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•Review•

# Probing the new strategy for the oral formulations of taxanes: changing the method with the situation

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**[ABSTRACT]** The first-generation taxanes (including paclitaxel and docetaxel) are widely used for the treatment of various cancers in clinical settings. In the past decade, a series of new-generation taxanes have been developed which are effective in the inhibition of tumor resistance. However, intravenous (i.v.) infusion is still the only route of administration, and may result in serious adverse reactions with respect to the utilization of Cremophor EL or Tween-80 as solvent. Besides, the dosing schedule is also limited. Therefore, oral administration of taxanes is urgently needed to avoid the adverse reactionss and increase dosing frequency. In this review, we first outlined the discovery and development of taxane-based anticancer agents. Furthermore, we summarized the research progress on the oral formulations of taxanes and proposed some thoughts on the future development of oral taxane formulations.

**[KEY WORDS]** Taxanes; Oral delivery; Oral bioavailability; Anti-tumor

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## Introduction

Nowadays, cancer is still the most serious threat to human health, leading to about 8.2 million annual deaths worldwide [1]. Current cancer treatment involves chemotherapy, surgical procedures, immunotherapy, and radio-therapy, where chemotherapy is one of the most common strategies used. In spite of the advances made in chemotherapy, poor tumor targeting, severe dose-related adverse effects, and various complications often cause treatment failure [2, 3].

Taxanes is a type of terpenoid compounds with unique taxane skeletons in structure. Notably, paclitaxel (PTX), docetaxel (DTX), and cabazitaxel (CTX) were approved by the FDA and are currently used to treat a variety of cancers. Furthermore, a series of new-generation taxanes have been developed to cope with tumor resistance. With focused efforts in the research of taxanes for treatment of cancer over the past several decades, nine types of formulations, such as Taxol®, Taxotere®, Jevtana® and Abraxane®, are now available in the commercial market [4, 5].

Currently, the administration route of taxanes is mainly restricted to intravenous injection (i.v.) in clinical settings. Some solubilizers need to be added into the formulations of taxanes due to poor water solubility. For instance, PTX, which is commercially available in the market under the brand name of Taxol®, utilizes Cremophor EL and ethanol as solvent. Similarly, DTX injection (Taxotere®), utilizes Tween-80 and ethanol as solvent. But the addition of solubilizers may exert adverse reactions like hypersensitivity. The narrow treatment windows and non-specific distribution after entry of drugs into systemic circulation also lead to severe toxicities, such as myelosuppression, neutropenia, and neurotoxicity [6, 7]. Furthermore, these formulations are physically unstable and therefore should be prepared 6 h in advance before administration. To recover from serious adverse reactions, patients usually need to be less frequently administered, which may affect the clinical efficacy of these formulations and limit their use.

Oral delivery is supposed to be a preferred route of administration for chemotherapy drugs, in light of good patient compliance [8], convenient drug administration, and low-cost therapy [9]. Hence, oral delivery of chemotherapeutics has received increased research interests, and now more than 20 oral chemotherapeutic drugs are commercially available [10]. However, due to (i) low water solubility [11]; (ii) low permeability in the intestinal tract caused by P-gp-mediated efflux [12, 13] and (iii) extensive first-pass effect [14], oral administration of taxanes is limited. Taxanes contribute to the largest sales volume of the current clinical anticancer drugs, while there are no oral formulations of taxanes available in China.

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Therefore, it is urgent to develop effective oral taxane formulations. With oral taxanes, “chemotherapy at home” would be realized. In the present review, we first outlined the development of taxanes, including their discovery, antitumor mechanism of action, progress, limitations, and challenges. Then, a series of strategies to facilitate oral delivery of taxanes were summarized. Finally, we gave some thoughts on the future development of oral taxane formulations .

## Development Process of Taxanes

### *The progress of classical taxanes*

In the early 1960s, paclitaxel, a natural terpenoid compound, was isolated from the bark of European yew trees [15]. Then, a boom of researching taxane anticancer drugs was launched around the world. Taxanes are typical cytotoxic drugs with high-efficiency and broad-spectrum anti-tumor activity, which can bind with tubulin subunits to inhibit microtubule dynamics, inducing cycle arrest of tumor cells in the $G_2$/M phase. It can also induce tumor cell apoptosis by activating multiple signal transduction pathways [16, 17].

