). It is an ATP-dependent transmembrane glycoprotein, produced through the post-translational glycosylation of the 140 kDa precursor protein, pro-P-gp. P-gp is 170-180 kDa in size, consisting of 1,280 amino acid residues, and shows a large degree of homology between the carboxyl and amino-terminal parts (Dewanjee et al. 2017).

P-gp is widely distributed throughout the body, including in the gut, liver, kidneys, pancreas, brain, and placenta, where it actively facilitates the removal of various

foreign substances from cells (Ferreira et al. 2015). In the gut, P-gp is present in the apical membrane of epithelial cells. However, P-gp is exclusively overexpressed in tumor cells, where it can enhance the efflux of anticancer drugs, causing tumor cells to become resistant to the drug (Nanayakkara et al. 2018).

The function of P-gp depends on where it is located. In the intestinal epithelium, P-gp can reduce the bioavailability of oral drugs and toxins, where P-gp acts to limit the absorption of substrates from the intestinal lumen and reduce the concentration of drugs in the blood so that P-gp can inhibit oral drug administration and reduce its therapeutic effects (Amin 2013). At the blood-brain barrier, P-gp functions to protect the brain from toxins in the blood by effluxing compounds that enter the blood compartment (König et al. 2013). At the apical syncytiotrophoblast membrane of the placenta, P-gp protects the fetus from drugs and xenobiotics present in the maternal blood circulation (Han et al. 2018). At the bile canalicular membrane of hepatocytes, the apical surface of small bile duct epithelial cells and the upper surface of renal proximal tubule epithelial cells, P-gp plays a role in eliminating drugs and toxins through urine and bile (Dewanjee et al. 2017).

P-gp-mediated efflux follows an active transport mechanism. In this process, ATP hydrolysis provides the driving force for xenobiotic extrusion. Generally, efflux occurs in a unidirectional manner where xenobiotics are discharged from intracellular to extracellular and transport only one molecule at a time. Therefore, P-gp is known as a uniporter carrier protein (Dewanjee et al. 2017).

In general, P-gp can be inhibited by three mechanisms: (i) blocking drug binding sites either competitively, non-competitively, or allosterically; (ii) interfering with ATP hydrolysis; and (iii) altering lipid cell membrane integrity (Lakshmi et al. 2012). In competitive inhibitors, when the substrate tries to bind to the P-gp protein transport site for translocation, the competitive inhibitor competes with the drug substrate to occupy all accessible protein transport sites so that P-gp cannot bind to the drug substrate. Whereas in non-competitive inhibitors, the inhibitor binds to allosteric modulation sites and non-competitively inhibits protein efflux. Therefore, non-competitive inhibitors are also known as non-transport inhibitors (Lakshmi et al. 2012). Figure 3 describes the action mechanism of P-gp.

Classification of P-gp inhibitors

P-gp inhibitors are divided into three groups, namely small molecules, natural bioactive constituents, and pharmaceutical excipients, which are described as follows (Nguyen et al. 2021):

Small molecules

Small molecules that include active pharmaceutical ingredients and new chemical entities are used as specific P-gp inhibitors to improve the bioavailability of oral drugs. However, both of these compounds have pharmacological activities that can lead to drug interactions and increased side effects (Nguyen et al. 2021).

Natural bioactive constituents

Various natural bioactive constituents are shown to have P-gp modulating effects. Natural bioactive constituents are considered as fourth-generation P-gp inhibitors due to their lower toxicity. Although they tend to be safe, there is a risk of adverse effects if natural bioactive constituents are administered together with drugs. Therefore, the interactions of

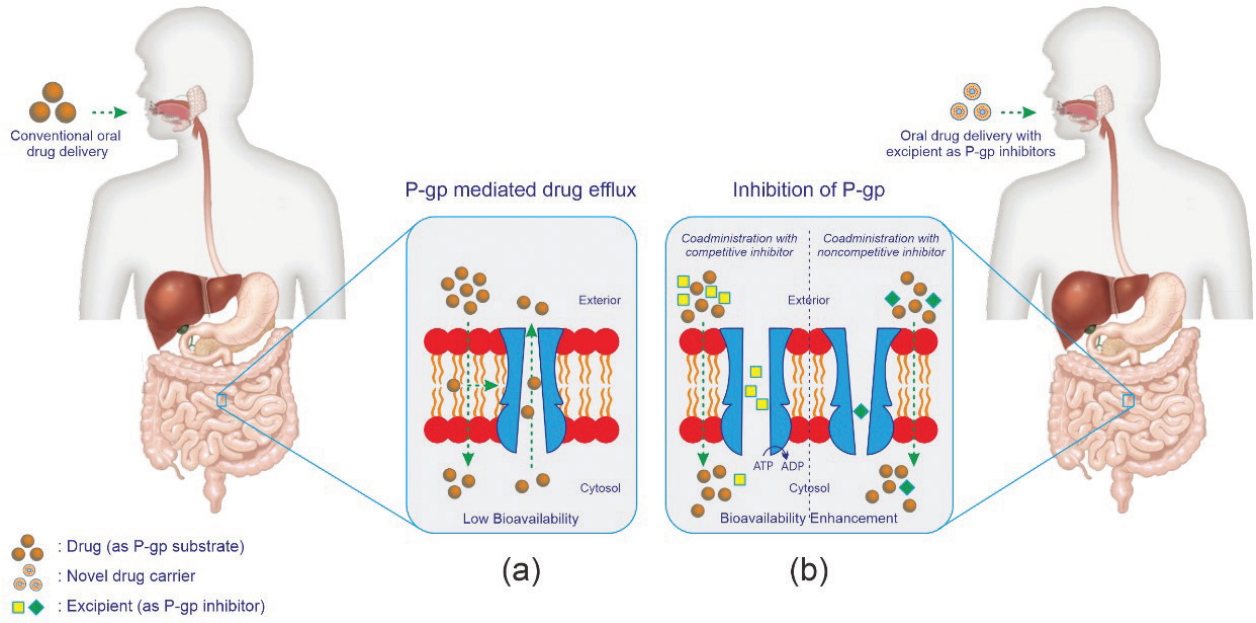

Figure 3. Action mechanism of P-gp: (**a**) P-gp-mediated drug efflux, (**b**) Inhibition of P-gp to prevent drug efflux, with a competitive inhibitor (left) and a non-competitive inhibitor (right).

food with drugs, plants with drugs, and chemical drugs with herbal drugs need to be considered before choosing this type of P-gp inhibitor. P-gp inhibitors obtained from natural bioactives can be alkaloids, flavonoids, coumarins, resins, saponins, terpenoids, and so on (Dewanjee et al. 2017).

