P-Glycoprotein Inhibitors

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P-gp inhibitors are compounds that block or bypass P-gp efflux. The concurrent administration of P-gp inhibitors with P-gp substrates can prevent the expulsion of these substrates and increase their therapeutic effects. Researchers have identified, studied, and evaluated various P-gp inhibitors, including small molecules, natural products, and pharmaceutically inert excipients.

P-gp inhibitors permeability drug delivery solid lipid nanoparticles micelles liposomes polymeric nanoparticles emulsions

1. Introduction

The role of P-gp efflux in the pharmacokinetics of P-gp substrates has been increasingly appreciated [1]. It is well-known that in the human intestine, P-gp is highly expressed in epithelial cells of the colon and ileum (apical side). The expression level in the jejunum, duodenum, and stomach is relatively reduced compared to the ileum [2]. During oral absorption, drug properties (solubility and permeability) and P-gp efflux across the intestinal apical membrane determine the rate and amount of drug diffusing across the basolateral membrane to enter the general circulation [3]. Therefore, P-gp efflux screening is a key step in the drug discovery stage, aided by in vitro, in situ permeability studies and transgenic mdr knockout mice. It has been found that in vitro and in situ P-gp function for a given drug is well correlated with in vivo P-gp activity [4].

To overcome these problems, various P-gp inhibitors have been widely studied. They include small molecule drugs (active pharmaceutical ingredients (APIs) and new chemical entities (NCEs)), natural constituents, and pharmaceutically inert excipients [5][6][7]. In general, P-gp inhibitors can block drug-binding sites competitively, non-competitively, or allosterically, interfere with ATP hydrolysis, and alter the integrity of cell membranes [8]. In particular, for oral drug delivery, these inhibitors improve intestinal absorption, tissue distribution, and reduce substrate metabolism and elimination, resulting in enhanced pharmacokinetic properties and oral bioavailability [8].

Small molecule P-gp inhibitors can be co-administered with P-gp substrates to enhance their oral bioavailability. However, this approach can result in drug-drug interactions and increased side effects because these small molecules have their own pharmacological activities. On the other hand, nonspecific P-gp inhibitors such as polymers, surfactants, and lipid-based excipients can be alternatives to these small molecules. They are safe, pharmaceutically acceptable, and are not absorbed by the gut [9]. They are incorporated in pharmaceutical formulations and indirectly inhibit P-gp by affecting the lipid membrane. Numerous formulations with inherent P-gp

inhibitory activity have been studied for many years. These include micelles, emulsions, liposomes, microspheres, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and solid dispersions [10][11]. In addition to the P-gp inhibitory effect of the excipients, the formulations themselves can improve drug solubility and affinity to the intestinal membrane, promote paracellular passage and endocytic uptake, and enable the lymph transport pathway, resulting in improved oral bioavailability [12][13].

2. Mechanism of P-gp Efflux and Functions of P-gp

P-gp inhibitors are often required to reduce the activity of P-gp. For oral drug administration, inhibiting P-gp can increase drug absorption and bioavailability and thus its therapeutic effects [14]. P-gp inhibition in the BBB can increase the transport of some brain-targeted drugs through the BBB and improve its effects in the brain [15]. In the case of an HIV treatment, P-gp inhibitors are useful to increase drug loading of the fetus shortly before birth, which can reduce the frequency of HIV transmission during birth [16]. P-gp inhibitors can reverse the MDR phenomenon associated with P-gp efflux, resulting in the improved efficiency of chemotherapeutic agents and enhanced pharmacokinetic and pharmacodynamic profiles of drugs.

In oral drug delivery, some models have been used to determine the drug permeability and evaluate the P-gp efflux, such as Caco-2 or Madin Darby canine kidney (MDCK)-MDR1 cell monolayers, inside-out vesicles, single-pass intestinal perfusion (SPIP), and everted gut sac permeability studies. P-gp efflux can be determined by comparing the permeability of a drug between a test sample (a formulation) and a control sample (usually a drug solution) [17][18][19].

3. Classification of P-gp Inhibitors

P-gp inhibitors are compounds that block or bypass P-gp efflux. The concurrent administration of P-gp inhibitors with P-gp substrates can prevent the expulsion of these substrates and increase their therapeutic effects. Researchers have identified, studied, and evaluated various P-gp inhibitors, including small molecules, natural products, and pharmaceutically inert excipients [20]. Additionally, prodrugs, synthetic peptides, and P-gp expression suppressors are also potential approaches to overcome P-gp efflux [21].