The first-generation taxanes includes paclitaxel and docetaxel. PTX (marketed as Taxol®, Fig. 1), was the first compound in this chemical group that was approved by the FDA in 1992 and introduced into clinical use in 1994 for the treatment of ovarian cancer [18]. Nowadays, PTX exhibits great antineoplastic efficacy against ovarian cancer, breast cancer, non-small cell lung cancer and AIDS-related Kaposi’s sarcoma. DTX is a semi-synthesized taxane derivative, which was modified based on noncytotoxic precursor compound 10-deacetylbaccatine III (10-DAB III) extracted from European yew tree and approved by the FDA in 1996 [19]. DTX is marketed as Taxotere® and the first treartment for patients with breast cancer. Later, cabazitaxel, as s second-generation taxane (now marketed as Jevtana®), overcame the drug resistance of paclitaxel and exhibited excellent clinical efficacy. It was approved by the FDA in 2010 for the treatment of hormone-resistant metastatic prostate cancer [20].

### *The advance of new-generation taxanes*

In recent years, PTX and DTX exert excellent anti-tumor efficacy, but such therapies face problems such as lack of tumor specificity and multi-drug resistance (MDR). CTX exhibits improved potency against MDR-expressing cells and tumors, but its clinical application is limited to prostate cancer so far. Hence, scientists are actively continuting to investigate new taxane anticancer agents. The third-generation taxanes were modified at the C2, C10, and C3′ positions to further overcome tumor resistance. Among them, tesetaxel and larotaxel are currently undergoing clinical evaluation in light of their outstanding properties [17]. Tesetaxel is one of the new types of oral semi-synthetic taxanes that can overcome P-gp-mediated multidrug resistance *in vitro* and *in vivo*. Phase I and II trials of it in solid tumors have been completed and phase III trial in metastatic breast cancer is now conducting [21, 22]. Larotaxel is a semi-synthetic diastereomer of 10-DABIII, which also exhibits effective inhibitory effects against tumor resistance. It is under clinical trials as a single agent or in combination therapy for urethral bladder cancer, advanced pancreatic cancer, advanced nonsmall-cell lung cancer (NSCLC) and metastatic breast cancer [23, 24]. Then, various new-generation taxanes emerged, such as SB-T-1214, with modifications at positions C10 and C13, which exhibits remarkable efficacy against drug resistance in preclinical studies. Most importantly, it can specifically target tumor-specific cancer stem cells (CSCs) by inhibiting some stemness-related signaling pathways and/or promoting their differentiation [25, 26].

Over the last decades, the structure of taxanes has been optimized to improve tumor specificity and inhibit drug resistance from generation to generation. However, intravenous injection is still the main route of administration, which may cause safety problems and reductions in dosing frequency. Therefore, oral administration of taxanes which acts as a safe and convenient delivery route is strongly needed, especially the strategies to increase the absorption of oral taxane formu-