Pharmaceutical excipients

Excipients that act as P-gp inhibitors can increase drug permeability by having the ability to cross lipid membranes. Several excipients used as cosolvents, surfactants, polymers, and lipid excipients have been shown to have P-gp inhibitor effects with different mechanisms (Gurunath et al. 2015). A summary of the excipients as P-gp inhibitors is presented in Table 2.

Oral drug delivery with excipients as P-gp inhibitors for enhancing oral bioavailability

Oral drug delivery developed using excipients as P-gp inhibitors has been shown to significantly improve drug permeability and bioavailability compared to conventional preparations (Shah et al. 2021). Various drug delivery systems have been developed as effective strategies to bypass and inhibit P-gp efflux. These systems include nanoemulsion (NE), self-microemulsifying delivery system (SMEDDS), self-nanoemulsifying delivery system (SNEDDS), solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC), liposomes, micelles, and nanoparticles. They not only leverage the P-gp inhibitory effects of their components but can also bypass P-gp efflux independently (Ni et al. 2016; Shah et al. 2021). Two common approaches for incorporating P-gp inhibitors are (i) co-administration of small drug molecules as specific P-gp inhibitors or natural compounds and (ii) co-encapsulation of both P-gp substrates and inhibitors within the same drug delivery system.

In addition to the P-gp inhibitory effects provided by the inhibitors in their composition, which lead to enhanced intestinal absorption and increased bioavailability of P-gp substrates, these drug delivery systems—particularly nanocarriers—can also boost oral bioavailability through various mechanisms, as demonstrated in several studies (Figure 4).

Various formulations have been developed and utilized to enhance the oral absorption and bioavailability of different P-gp substrates. The upcoming sections will detail recent advancements in pharmaceutical formulations for the oral delivery of an extensive range of P-gp inhibitors.

Nanoparticles (NPs)

Nanoparticles (NPs) (Figure 4A.a) are nano-colloidal or nano-particle systems created using polymers and/or surfactants as stabilizers or emulsifiers. They offer significant advantages, including high stability in the gastrointestinal tract and the ability to encapsulate various drug mole-

Table 2. The excipients as P-gp inhibitors.

Type	Group	Material	References
Surfactant	Polysorbates	– Polysorbate 80	(Constantinides and Wasan 2007; Kou et al. 2018)
		– Polysorbate 20	
	Sucrose esters	Sucrose monolaurate	
	Tocopheryl ester	Tocopheryl polyethylene glycol succinate (TPGS)	
	PEG esters	– PEG-35 castor oil (Cremophor® EL)	
		– PEG-12-hydroxystearate (Kolliphor® HS 15/Solutol® HS-15)	
		– PEG-8 glyceryl caprylate/caprate (Labrasol®)	
		– PEG-6 glyceryl caprylate/caprate (Softigen® 767)	
		– PEG-32 Glyceryl laureate (Gelucire 44/14)	
		– Polyoxyethylene (40) stearate (Myrj 52)	
	PEG ethers	Polyoxyethylene (20) stearyl ether (Brij 78)	
	Others	– Natrium 1,4-bis (2-etilheksioksi)-1,4 – dioxobutane– 2-sulfonate (AOT)	
		– Cetyltrimethylammonium bromide (CTAB)	
Polymer	Natural polymers	Dextrans, Agar, Gellan gum, Gum arabic, Gum traganth, Guar gum, Carrageenan gum, Xanthan gum, Alginates, Chitosan.	(Constantinides and Wasan 2007; Kou et al. 2018)
	Amphiphilic diblock copolymers	– MethoxyPEG-block-polycaprolactone (MePEG-b-PCL)	
		– Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®)	
	Pluronic block copolymers	– Pluronic F127/Poloxamer 407	
		– Pluronic F68/Poloxamer 188	
Lipid-based excipients	Glycerides	– Monoolein (Peceol™)	(Constantinides and Wasan 2007; Kou et al. 2018)
		– Monostearin	
	Phospholipids	– 1,2-dioctanoyl-sn-glycero-3-phosphocholine (8:0 PC)	
		– 1,2-didecanoyl-sn-glycero-3-phosphocholine (10:0 PC)	
	Methylated cyclodextrin	Methyl-β-cyclodextrin	