A summary of the P-gp inhibitors is presented in **Table 1**.

Table 1. Classification of P-glycoprotein inhibitors.

Classification		Examples
Small molecules	First generation	Verapamil, cyclosporine, trifluoperazine, quinidine, reserpine, yohimbine, tamoxifen, toremifene, and vincristine
	Second generation	Dexverapamil and PSC 833 (valspodar)

Classification		Examples
	Third generation	VX-710 (biricodar), GF120918 (elacridar), LY335979 (zosuquidar), XR9576 (tariquidar), R101933 (laniquidar), WK-X-34, and OC144-093 (ontogeny)
	Alkaloids	Glaucine, pervilleine, berberine, kopsiflorine, lobeline, cepharanthine, ibogaine, theobromine
Natural products	Flavonoids	Quercetin, morin, phloretin, rhamnetin, plagiochin E, daidzin, procyanidine, rotenone
	Coumarins	Decursinol, bergaptol, galbanic acid, farnesiferol
	Terpenoid	Citral, latilagascene, paraliane, pepluanin A, jolkinol B, euphoportlandol lhelioscopinolide, tuckeyanols, euphotuckeyanol, isopimaric acid, totarol
	Saponins	Gracillin, tenacissimoside A, karavilagenin C, balsaminol, ginsenoside F1, protopanaxatriol
	Peptides	Discodermolide, kendarimide, hapalosin, nocardioazine
	Resins	Gambogic acid, orizabin
	Miscellaneous natural compounds	Acetoxy cavicolacetate, arctigenin, pheophorbide, porphyrin, cannabinol, gomisin, pregomisin, phenylbutanoid
	Surfactants	Polysorbates: polysorbate 80, 20 Sucrose esters: sucrose monolaurate Tocopheryl ester: TPGS PEG esters: Cremophor EL, Solutol HS-15, Labrasol, Softigen 767, Myrj 52, Gelucire 44/14 PEG ethers: Brij 78 Other: sodium 1,4-bis (2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate (AOT), cetyltrime-thylammonium bromide (CTAB)
Pharmaceutical excipients	Polymers	Natural polymers: dextrans, agar, gellan gum, gum arabic, gum traganth, guar gum, carrageenan gum, xanthan gum, alginates, chitosan Amphiphilic diblock copolymers: methoxyPEG-block-polycaprolactone (MePEG-b-PCL), Soluplus Pluronic block copolymers: poloxamer 407 and 188
	Others	Glycerides: monoolein (Peceol^{TM}), monostearin Phospholipids: 8:0 PC, 10:0 PC Methylated cyclodextrin

TPGS: α-tocopheryl polyethylene glycol-1000-succinate, PEG: polyethylene glycol.

4. Recently Developed Formulations to Bypass P-gp and Enhance Oral Bioavailability of P-gp Substrates

In addition to P-gp inhibitory effects due to the presence of P-gp inhibitors in their components, which result in increased intestinal absorption and bioavailability of P-gp substrates, these drug delivery systems, particularly nanocarriers, can also enhance oral bioavailability by various effects [22]. (1) They increase drug solubility, dissolution, and affinity to the intestinal membrane, leading to an increase in drug absorption by enterocytes [5]. Most drug delivery systems can also protect drugs from degradation in the gastrointestinal tract [23]. (2) Some formulations can improve mucoadhesion due to the interaction between the nanocarrier (positive charge) and mucin (negative charge) [24]. (3) Nanocarriers may interact with tight junction proteins and modulate tight junctions in the intestinal epithelium, resulting in paracellular transport [25]. (4) Receptor-mediated endocytosis and the transcytosis of enterocytes can enhance the transcellular transport of nanocarriers [26]. Particles <500 nm in size can be absorbed by intestinal enterocytes and bypass P-gp efflux, making this route an essential transport pathway for nanocarriers [27]. The endocytosis mechanisms of drug delivery systems can be explored by using the everted intestinal ring model. (5) Some nanocarriers, such as SLNs, NLCs [22], polymer–lipid hybrid nanoparticles (PLHNs) [28], and micelles [27], can be phagocytosed by microfold cells (M cells). These are specialized cells in the lymphoid tissue of Peyer's patches in the small intestine. In other parts of the gastrointestinal tract, M cells are located in the mucosa-associated lymphoid tissue. They allow the transport of microbes and small particles across the epithelial cell layer. After the selective endocytosis of antigens, M cells transport them to intraepithelial macrophages and lymphocytes prior to their migration to lymph nodes [29]. Thus, the drug can bypass the P-gp efflux and liver metabolism. (6) Another effect that occurs with various lipid-based drug delivery systems is lymphatic absorption from enterocytes (mediated by lipase and chylomicron uptake). It is one of the major absorption mechanisms for drugs encapsulated in SLNs, NLCs, emulsions, and liposomes [30][31]. Lipase digests triglycerides in the stomach to form crude emulsified lipid systems. They are subsequently exposed to bile salts, cholesterol, and pancreatic lipase and further digested to form mixed micelles of the lipidic system containing drugs. Then, these micelles are absorbed by enterocytes and converted to chylomicrons, which can be transported via the mesenteric lymph to enter the lymphatic transport system. The chylomicrons ultimately enter the systemic circulation via lymphatic drainage at the thoracic duct [32].