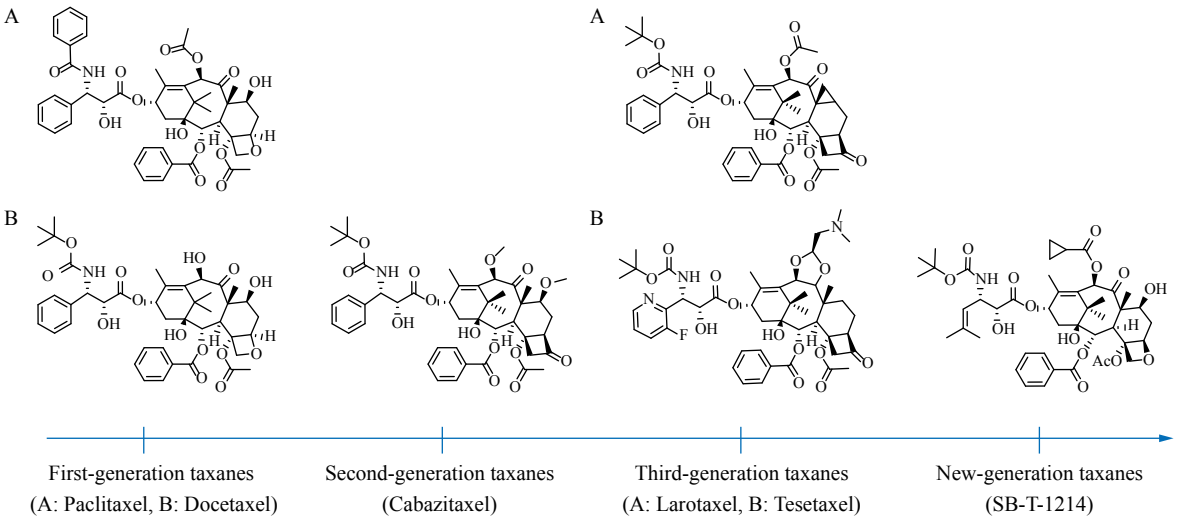


**Fig. 1 Structures of different generations of taxanes**

lations.

## Strategies to Improve Oral Delivery of Taxanes

Oral delivery of taxanes is preferred by both patients and physicians due to good patient compliance, convenient drug administration, low-cost therapy, and frequent dosing schedule. However, poor water solubility, low permeability in the intestinal tract caused by P-gp-mediated efflux and extensive first-pass effect lead to the low bioavailability of taxanes, which seriously limit their oral administration. Therefore, to develop oral formulations of taxanes, it is essentail to first deal with the issues mentioned above. The strategies to improve the oral bioavailability of taxanes are illustrated as Fig. 2, and summarized in Table 1.

*Increase the solubility*

Drugs can be absorbed after dissolving in the gastrointestinal tract with a water-soluble environment. Taxanes represent the most effective class of anti-tumour agents. However, poor aqueous solubility limit their dissolution in the gastrointestinal tract, which further hampers oral absorption. To improve the low water solubility, several strategies have been empolyed, such as solid dispersion, nanocrystals, and lipid-based formulations, etc.

*Solid dispersion*

Solid dispersion consists of a crystalline or amorphous drug that is molecularly dispersed in a hydrophilic matrix or carrier. Solid dispersion inhibits the aggregation of drug particles and then increases their surface area [37]. In addition, the carrier itself can promote the dissolution of drugs. Compared with pure drug and physical mixture formulations, solid dispersion can greatly improve the solubility and dissolution rate of taxanes, and enhance drug absorption and