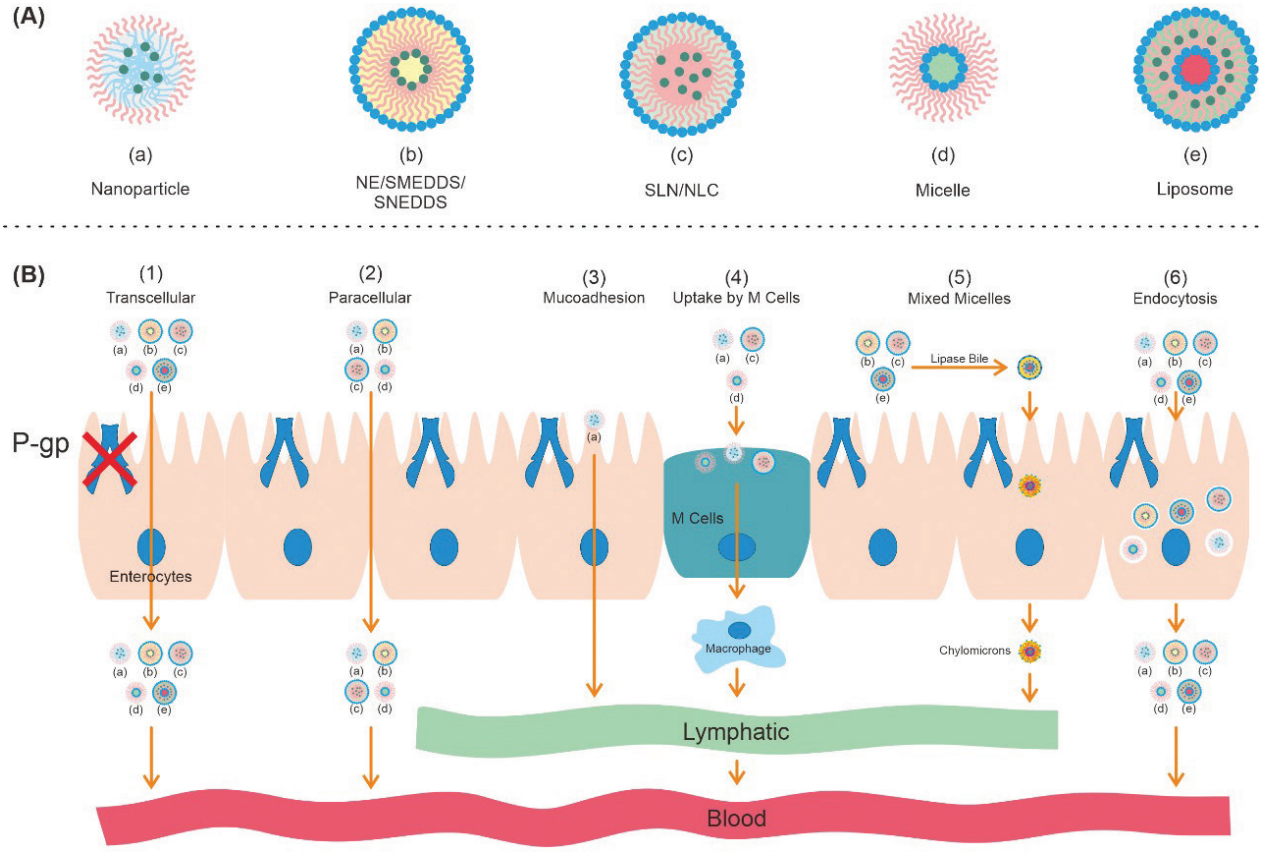

Figure 4. (**A**) Oral drug delivery systems: (**a**) NE/SMEDDS/SNEDDS, (**b**) Liposome, (**c**) SLN/NLC, (**d**) Micelle, (**e**) Nanoparticle; (**B**) Bypass and inhibit mechanism of P-gp efflux by various effects on oral drug delivery systems using pharmaceutical excipients as P-gp inhibitors: (1) Transcellular, (2) Paracellular, (3) Mucoadhesion, (4) Uptake by M Cells, (5) Mixed micelles, (6) Endocytosis. Figure modified with permission from Nguyen et al. (Nguyen et al. 2021).

cules (Plapied et al. 2011). The polymers used to produce NPs can be natural, such as chitosan, gelatin, dextran, albumin, and alginate, or synthetic and biodegradable, including polylactic acid (PLA), polyglycolic acid (PGA), polylactic-polyglycolic acid (PLGA) copolymers, polyethyleneimine (PEI), poly alkyl cyanoacrylate (PACA), and poly(ε-caprolactone) (PCL) (Kumari et al. 2010). Some polymeric NPs, like chitosan and PLGA, possess mucoadhesive properties that increase their retention time and diffusion within mucus. NPs are primarily absorbed in the gastrointestinal tract through endocytosis, such as clathrin-dependent endocytosis. Nonionic surfactants, including polysorbate 80, or Tween 80, and sorbitan monostearate, or Span 60, are used as stabilizers or emulsifiers in NP preparation, as they reduce the saturable paracellular pathway by facilitating electrostatic interactions between the diffused substances and the anionic residues in the lateral space or tight junctions. Moreover, some polymers and surfactants used in NP preparation can open tight junctions, promoting paracellular drug transport. Many P-gp substrates have been encapsulated into polymeric-surfactant micelles to bypass P-gp efflux, improving oral bioavailability (X. Wang et al. 2020).

Table 3 summarizes the previous features of nanoparticles with P-gp inhibitory effects on the enhancement of oral absorption and bioavailability of various P-gp substrates.

NE, SMEDDS, and SNEDDS

Nanoemulsions (NEs) (Figure 4A.b) are isotropic systems where two immiscible liquids are mixed into a single phase using an emulsifying agent, such as a surfactant and co-surfactant. The droplet size of nanoemulsions typically ranges from 20 to 200 nm. Common methods for preparing nanoemulsions include ultrasonication, high-pressure homogenization, microfluidization, phase inversion temperature, and spontaneous emulsification (Jaiswal et al. 2015).

Self-microemulsifying delivery system (SMEDDS) and self-nanoemulsifying delivery system (SNEDDS) are lipid-based nanocarriers that spontaneously form oil-in-water emulsions. These systems consist of stable mixtures of oils, surfactants, and co-surfactants. SMEDDS generally contains a lower amount of lipids and a higher proportion of hydrophilic surfactants and co-surfactants than SNEDDS. SMEDDS forms thermodynamically stable emulsions with droplet sizes ranging from 100 to 250 nm, whereas SNEDDS produces droplets smaller than 100 nm. Both SMEDDS and SNEDDS are commonly employed as drug delivery systems to enhance the absorption and bioavailability of lipophilic drugs. Additionally, the lipids and surfactants in these systems exhibit P-gp inhibitory effects, reducing or blocking P-gp efflux and thereby improving drug absorption (Krstić et al. 2018).

Table 3. NPs with P-gp inhibitory effects.