Different formulations have been developed and employed to enhance the oral absorption and bioavailability of various P-gp substrates. The following sections describe the recent development of pharmaceutical formulations for the oral delivery of a wide range of P-gp substrates.

4.1. Emulsion, Self-Micro, and Nano Emulsifying Drug Delivery Systems

Emulsions are colloidal systems prepared from two immiscible liquids with force and the addition of surfactants, in which one phase is dispersed as tiny droplets in the other phase [33]. The dispersed phase is also called the discontinuous phase or internal phase. The outer phase is also termed as the continuous phase, external phase, or dispersion medium. The surfactants have affinities for both phases and are located on the interfacial surface of the two liquids to stabilize the emulsions. Two types of emulsions are oil-in-water and water-in-oil emulsions,

depending on the volume ratio of the two liquids. Methods used to prepare emulsions include ultrasonication, high-pressure homogenization, microfluidization, phase inversion temperature, and spontaneous emulsification [34]. SMEDDS and SNEDDS are lipid-based nanocarriers that spontaneously emulsify to form fine oil-in-water emulsions after exposure to gastrointestinal fluids. SMEDDS and SNEDDS are stable mixtures of oil, surfactants, and cosurfactants. SMEDDS contain a lower percentage of lipids and a higher percentage of hydrophilic surfactants and cosurfactants compared with SNEDDS. SMEDDS usually form thermodynamically stable emulsions <100 nm in size. Emulsions derived from SNEDDS range in size from 100 to 250 nm. Emulsions, SMEDDS, and SNEDDS have been widely used as drug delivery systems to enhance the oral absorption and bioavailability of various lipophilic drugs [35]. These benefits are attributed to the endocytosis of enterocytes, paracellular transport, and lymphatic absorption via chylomicron uptake. In addition, the lipids and surfactants used for the preparation of emulsions, SMEDDS, and SNEDDS may have P-gp inhibitory effects, which considerably reduce P-gp efflux and increase the absorption of P-gp substrates.

4.2. Liposomes

Liposomes are spherical vesicles composed of bilayer membranes, such as those formed by phospholipids. They can incorporate hydrophilic drugs into the water-soluble central compartment and hydrophobic drugs into the bilayer membrane [36]. Liposomes can enhance oral absorption of hydrophobic drugs through several mechanisms that include mucoadhesion, translocation across mucus layers, improved permeation across the enteric epithelia, endocytosis, uptake by M cells, and lymphatic absorption via chylomicron uptake [37]. In addition, phospholipids and other components in liposomes can inhibit P-gp to further improve the permeability of P-gp substrates. However, liposomes are unstable in the harsh gastrointestinal environment because phospholipids aggregate at low pH and with the presence of enzymes, such as pancreatic lipase. Therefore, liposomes are modified by PEGylation, mucin coating, and polymer coating [22]. Some P-gp substrates have been encapsulated in liposomes to improve drug absorption and oral bioavailability.