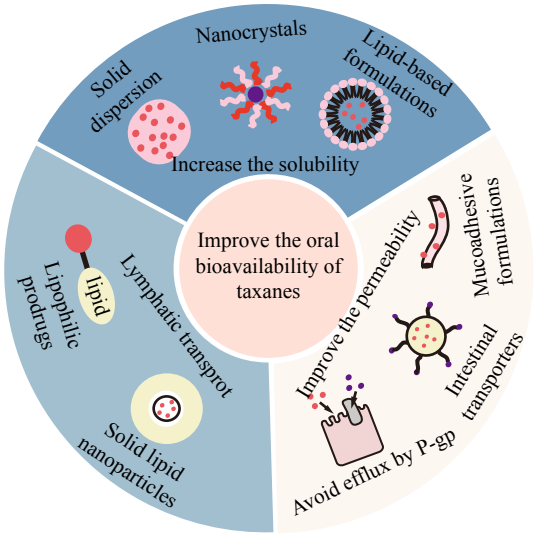


**Fig. 2 Schematic representation of strategies to improve the oral bioavailability of taxanes**

**Table 1 Summary of various types of oral taxane formulations for the improvement of oral bioavailability**

| Strategies | Formulations | Examples | Characteristics | Ref. |
|---|---|---|---|---|
| Increase the solubility | Solid dispersion | ModraDoc001 and ModraDoc006 | Increase drug surface area, promote the dissolution of the drug with carriers | [27] |
| | Nanocrystals | Pluronic-grafted chitosan (Pl-g-CH) copolymer nanocrystal | Huge surface area of drug crystals, surfactant and polymeric stabilizer as stabilizers | [28] |
| | Lipid-based formulation | O/W microemulsion with Capryol 90, Cremophor EL and Transcutol | High dispersion of drugs, increase the solubility of dispersed phases with oil phase and surfactant | [29] |
| Improve the permeability | Intestinal transporters | L-Carnitine conjugated chitosan-stearic acid polymeric micelle | L-Carnitine (substrate of OCTN2) can target to OCTN2 and improve intestinal absorption | [30] |
| | Mucoadhesive formulation | Liporaxel® (RMX3001/DHP107) | Adhering on the mucosa of the digestive tract to prolong the retention time of drugs in the gastrointestinal tract | [31] |
| | Polymeric micelles | Amphipathic chitosan derivative (*N*-octyl-*N*′-phthalyl-*O*-phosphoryl chitosan) | Chitosan exhibits mucoadhesive feature and reversibly mediates the opening of tight junctions between epithelial cells | [32] |
| | New-generation taxanes without multidrug resistance | Tesetaxel (DJ-927) | Modified the taxanes with stability groups that has poor affinity to P-gp | [33] |
| | Co-administered with P-gp inhibitor | Oraxol® (co-administered with encequidar) | Not be absorbed in the body system, locally inhibit the P-gp in the intestine and not interact with the P-gp in other parts of the body | [34] |
| Intestinal lymphatic transport | Lipophilic prodrugs | Chylomicron-like emulsion of triglyceride-mimetic prodrugs | Imitate the absorption process of natural triglycerides, and promote the transport of lymphatic system | [35] |
| | Surface-modified solid lipid nanoparticles | Solid lipid nanoparticles surface-modified by Tween 80 or D-alpha-tocopheryl poly (ethylene glycol 1000) succinate (TPGS 1000) | Lipid core of SLNs can stimulate chylomicron formation and facilitate lymphatic uptake | [36] |

bioavailability [38].

ModraDoc001 and ModraDoc006 are oral docetaxel formulations, which are currently developed as solid dispersion in phase II clinical trials. ModraDoc001 is designed in the form of capsule, while ModraDoc006 is designed as a tablet. Both formulations consist of docetaxel, polyvinylpyrrolidone-K30, and sodium lauryl sulphate (1 : 9 : 1) [39, 40]. ModraDoc001 and ModraDoc006 were co-administered with ritonavir for the treatment of solid tumors by Dutch scholars. As shown in the result of the study, the area under the plasma concentration versus time curve (*AUC*) of ModraDoc001 and ModraDoc006 were 2.19-fold and 3.44-fold higher than the control group, respectively [27]. In summary, solid dispersion is easy to be prepared with an excellent ability to increase solubility. However, it is unstable for long-term storage and the drug loading efficiency is low. The adverse events that are commonly seen during treatment include nausea, vomiting, diarrhea, and fatigue, with grade 1 or 2 in severity for most of these adverse reactions.

*Nanocrystals*

Nanocrystals are one of the most investigated novel drug delivery systems, especially for oral delivery. The extremely small size of particles results in a huge specific surface area of drugs, which can improve the solubility and dissolution rate of the drugs. Nanocrystals are composed of drug crystals stabilized with stabilizers, which play important roles in the formulations. Typical stabilizers include different types of polymers, such as cellulose derivatives, polyvinylpyrrolidone (PVP), and poloxamers, as well as amphiphilic surfactants, such as poly sorbents, and sodium lauryl sulfate [41, 42].

Liu *et al*. prepared PTX nanocrystals using poly (styrene sulfonate) (PSS) as a stabilizer to keep PTX monodisperse in varied biological environments [43]. PSS-modified PTX nanocrystals presented good dispersity and stability in gastrointestinal environments for at least 24 h. The nanocrystals passed through intestinal epithelial cells with a transmittance of approximately 25%, which presented a comparatively high oral bioavailability for the human body. Later, Shweta Sharma *et al*. designed a type of PTX nanocrystals with Pluronic-grafted chitosan (Pl-g-CH) copolymer as a functional stabilizer to improve the oral bioavailability of PTX [28], which showed 9-fold higher dissolution rate than PTX coarse suspension. Furthermore, PTX nanocrystals showed 12.6-fold increases in relative bioavailability compared with the Taxol group in the pharmacokinetics experiment. Nanocrystals as a strategy to increase the solubility of taxanes, has no restriction on the encapsulation rate with only a small amount of stabilizers and emulsifiers in the formulation. The use of surfactants and polymers as stabilizers can impart several additional properties to nanocrystals and further enhance oral bioavailability.