Drug (as P-gp substrate)	BCS	Excipient on NPs (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Tacrolimus	II	CD-PVM/MA amphiphilic copolymer*	– **SPIP** The K_a and Papp of tacrolimus NPs group had improved in the ileum compared with tacrolimus solution. – **Everted gut sac** The Papp of tacrolimus NPs had improved in the duodenum and ileum compared with tacrolimus solution.	*Solution:* – **t_{max}**: 1.2 ± 0.3 h – **C_{max}**: 20.7 ± 4.2 ng/mL – **K_e**: 0.11 ± 0.33 h^{-1} – **$t_{1/2}$**: 5.76 ± 0.95 h – **AUC_{0-24}**: 173.3 ± 10.8 ng/mL.h – **F_{rel}**: 100% – **F_{abs}**: 2.6 ± 0.2% *NPs:* – **t_{max}**: 2.4 ± 0.4 h – **C_{max}**: 238.9 ± 95.8 ng/mL – **K_e**: 0.13 ± 0.02 h^{-1} – **$t_{1/2}$**: 4.93 ± 0.46 h – **AUC_{0-24}**: 1648.0 ± 560.0 ng/mL.h – **F_{rel}**: 951 ± 323% – **F_{abs}**: 24.5 ± 8.3%	(Zhang et al. 2015)
Rapamycin	II	TPGS-Lecithin-Zein*	– **Caco-2 cell** Rapamycin solution: Papp (A-to-B) 1.73 ± 0.14 ($\times 10^{-6}$) cm/s, Papp (B-to-A) 2.54 ± 0.37 ($\times 10^{-6}$) cm/s, ER 1.47. Rapamycin NPs: Papp (A-to-B) 2.41 ± 0.10 ($\times 10^{-6}$) cm/s, Papp (B-to-A) 2.47 ± 0.19 ($\times 10^{-6}$) cm/s, ER 1.02.	*Solution:* – **C_{max}**: 516.80 ± 33.05 ng/mL – **t_{max}**: 4.00 ± 0.36 h – **$t_{1/2}$**: 34.12 ± 2.65 h – **MRT**: 43.80 ± 4.23 h – **AUC_{0-t}**: 7313.65 ± 934.83 ng/mL.h – **Cl**: (2.1 ± 0.4) × 10^{-3} ((mg/kg)/(ng/mL)/h) – **$AUCM_{0-\infty}$**: (4.06 ± 0.72) × 10^{5} ($ng/mL.h^2$) *NPs:* – **C_{max}**: 1052.05 ± 173.11 ng/mL – **t_{max}**: 2.00 ± 0.64 h – **$t_{1/2}$**: 55.95 ± 3.39 h – **MRT**: 65.63 ± 4.47 h – **AUC_{0-t}**: 18021.44 ± 1300.29 ng.h/mL – **Cl**: (7.5 ± 1.5) × 10^{-4} ((mg/kg)/(ng/mL)/h) – **$AUCM_{0-\infty}$**: (1.76 ± 0.69) × 10^{6} ($ng/mL.h^2$)	(Xie et al. 2019)
Doxorubicin and Metformin	III	PLGA-TPGS*	– **Rhodamine-123 accumulation assay** showed an increase between blank NPs and doxorubicin and metformin NPs loaded with PLGA-TPGS by about 2-fold. – **Intracellular ATP content** NPs blank: ATP content 25 nmol/10^6 cells NPs PLGA-TPGS: ATP content 15 nmol/10^6 cells	*None*	(Shafiei-Irannejad et al. 2018)
Metformin HCl	III	– Span 60* – Tween 80*	– **Non everted gut sac** Metformin pure drug: Papp: 4.723 ($\times 10^{-4}$) cm/s Total permeation: 21.860 ± 0.222% Metformin-tween 80: Papp: 6.706 ($\times 10^{-4}$) cm/s Total permeation: 36.524 ± 0.259% Metformin-span 60-tween 80: Papp: 18.239 ($\times 10^{-4}$) cm/s Total permeation: 64.960 ± 0.400%	*None*	(Mady et al. 2021)

Description: PLGA: polyglycolic acid copolymers; TPGS: D-α-tocopheryl polyethylene glycol succinate; CD-PVM/MA: poly(methyl vinyl ether-co-maleic anhydride)-graft-hydroxypropyl-β-cyclodextrin amphiphilic copolymer; ATP: adenosine triphosphate; SPIP: single-pass intestinal perfusion; Papp: apparent permeability coefficient; Papp (A-to-B): apparent permeability in the apical-to-basolateral direction; Papp (B-to-A): apparent permeability in the basolateral-to-apical direction; ER: efflux ratio; C_{max}: maximum concentration in blood; $t_{1/2}$: half-life; t_{max}: time maximum; K_a: Absorption rate constant; K_e: elimination rate constant; AUC: area under curve; AUCM: area under minimum concentration; MRT: mean residence time; Cl: clearance; F_{abs}: absolute bioavailability; F_{rel}: relative bioavailability.

Table 4. NE, SMEDDS, and SNEDDS with P-gp inhibitory effects.

Drug (as P-gp substrate)	BCS	Excipient on NE/ SMEDDS/SNEDDS (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Paeonol	II	– Isopropyl myristate – Cremophor EL35* – Ethanol	**– SPIP** The K_a and Papp of the Paeonol NE group had improved by 1.64- and 0.65-fold in colon compared with the Paeonol solution group. **– Everted gut sac** The Papp of the Peonol NE group had improved by 2-fold compared with the Paeonol solution group. **– Caco-2 cell monolayer** Paeonol solution: Papp (A-to-B) 1.40 ± 0.23 ($\times10^{-6}$) cm/s, Papp (B-to-A) 1.33 ± 0.05 ($\times10^{-6}$) cm/s, ER 0.98 ± 0.14. Paeonol NE: Papp (A-to-B) 2.39 ± 0.26 ($\times10^{-6}$) cm/s, Papp (B-to-A) 1.19 ± 0.18 ($\times10^{-6}$) cm/s, ER 0.57 ± 0.13.	*Suspension:* – **C_{max}**: 1.351 ± 0.130 mg/L – **t_{max}**: 0.08 h – **AUC_{0-t}**: 6.378 ± 0.44 mg.h/L – **$AUC_{0-\infty}$**: 12.828 ± 3.640 mg.h/L – **$t_{1/2\alpha}$**: 0.157 ± 0.082 h – **$t_{1/2\beta}$**: 6.751 ± 3.424 h *NE:* – **C_{max}**: 5.433 ± 1.254 mg/L – **t_{max}**: 0.75 h – **AUC_{0-t}**: 27.244 ± 8.068 mg.h/L – **$AUC_{0-\infty}$**: 28.228 ± 8.684 mg.h/L – **$t_{1/2\alpha}$**: 3.358 ± 0.536 h – **$t_{1/2\beta}$**: 32.471 ± 2.767 h	(Chen et al. 2018)
Etoposide	IV	– Ethyl oleate, medium-chain triglyceride – Polysorbate 80*	**– Caco-2 cell** Polysorbate 80-based SMEDDS showed a 3-fold increase in inhibitory effect on P-gp compared with etoposide solution. **– SPIP** Polysorbate 80-based SMEDDS resulted in a 2.7-fold increase in permeability compared with etoposide solution.	*Suspension:* – **AUC_{0-24}**: 2.20 ± 0.60 h.µg/mL – **C_{max}**: 0.39 ± 0.07 µg/mL – **t_{max}**: 1.00 ± 0.52 h – **F_{abs}**: 25.44 ± 6.94% *SMEDDS:* – **AUC_{0-24}**: 5.46 ± 1.30 h.µg/mL – **C_{max}**: 1.37 ± 0.64 µg/mL – **t_{max}**: 0.83 ± 0.13 h – **F_{abs}**: 63.21 ± 13.75%	(Zhao et al. 2013)
Irinotecan	II	– Capmul MCM-C8 – Cremophor EL* – Pluronic L-121*	**– Caco-2 cell** (by FACS) The enhancement in uptake of fluorescence from 51.2 ± 2.6% for irinotecan solution with rhodamine to as high as 72.4 ± 3.9% for irinotecan with rhodamine in SMEDDS.	*Suspension:* – **t_{max}**: 2 h – **C_{max}**: 1100 ± 197.2 ng/mL – **AUC_{0-t}**: 6516 ± 433.9 ng.h/mL – **$t_{1/2}$**: 2.23 h *SMEDDS:* – **t_{max}**: 6 h – **C_{max}**: 1950 ± 365.5 ng/mL – **AUC_{0-t}**: 27957.5 ± 981.2 ng.h/mL – **$t_{1/2}$**: 5.56 h	(Negi et al. 2013)
Candesartan Cilexetil	II	– Peppermint oil – Cremophor RH40* – Labrasol*	**– Everted gut sac** Candesartan solution: Papp (A-to-B) 1.57 ± 0.185 ($\times10^{-6}$) cm/s, Papp (B-to-A) 1.38 ± 0.388 ($\times10^{-6}$) cm/s, ER 0.88. Candesartan SNEDDS: Papp (A-to-B) 3.12 ± 0.082 ($\times10^{-6}$) cm/s, Papp (B-to-A) 0.77 ± 0.214 ($\times10^{-6}$) cm/s, ER 0.25.	*Tablet (Atacand®):* – **AUC_{0-24}**: 17.23 ± 3.92 µg.h/mL – **AUC_{0-t}**: 18.04 ± 3.97 µg.h/mL – **t_{max}**: 4 h – **C_{max}**: 1.37 ± 0.35 µg/mL – **F_{rel}**: 1% *SNEDDS:* – **AUC_{0-24}**: 25.44 ± 2.48 µg.h/mL – **AUC_{0-t}**: 30.42 ± 3.84 µg.h/mL – **t_{max}**: 3 h – **C_{max}**: 2.4 ± 0.29 µg/mL – **F_{rel}**: 1.69%	(Gurunath et al. 2015)