4.3. SLNs and NLCs

SLNs and NLCs are lipid-based nanoparticles with a solid matrix, which have emerged as alternatives to emulsions, liposomes, and polymeric nanoparticles [38]. SLNs are prepared from solid lipids, surfactants, and co-surfactants. In contrast, in NLCs, liquid oils are added to create imperfect structures that can accommodate more drug [39]. NLCs can increase drug loadings and reduce drug expulsion during storage compared to SLNs. SLNs and NLCs are produced from physiological and biodegradable lipids and other generally recognized as safe (GRAS) materials. Therefore, they are both safe and biocompatible. They can also increase the solubility and stability of drugs encapsulated in solid matrices. SLNs and NLCs can be prepared by various methods that include high-pressure homogenization, emulsion/solvent evaporation, microemulsion, phase inversion, and solvent injection [40][41][42]. SLNs and NLCs can enhance drug absorption and the bioavailability of hydrophilic drugs through several mechanisms, such as uptake by M cells [22], lymphatic absorption from enterocytes via chylomicron uptake [30], paracellular transport through tight junction opening [43], and receptor-mediated

endocytosis and transcytosis of enterocytes [26]. In the case of P-gp substrates, lipids and surfactants in SLNs and NLCs could also inhibit P-gp efflux and increase drug permeation [44].

4.4. Micelles

Micelles are spherical amphiphilic structures formed by the self-assembly of amphiphilic molecules. They have a hydrophobic core that is suitable for the encapsulation of poorly water-soluble drugs. A hydrophilic shell can stabilize the hydrophobic core and make the micelles water-soluble [45]. Micelles are nanosized colloidal dispersions with a diameter of 10–200 nm, which avoids elimination by the reticuloendothelial system and increases their circulation time [46]. Polymeric micelles are produced by increasing the polymer concentration above the corresponding CMC. Micelles have the advantages of easy drug encapsulation and easy surface manipulation. Drugs can be encapsulated by chemical covalent attachments or physical methods. In chemical methods, the drugs are covalently cross-linked with polymers, which considerably improves circulation kinetics, biodistribution, and the accumulation of micelles at target sites. However, cross-linking chemical reactions can be challenging and complicated. However, physical methods are practical and simpler. Several widely used techniques include solvent evaporation, oil-in-water emulsion, direct dissolution, dialysis, and freeze-drying [47]. Many surfactants with P-gp inhibitory activity can be used for the preparation of micelles. These include Tween 80, TPGS, Cremophor EL, and Pluronic 85. They can effectively improve the intestinal permeability of P-gp substrates.

4.5. Polymeric Nanoparticles (NPs)

Polymeric NPs are nano-colloidal systems produced from different polymers. They have been widely used for the oral delivery of various chemotherapeutic agents. Polymeric NPs have the advantages of high stability in the gastrointestinal tract and the ability to encapsulate a variety of drug molecules [48]. Polymers used for the preparation of polymeric NPs include natural polymers, such as chitosan, gelatin, dextran, albumin, and alginate, and synthetic biodegradable polymers that include polylactic acid, polyglycolic acid, polylactic and polyglycolic acid copolymers (PLGA), polyethylene imine (PEI), polyalkyl cyanoacrylate (PACA), and PCL [49]. Some polymeric NPs, such as chitosan, typically have mucoadhesive properties that increase their residence time and diffusion in the mucus. They are mainly absorbed in the gastrointestinal tract via endocytosis, such as clathrin-dependent endocytosis for various chitosan and PLGA-NPs. Phagocytosis by M cells is also involved in the absorption of polymeric NPs via lymphatic organs [50]. In addition, some components in polymeric NPs can open tight junctions to increase the paracellular transport of drugs, such as chitosan and its derivatives [48]. Many P-gp substrates have been encapsulated into polymeric micelles to bypass P-gp efflux, thereby enhancing oral bioavailability.

4.6. Other Pharmaceutical Formations for Inhibition of P-gp

In addition to the drug delivery system discussed above, other pharmaceutical formulations can also inhibit or bypass P-gp efflux and enhance drug absorption and oral bioavailability. These include microspheres, solid dispersions, and dendrimers. Microspheres are spherical microparticles 1–1000 μm in size that incorporate drugs within their core. Solid dispersions are dispersions of drugs in solid matrices of polymers or small molecules. The dispersed state can be eutectic mixtures, amorphous/crystalline suspensions, or crystalline/glass solutions [51].

Dendrimers are tree-like branched structures that are used in various targeted drug delivery systems. They consist of an initial core, interior layers with repeating units, and an exterior with terminal functionality [52].

Features of the pharmaceutical formulations in 4.1-4.6 are summarized in Tables 2-6 of the articles.

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