*Lipid-based formulations*

Lipid-based formulations (LBFs) have gained significant popularity as a promising strategy for delivering poorly water-soluble lipophilic compounds. They are usually consisted of natural or synthetic lipid-based excipients which can dissolve lipophilic drugs. Sometimes, surfactants are also used to solubilize drugs. If the lipids in LBFs are digestible, the lipid digestion products will form the micelles with bile salts and phospholipids secreted by the pancrea. The drug carried by this kind of LBFs can hitch a ride on the bile salt micelles. The micelles then increase the luminal solubility of the drugs and facilitates their passage through the unstirred water layer (UWL). Among the other developed LBFs, microemulsions and self-emulsifying drug delivery system (SEDDS) are of special interest as promising approaches for the delivery of taxanes.

Microemulsion is a nano-sized (generally less than 100 nm) two-phase dispersion system with surfactants and co-surfactants as stabilizers, where the oil phase in the inner core and the surfactants can increase the solubility of lipophilic drugs. Microemulsion can be categorized into two types: oil-in-water (O/W) for lipophilic drugs and water-in-oil (W/O) for aqueous drugs. Among these, the O/W microemulsion increased the drug solubility in oil phase up to 60%, while the co-surfactant such as ethanol, propylene glycol, and PEG promoted the dissolution of the drug in the lipid [44, 45]. Furthermore, high dispersion of drugs in the microemulsion improved the solubility of insoluble drugs [46]. Yin *et al*. prepared an O/W microemulsion formulation of Docetaxel composed of Capryol 90 (oil), Cremophor EL (surfactant) and Transcutol (co-surfactant) [29]. It can enhance the solubility of docetaxel up to 30 $mg \cdot mL^{-1}$, and in the pharmacokinetics study, the oral bioavailability of docetaxel of the microemulsion group (34.42%) in rats resulted in 5.2-fold increases compared with that of the orally administered Taxotere® (6.63%). Nevertheless, there are still some problems concerning microemulsion, such as poor drug loading, low stability, and rapid release in the gastrointestinal tract, which require further investigation.

After that, self-emulsifying drug delivery system (SEDDS) which was considered as a novel type of microemulsion, was developed to overcome the limitations above, and hence improve the oral bioavailability of drugs [47, 48]. After SEDDS enters the gastrointestinal tract, it immediately self-emulsifies into micron-sized or nano-sized particles. The large interfacial area of these particles can enhance solubilisation capacity of drugs. Furthermore, the lipid digestion properties facilitates the drug's intestinal solubility and penetration through the UWL. Meher *et al*. developed a tocopheryl polyethylene glycol succinate-assisted self-nano emulsifying system for the oral delivery of PTX, which increased the solubility of PTX and improved the oral absorption [49, 50]. Another pharmacokinetic study showed approximately 4-folds higher oral bioavailability of PTX-SEDDS than Taxol. Although LBFs possess lots of advantages, the selection of proper lipid excipient is still challenging.

*Improve the permeability in the gastrointestinal tract*

Low aqueous solubility and intestinal permeability are the two problems that limit the oral delivery efficacy of tax-

anes. The strategies mentioned above showed excellent aqueous solubility that can improve the bioavailability of taxanes. However, the poor permeability of taxanes in the gastrointestinal tract still restricts the improvement of oral drug delivery. The intestinal epithelium is the major barrier for the absorption of macromolecules from the intestinal lumen into the systemic circulation. The poor permeability of taxanes in the gastrointestinal tract results in little drugs entering the enterocytes and directly influences the oral absorption of taxanes. The low permeability of taxanes is attributable to multiple factors, especially the efflux of P-gp which is critical for poor permeability. Moreover, the rigid structure and high molecular weight of taxanes also limit the membrane transport [51]. To improve permeability, several strategies have been taken, such as prolonging the residence time in the absorption sites, increasing the lipophilicity, taking advantage of the intestinal transporters, and adding enhancers to promote membrane absorption or avoid P-gp-mediated efflux.