Description: SPIP: single-pass intestinal perfusion; Papp: apparent permeability coefficient; Papp (A-to-B): apparent permeability in the apical-to-basolateral direction; Papp (B-to-A): apparent permeability in the basolateral-to-apical direction; K_a: absorption rate constant; ER: efflux ratio; C_{max}: maximum concentration in blood; t_{max}: time maximum; $t_{1/2}$: half-life; AUC: area under curve; F_{abs}: absolute bioavailability; F_{rel}: relative bioavailability.

Table 4 summarizes the previous features of NE, SMEDDS, and SNEDDS with P-gp inhibitory effects to enhance the oral absorption and bioavailability of various P-gp inhibitors.

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are lipid-based nanoparticles with a solid matrix, offering alternatives to emulsions, liposomes, and polymeric nanoparticles (Müller et al. 2002). SLNs are formulated from solid lipids, surfactants, and co-surfactants, while NLCs incorporate liquid oils to create imperfect structures that can accommodate higher drug loads and reduce drug expulsion during storage (Duong et al. 2019). Both SLNs and NLCs are produced using physiological and biodegradable lipids, classified as generally recognized as safe, making them safe and biocompatible. These

systems can enhance the solubility and stability of drugs encapsulated in their solid matrices.

SLNs and NLCs can be prepared using various methods such as high-pressure homogenization, emulsion or solvent evaporation, microemulsion, phase inversion, and solvent injection (Duong et al. 2019; Duong et al. 2020). They improve drug absorption and bioavailability, especially for hydrophilic drugs, through several mechanisms, including uptake by M cells (Thanki et al. 2013), lymphatic absorption via chylomicron uptake from enterocytes (Trevaskis et al. 2008; Chalikwar et al. 2012), paracellular transport through tight junction opening (Yao et al. 2015), and receptor-mediated endocytosis and transcytosis (Beloqui et al. 2013). For drugs that are P-glycoprotein (P-gp) substrates, the lipids and surfactants in SLNs and NLCs can also inhibit P-gp efflux, increasing drug permeation (Lasa-Saracibar et al. 2012). SLNs and NLCs have been widely used to encapsulate various drugs, with many of them being P-gp substrates (Estella-Hermoso De Mendoza et al. 2011).

Table 5 summarizes the components and major results of SLNs and NLCs formulations with P-gp inhibitory effects on the enhancement of oral absorption and bioavailability of various P-gp substrates.

Micelles

Micelles are spherical, amphiphilic structures formed through the self-assembly of amphiphilic molecules. They feature a hydrophobic core, which is ideal for encapsulating poorly water-soluble drugs, while the hydrophilic shell stabilizes the core and makes the micelles water-soluble. Micelles are nanosized colloidal dispersions, typically ranging from 10 to 200 nm in diameter, which allows them to evade elimination by the reticuloendothelial system and increases their circulation time. Polymeric micelles are

Table 5. SLNs and NLCs with P-gp inhibitory effects.

Drug (as P-gp substrate)	BCS	Excipient on SLNs/ NLCs (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Raloxifene	II	– Glyceryl monostearate – Compritol 888 ATO – TPGS-1000* – Phospholipid S-100	– **Caco-2 cell** The cellular uptake of raloxifene was increased by 3.18-fold after encapsulation in SLNs.	*Solution:* – **C_{max}**: 53.2 ± 18.0 ng/mL – **K_a**: 0.70 ± 0.54 h^{-1} – **$t_{1/2}$**: 8.96 ± 2.96 h – **t_{max}**: 23 ± 2.45 h – **MRT**: 14.09 ± 5.96 h – **AUC_{0-72}**: 959.2 ± 189.3 ng.h/mL – **$AUC_{0-\infty}$**: 962.9 ± 195.1 ng.h/mL *SLNs:* – **C_{max}**: 216.1 ± 78.3 ng/mL – **K_a**: 1.08 ± 1.21 h^{-1} – **$t_{1/2}$**: 19.10 ± 1.21 h – **t_{max}**: 28.01 ± 3.56 h – **MRT**: 18.80 ± 1.95 h – **AUC_{0-72}**: 4215.5 ± 948.5 ng.h/mL – **$AUC_{0-\infty}$**: 4394.2 ± 987.5 ng.h/mL	(Jain et al. 2022)
Linagliptin	II/ IV	– Palmitic acid – Poloxamer 188* – Tween 80*	– **Everted gut sac** Linagliptin solution: Papp (A-to-B) 10.24 ± 0.32 ($\times 10^{-6}$) cm/s. Linagliptin SLNs: Papp (A-to-B) 18.67 ± 0.74 ($\times 10^{-6}$) cm/s. – **SPIP** Linagliptin solution: Peff 16.32 ± 2.03 ($\times 10^{-6}$) cm/s. Linagliptin SLNs: Peff 28.75 ± 2.76 ($\times 10^{-6}$) cm/s.	*Solution:* – **C_{max}**: 2.03 ± 1.16 µg/mL – **t_{max}**: 4 h – **$t_{1/2}$**: 28.131 ± 2.04 h – **K_e:** 0.0246 ± 0.0017 h^{-1} – **AUC_{0-t}:** 52.09 ± 7.58 µg/mL.h – **$AUC_{0-\infty}$**: 77.252 ± 15.72 µg/mL.h – **$MRT_{0-\infty}$**: 42.767 ± 5.85 h – **F_{rel}**: - *SLNs:* – **C_{max}**: 4.8700 ± 1.76 µg/mL – **t_{max}**: 12 h – **$t_{1/2}$**: 33.1968 ± 2.48 h – **K_e:** 0.0209 ± 0.0015 h^{-1} – **AUC_{0-t}**: 157.95 ± 12.5 µg/mL.h – **$AUC_{0-\infty}$**: 270.9773 ± 23.39 µg/mL.h – **$MRT_{0-\infty}$**: 53.2365 ± 7.13 – **F_{rel}**: 303%	(Shah et al. 2021)

Drug (as P-gp substrate)	BCS	Excipient on SLNs/ NLCs (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Tilmicosin	II	– Stearic acid – Oleic acid – Tween 80*	– **Caco-2 cell monolayers** Tilmicosin solution: Papp (A-to-B) 0.31 ± 0.08 (×10^{-6}) cm/s, Papp (B-to-A) 0.95 ± 0.06 (×10^{-6}) cm/s, ER 3.04. Tilmicosin NLCs: Papp (A-to-B) 0.57 ± 0.03 (×10^{-6}) cm/s, Papp (B-to-A) 0.83 ± 0.03 (×10^{-6}) cm/s, ER 1.45.	*Suspension:* – **t_{max}**: 1.30 ± 0.71 h – **C_{max}**: 1.56 ± 0.14 μg/mL – **$t_{1/2}$**: 11.27 ± 2.11 h – **Vd/F**: 24008.35 ± 6894.42 h – **Cl/F**: 1594.95 ± 241.64 h – **MRT**: 8.09 ± 0.90 h – **AUC_{0-t}**: 10.72 ± 1.15 μg/mL.h *NLCs:* – **t_{max}**: 3.40 ± 0.55 h – **C_{max}**: 1.54 ± 0.29 μg/mL – **$T_{1/2}$**: 11.68 ± 268 h – **Vd/F**: 20159.66 ± 5249.61 h – **Cl/F**: 1217.41 ± 237.18 h – **MRT**: 10.60 ± 1.73 h – **AUC_{0-t}**: 15.26 ± 2.45 μg/mL.h	(Zhang et al. 2020)
Tilmicosin	II	– Lauric acid – Oleic acid – Tween 80*	– **Caco-2 cell monolayers** Tilmicosin solution: Papp (A-to-B) 0.32 ± 0.08 (×10^{-6}) cm/s, Papp (B-to-A) 0.74 ± 0.07 (×10^{-6}) cm/s, ER 2.29. Tilmicosin NLCs: Papp (A-to-B) 0.65 ± 0.10 (×10^{-6}) cm/s, Papp (B-to-A) 1.01 ± 0.07 (×10^{-6}) cm/s, ER 1.56.	*Suspension:* – **t_{max}**: 1.85 ± 0.67 h – **C_{max}**: 1.45 ± 0.88 μg/mL – **AUC_{0-t}**: 32.42 ± 12.86 μg/mL.h – **MRT_{0-t}**: 43.82 ± 4.19 h – **F_{rel}**: - *NLCs:* – **t_{max}**: 2.85 ± 1.53 h – **C_{max}**: 1.51 ± 0.32 μg/mL – **AUC_{0-t}**: 35.23 ± 5.39 μg/mL.h – **MRT_{0-t}**: 42.04 ± 4.90 h – **F_{rel}**: 108.67%	(Sahito et al. 2020)

Description: SPIP: single-pass intestinal perfusion; Papp: apparent permeability coefficient; Papp (A-to-B): apparent permeability in the apical-to-basolateral direction; Papp (B-to-A): apparent permeability in the basolateral-to-apical direction; Peff: effective permeability coefficient; ER: efflux ratio; C_{max}: maximum concentration in blood; $t_{1/2}$: half-life; t_{max}: time maximum; K_a: absorption rate constant; K_e: elimination rate constant; MRT: mean residence time; Vd: volume distribution; Cl: clearance; AUC: area under curve; F_{abs}: absolute bioavailability; F_{rel}: relative bioavailability.

formed when the polymer concentration exceeds the critical micelle concentration (CMC). They offer the advantages of easy drug encapsulation and surface modification.

Drugs can be encapsulated in micelles either by chemical covalent attachment or by physical methods. The chemical method involves covalent cross-linking of drugs with polymers, which enhances circulation kinetics, biodistribution, and accumulation of micelles at target sites, though this method can be complex. Physical methods, such as solvent evaporation, oil-in-water emulsion, direct dissolution, dialysis, and freeze-drying, are simpler and more practical. Several surfactants with P-gp inhibitory activity, such as Tween 80, TPGS, Cremophor EL, and Pluronic 85, are commonly used to prepare micelles, effectively improving the intestinal permeability of P-gp substrates (Zhang et al. 2017).

Encapsulating hydrophobic drugs in micelles not only improves their aqueous solubility but also increases their affinity to the intestinal membrane (Zhao et al. 2021). Micelles are absorbed into systemic circulation through the lymph transport pathway (Ni et al. 2016), and their nano-sized structure enhances active drug uptake across intestinal epithelial cells via transcytosis or endocytosis (X. Wang et al. 2020). Furthermore, micelles with neutral or positive charges exhibit a higher affinity for intestinal epithelial cells than negatively charged ones, which contributes to improved transport across the intestinal barrier. Additionally, drug residence time in systemic circulation can be prolonged with micelles (Hu et al. 2017).