*Intestinal transporters*

The impact of intestinal transporters on oral drug absorption becomes increasingly obvious, and many interests have focused on the role of drug transporters in the gastrointestinal tract. The drug carrier systems designed to target intestinal transporters, such as oligopeptide transporter (PEPT), glucose transporter (SGLTs/GLUTs), organic cation transporter (OCTs), and organic anion transporter (OATs) have become one of the most prevalent trends in drug delivery [52]. The representation of intestinal transports that promote oral absorption is displayed in Fig. 3.

The organic cation/carnitine transporter (OCTN) is an intestinal transporter located in intestinal epithelial cells. L-Carnitine (LC), as the endogenic substrate of OCTN2, is a utilizable ligand for OCTN2-targeted carrier system improving the intestinal absorption of drugs [53]. An L-carnitine conjugated chitosan-stearic acid polymeric micelle was developed by Yang *et al*. to enhance the intestinal permeability of PTX through targeting OCTN2 [30]. The intracellular uptake of Caco-2 cells confirmed the enhancement of intestinal absorption and the relative bioavailability of PTX reached 165.8% against the control group. Oligopeptide transporter (PEPT1) is another important target during the process of oral absorption, which is mainly expressed in intestinal epithelial cells with high protein activity. The substrates of PEPT1 are mainly dipeptides, tripeptides, and their analogs and the peptide-mimetic derivatives formed by drug-amino acid linkage can also serve as PEPT1 substrates [54]. Li *et al*. used one of PEPT1 substrates, L-valine (Val), and linked it with PTX to design a prodrug, which was mediated by PEPT1 transporter across the intestinal cell membrane [55]. The experiments of rat single-pass intestinal perfusion confirmed excellent intestinal permeability, while oral pharmacokinetic experiments exhibited the improvement of oral bioavailability. In summary, intestinal transporters play an essential role in intestinal absorption, and the strategies based on intestinal transporters may be promising through the prodrug or carrier paths.

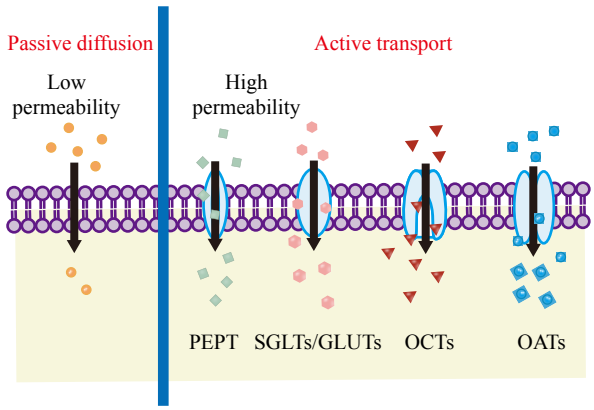


**Fig. 3 The transport mechanism of different drugs in the intestinal tract**

*Mucoadhesive formulations*

Mucoadhesive formulations can interact with the surface of mucosa before adhesion. To improve the absorption of oral formulations in the gastrointestinal tract, a gastrointestinal bio-adhesive drug delivery system was established. After oral administration, the formulation can adhere to the mucosal surface of the digestive tract to extend the retention time of drugs in the gastrointestinal tract [56, 57], which will then increase the permeability and promote the absorption of low-permeability drugs like taxanes.

As the first developed and approved oral paclitaxel formulation around the world, Liporaxel® (DHP107) was designed as a gastrointestinal bio-adhesive formulation, consisting of monoolein, tricarprylin, and tween-80. The ingredients in the formulation can facilitate drug adhesion to the gastrointestinal mucosa and improve the gastrointestinal tract absorption [58, 59]. The formulation was approved by Korean Drug Administration (MFDS) for the treatment of gastric cancer in 2016 and the drug is currently undergoing phase III clinical trials in China [60]. As shown in the clinical trials, the *AUC* of PTX reached up to 10.4 ± 2.4 μg·mL$^{-1}$·h after oral administration of Liporaxel®, and the oral bioavailability was calculated as 22.7%, which indicated that the oral absorption of PTX was significantly improved [31]. However, mucoadhesion may cause some damages to the gastrointestinal tract. Vomiting, diarrhea, and mucositis are more common with oral Liporaxel®.

*Polymeric micelles*

The emerging nano-drug delivery system brings about remarkable improvement on the oral bioavailability of taxane drugs, where polymeric micelles have attracted a great deal of attention as oral delivery nanocarriers. Polymeric micelles are composed of a core-shell structure, in which the inner hydrophobic core acts as a micro-reservoir for poor solubility drugs and the outer hydrophilic shell can improve the absorption of drugs across the gastrointestinal mucosa by enhancing membrane permeability [61, 62]. Chitosan, one of the most popular vehicles that increases cell membrane permeability, can not

only exhibit excellent mucoadhesive properties to prolong the retention time of drugs in the gastrointestinal tract but also reversibly mediate the opening of tight junctions between epithelial cells, thus facilitating the paracellular transport of hydrophilic macromolecules [63, 64].

Qu *et al*. designed a novel self-assembled micelle based on *N*-octyl-*N*′-phthalyl-*O*-phosphoryl chitosan (OPPC) derivative as an effective oral carrier of PTX [32]. In the in-situ permeability studies, significantly enhanced permeability of PTX was detected in PTX/OPPC micelles compared with Taxol, which was about 3.0-fold and 4.2-fold increments in the duodenum and jejunum segment, respectively. Moreover, in the *in vivo* pharmacokinetic study, the *AUC* of PTX/OPPC micellar was 5.5-fold higher compared with free PTX. Another kind of PTX-loaded polymeric nanomicelles was introduced by He *et al*. using a TPGS-succinic acid-mercaptoethylamine (TPGS-SH) material to improve the mucosal penetration [65]. The absorption rate and permeability coefficient were significantly improved in the intestine, with a 3.68- and 3.22-fold enhancement being detected after perfusion with CS-VES/TPGS-SH nanomicelles, while 3.58-fold improvement was found in the *AUC* values of hybrid nanomicelles, compared with PTX solution in rats. With the application of various polymeric vectors, prominent improvement in oral absorption is seen in polymeric micelles. However, the stability of micelles is often greatly reduced after entering of the micelles into the gastrointestinal tract, and causes the pre-release of drugs, which may lead to some safety issues and affect drug delivery efficiency.

*Avoid efflux by P-gp*

P-gp acts as an efflux pump to prevent taxanes from crossing through the epithelial cells, which hence decreases drug transport into the gastrointestinal tract, and results in low oral bioavailability of taxane drugs. In the traditional method, P-gp inhibitors such as ritonavir and cyclosporin A areco-administeredwithtaxanestoimproveoraldeliveryefficiency [66]. However, these strategies have their limitations, because they may cause severe medical complications by suppressing the immune system [67]. Therefore, finding an efficient method to inhibit P-gp-medicated efflux and assuring safety at the same time is a hot topic at present.

*New-generations taxanes without multidrug resistance*

Over the past several decades, several new-generation taxanes have been developed to confront drug resistance. Some of them are currently undergoing clinical evaluation, such as larotaxel, milataxel, ortataxel, and tesetaxel. Stability groups with poor affinity to P-gp in structure is the most remarkable features of them. Among them, tesetaxel (DJ-927) showed quite high oral absolute bioavailability with 107%, 47% and 63% for mice, beagle dogs, and monkeys in preclinical research. Moreover, it has been applied on phase III clinical trial for the treatment of metastatic breast cancer by odonate therapeutics as a novel oral taxane. The significantly improved oral absorption of tesetaxel was attributed to increased water solubility and weak intestinal P-gp efflux. However, this treatment presents some safety problems. Compared with the free capecitabine group, peatients receiving the tesetaxel combination therapy presented neutropenia, febrile neutropenia, leukopenia, neuropathy and other adverse events [33]. The development of tesetaxel was then discontinued by the FDA. Although safety is still a critical concern, oral administration of new-generation taxanes is still promising through avoiding intestinal efflux by P-gp along with further optimization of the structure.