Table 6 summarizes the components and major results of micelles with P-gp inhibitory effects on the enhancement of oral absorption and bioavailability of various P-gp substrates.

Liposomes

Liposomes (Figure 4A.e) are spherical vesicles with bilayer membranes, typically composed of phospholipids. They can encapsulate hydrophilic drugs in their aqueous core and hydrophobic drugs within the bilayer membrane. Liposomes improve the oral absorption of hydrophobic drugs through various mechanisms, including mucoadhesion, passage through mucus layers, enhanced permeability across the intestinal epithelium, endocytosis, uptake by M cells, and lymphatic absorption via chylomicron uptake (Zhang et al. 2017).

Table 6. Micelles with P-gp inhibitory effects.

Drug (as P-gp substrate)	BCS	Excipient on micelles (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Paclitaxel (PTX)	IV	OPPC*	**– Caco-2 cell monolayer** The Papp (A-to-B) of PTX micelles had improved by 2.7-fold compared with Taxol®. The Papp (B-to-A) of PTX micelles decreased 2-fold compared to Taxol®. **– SPIP** Taxol®: Peff 4.27 ± 0.34 ($\times10^{-4}$) cm/s in the duodenum and Peff 3.58 ± 0.82 ($\times10^{-4}$) cm/s in the jejunum. PTX micelles: Peff 12.73 ± 2.27 ($\times10^{-4}$) cm/s in the duodenum and Peff 14.96 ± 0.86 ($\times10^{-4}$) cm/s in the jejunum.	*Taxol®:* – **C_{max}**: 0.17 ± 0.03 μg/mL – **t_{max}**: 0.10 ± 1.68 h – **AUC_{0-24}**: 1.22 ± 0.18 μg.h/mL – **$t_{1/2}$**: 5.40 ± 1.83 h – **MRT**: 8.73 ± 1.12 h – **Cl**: 0.71 ± 0.19 h – **F**: 5.68 ± 0.84% *Micelles:* – **C_{max}**: 0.55 ± 0.09 μg/mL – **t_{max}**: 4.00 ± 2.00 h – **AUC_{0-24}**: 6.75 ± 1.66 μg.h/mL – **$t_{1/2}$**: 3.64 ± 0.51 h – **MRT**: 10.27 ± 0.35 h – **Cl**: 0.15 ± 0.05 h – **F**: 31.45 ± 7.73%	(Qu et al. 2019)
Paclitaxel (PTX)	IV	Gallic acid-chitosan-TPGS* copolymer	**– Caco-2 cell monolayer** The permeation of PTX micelles increased 2-fold compared to PTX suspension.	*Taxol®:* – **C_{max}**: 78 ± 34 ng/mL – **t_{max}**: 1.5 ± 0 h – **$t_{1/2}$**: 12.7 ± 3.4 h – **Vz/F:** 282 ± 93 L/kg – **Clz/F:** 15.5 ± 3.1 L/h/kg – **AUC_{0-t}**: 622 ± 126 ng/mL.h – **$AUC_{0-\infty}$**: 665 ± 129 ng/mL.h – **F_{rel}**: 100% *Micelles:* – **C_{max}**: 308 ± 103 ng/mL – **t_{max}**: 3.0 ± 0 h – **$t_{1/2}$**: 19.8 ± 10.4 h – **Vz/F:** 109 ± 44 L/kg – **Clz/F:** 4.0 ± 0.4 L/h/kg – **AUC_{0-t}**: 2198 ± 93 ng/mL.h – **$AUC_{0-\infty}$**: 2528 ± 294 ng/mL.h – **F_{rel}**: 380%	(Wang et al. 2020)
Dabigatran etexilate (DBAE)	II	– Soluplus – TPGS*	**– Caco-2 cell** DBAE micelles compared with DBAE suspension were enhanced about 2.1-, 3.2-, and 7.8-fold at 2 hours and obviously increased 3.1-, 3.5-, and 5.2-fold after oral administration in the duodenum, jejunum, and ileum at 4 hours, respectively.	*Solution:* – **AUC_{0-t}**: 1329.526 ± 144.096 ng/mL.h – **MRT_{0-t}**: 3.15 ± 0.218 h – **t_{max}**: 0.6 ± 0.279 h – **C_{max}**: 455.771 ± 20.656 ng/mL – **F_{rel}**: - *Micelles:* – **AUC_{0-t}**: 4485.182 ± 708.893 ng/mL.h – **MRT_{0-t}**: 3.296 ± 0.198 h – **t_{max}**: 0.867 ± 0.298 h – **C_{max}**: 1331.492 ± 273.469 ng/mL – **F_{rel}**: 337.35%	(Hu et al. 2017)
Doxorubicin	III	Lysine-linked ditocopherol PEG 2000 succinate (PLV_{2K})*	**– SPIP** K_a of doxorubicin micelles significantly increased compared with doxorubicin solution by 3.19, 1.61, and 1.80-fold in the duodenum, jejunum, and ileum, respectively. Peff of doxorubicin micelles was 3.7, 1.8, and 2.0-fold higher than doxorubicin solution in the duodenum, jejunum, and ileum, respectively. **– Caco-2 cell monolayer** Doxorubicin solution: Papp (A-to-B) 7.48 ± 2.18 ($\times10^{-8}$) cm/s. Doxorubicin micelles: Papp (A-to-B) 35.75 ± 2.30 ($\times10^{-8}$) cm/s.	*Solution:* – **C_{max}**: 167.9 ± 149.6 ng/mL – **t_{max}**: 0.15 ± 0.04 h – **$t_{1/2}$**: 9.83 ± 6.13 h – **AUC_{0-t}**: 187.19 ± 78.16 ng/mL.h – **$AUC_{0-\infty}$**: 329.41 ± 127.2 ng/mL.h *Micelles:* – **C_{max}**: 167.9 ± 149.6 ng/mL – **t_{max}**: 0.15 ± 0.04 h – **$t_{1/2}$**: 9.83 ± 6.13 h – **AUC_{0-t}**: 187.19 ± 78.16 ng/mL.h – **$AUC_{0-\infty}$**: 329.41 ± 127.2 ng/mL.h	(Wang et al. 2015)

Description: OPPC: N-octyl-N'-phthalyl-O-phosphoryl chitosan; SPIP: single-pass intestinal perfusion; Papp: apparent permeability coefficient; Papp (A-to-B): apparent permeability in the apical-to-basolateral direction; Papp (B-to-A): apparent permeability in the basolateral-to-apical direction; Peff: effective permeability coefficient; ER: efflux ratio; C_{max}: maximum concentration in blood; $t_{1/2}$: half-life; t_{max}: time maximum; K_a: absorption rate constant; MRT: mean residence time; Vz: volume distribution; Clz: clearance rate; AUC: area under curve; F_{rel}: relative bioavailability.

Table 7. Liposomes with P-gp inhibitory effects.

Drug (as P-gp substrate)	BCS	Excipient on liposomes (*as P-gp Inhibitor)	Outcomes		References
			Permeability	Pharmacokinetic	
Docetaxel	IV	– Dipalmitoylphosphatdly choline – Phosphatidylcholine – Cholesterol – Oleic acid – Folate grafted thiolated chitosan*	**– Non-everted gut sac** Docetaxel solution: Papp (A-to-B) 0.08 ± 0.01 ($\times10^{-6}$) cm/s, Papp (B-to-A) 0.48 ± 0.7 ($\times10^{-6}$) cm/s, ER 5.78. Docetaxel liposome: Papp (A-to-B) 0.77 ± 0.1 ($\times10^{-6}$) cm/s, Papp (B-to-A) 1.82 ± 0.1 ($\times10^{-6}$) cm/s, ER 2.36.	*Solution:* – **C_{max}**: 41.78 ± 2.43 ng/mL – **t_{max}**: 3.03 ± 1.82 h – **$t_{1/2}$**: 33.04 ± 3.89 h – **AUC_{0-96}**: 963.30 ± 14.31 ng/mL.h – **$AUCM_{0-96}$**: 30410.01 ± 15.44 ng/mL.h – **MRT_{0-96}:** 31.57 ± 65.32 h – **F**: 1% *Liposome:* – **C_{max}**: 174.59 ± 6.71 ng/mL – **t_{max}**: 2.02 ± 2.43 h – **$t_{1/2}$**: 72.18 ± 6.51 h – **AUC_{0-96}**: 5956.98 ± 38.54 ng/mL.h – **$AUCM_{0-96}$**: 225353.19 ± 28.86 ng/mL.h – **MRT_{0-96}:** 37.83 ± 5.32 h – **F**: 6.2%	(Sohail et al. 2016)
Paclitaxel (PTX)	IV	– Pluronic F127*-polyethylenimine copolymer – Sodium cholate – Soybean phosphatidylcholine	**– Caco-2 cell by fluorescence microscopy** In PTX liposome, the amount of Rhodamine-123 in the cells increased compared to the pure drug. **– SPIP** PTX solution: Peff 0.59 ± 0.17 ($\times10^{-6}$) mL/min. PTX liposome: Peff 7.57 ± 1.27 ($\times10^{-6}$) mL/min.	*Solution:* – **$AUC_{0-\infty}$**: 0.43 ± 0.014 mg/L.h – **C_{max}**: 0.067 ± 0.010 mg/mL – **$MRT_{0-\infty}$:** 8.48 ± 1.65 h – **Clz**: 46.66 ± 4.19 h – **F**: 8.75 ± 1.57% *Liposome:* – **$AUC_{0-\infty}$**: 1.86 ± 0.17 mg/L.h – **C_{max}**: 0.22 ± 0.020 mg/mL – **$MRT_{0-\infty}$:** 18.86 ± 2.86 h – **Clz**: 10.76 ± 1.22 h – **F**: 37.91 ± 4.09%	(Li et al. 2017)
Lovastatin	II	– Phosphatidylcholine*, – Cholesterol – 1,2-distearoyl-sn-glycero-3-phospho-10-rac-glycerol sodium salt – TPGS*	**– Caco-2 cell monolayer** The Papp of Lovastatin liposome (A-to-B) direction increased by 1.23-fold and in the secretory (B-to-A) direction by 3.53-fold, compared with lovastatin solution.	*None*	(Romana et al. 2020)

Description: SPIP: single-pass intestinal perfusion; TPGS: D-α-tocopheryl polyethylene glycol succinate; Papp: apparent permeability coefficient; Papp (A-to-B): apparent permeability in the apical-to-basolateral direction; Papp (B-to-A): apparent permeability in the basolateral-to-apical direction; Peff: effective permeability coefficient; ER: efflux ratio; C_{max}: maximum concentration in blood; $t_{1/2}$: half-life; t_{max}: time maximum; MRT: mean residence time; Clz: clearance rate; AUC: area under curve; AUCM: area under minimum concentration; F: bioavailability.

Additionally, phospholipids and other liposomal components can inhibit P-gp, further enhancing the permeability of P-gp substrates. However, liposomes are unstable in the gastrointestinal environment due to phospholipid aggregation at low pH and enzyme degradation, such as by pancreatic lipase. To address this, liposomes are modified with PEGylation, mucin, or polymer coatings to increase stability (Thanki et al. 2013). Several P-gp substrates have been encapsulated in liposomes to enhance drug absorption and bioavailability.

Table 7 summarizes the previous features of liposomes with P-gp inhibitory effects to enhance the oral absorption and bioavailability of various P-gp inhibitors.

Conclusion

The review highlights the use of pharmaceutical excipients as P-gp inhibitors in oral drug delivery nanosystems, which significantly enhance permeability and bioavailability. These excipients are sourced from surfactant and polymer groups like TPGS and poloxamer 188. All nanosystems incorporating pharmaceutical excipients as P-gp inhibitors show potential in enhancing the permeability and bioavailability of oral drugs when compared to conventional formulations. The effectiveness of these systems has been evaluated through in vitro (Caco-2 cells), ex vivo (everted gut sac), in situ (SPIP), and in vivo (AUC) methods. The pharmaceutical excipients have been commonly utilized in oral drug formulations to improve solubility and dissolution rates, which contribute to enhanced bioavailability. However, the application of pharmaceutical excipients as P-gp inhibitors in oral drug delivery nanosystems is still limited. In the future, this review could serve as a useful reference for choosing suitable pharmaceutical excipients as P-gp inhibitors and for selecting the appropriate methods to evaluate the permeability performance of oral drugs.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
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Data availability

All of the data that support the findings of this study are available in the main text.

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