*Co-administered with P-gp inhibitor*

Oraxol® is a novel oral formulation of PTX, which is administered with a combination of encequidar (HM30181M) mesylate tablets and paclitaxel capsules. HM30181M is a new type of P-gp inhibitors, which is not able to be absorbed by the gastrointestinal tract. The local effect of HM30181M is to improve the absorption of paclitaxel while avioding immune suppression, which is superior to other P-gp inhibitors. [68, 69]. In 2019, the phase III clinical results of Oraxol® for the treatment of metastatic breast cancer reached the primary research endpoint. As shown in the trials, the maximum plasma concentration ($C_{max}$) and *AUC* were significantly higher for PTX co-administered with HM30181M in breast cancer patients compared with those treated with PTX alone [34]. Additionally, Oraxol® has also shown good performance in terms of efficacy and safety.

HM30181M can assist to avoid the efflux by P-gp, while exhibiting inhibitory activity on multidrug resistance in cancer cells. However, poor water solubility limits its application. Kim *et al*. optimized this strategy by encapsulating HM30181M and PTX into microcapsules to increase the solubility of HM30181M as well as PTX [70]. Compared with oral PTX, the PTX-HM30181M microcapsule group showed a 56.4-fold higher *AUC*, with 5467.9 ± 1106.5 against 79.9 ± 53.8 ng·mL$^{-1}$·h.

*Intestinal lymphatic transport*

After intestinal absorption, most of taxanes will flow into the liver and then be metabolized into inactive metabolites before being absorbed into the blood circulation. Cytochrome P450 (CYP450) is the essential metabolic enzyme in the liver. It can bio-transform taxanes into inactive metabolites, which reduces the amounts of drugs entering the systemic circulation and severely restricts the oral bioavailability of taxanes [71]. Several strategies such as co-administration of taxanes with CYP450 inhibitors and promoting the transport of the lymphatic system are applied to solve the problem. However, co-administration of taxanes with CYP450 may cause severe medical complications due to immunosuppression. Therefore, promoting the transport of the lymphatic system is supposed as a preferred strategy.

*Lipophilic prodrugs*

For highly lipophilic drugs, it is preferred to enter the lymphatic circulation instead of the portal circulation. During transit across the enterocytes, highly lipophilic drugs with logP (> 5) and long-chain triglyceride (LCT) solubility (> 50 mg·g$^{-1}$) will combine with enterocyte lipoproteins, especially

chylomicrons. Then, the chylomicron-related drugs secret into the mesenteric lymphatic circulation, rather than the portal circulation where drugs will be directly metabolized by the liver. Therefore, drugs that are lymphatically- rather than portally-transported can avoid first-pass metabolism by the liver [72, 73]. Based on the mechanism above, several lipophilic prodrugs (including the prodrug of fatty acids, glycerides, and phospholipids) have been designed to bypass the liver for a decreased first-pass effect and improve oral absorption. The mechanism of the lymphatic transport of lipophilic prodrugs is shown in Fig. 4.

A lipophilic thioether-bridged oleate prodrug of DTX was synthesized by Cui *et al*. to increase the lipid solubility and facilitate the lymphatic transport of DTX [9]. Lymphatic transport research confirmed that the prodrug showed significantly enhanced intestinal lymphatic transport. Moreover, the bioavailability of the lipophilic prodrug was 6.2-fold higher than that of DTX solution. We used to design a triglyceride-mimetic oral prodrug of DTX to mimic the absorption process of natural triglycerides by conjugating DTX to triglyceride skeleton *via* disulfide bond [35]. The prodrug first targeted into the mesenteric lymph system and then into the circulation without liver metabolism. The *AUC* of the oral prodrug emulsion was 4.71-fold higher than that of oral DTX and the oral absolute bioavailability reached up to 44.3%. There is no doubt that lipophilic prodrugs are an efficient strategy for the oral delivery of taxanes, which can both increase lipidic solubility and avoid the first-pass effect. However, when designing lipophilic prodrugs, it is difficult to guarantee the release of parent drugs in target tissues, rather than pre-release within the gastraintestinal tract.

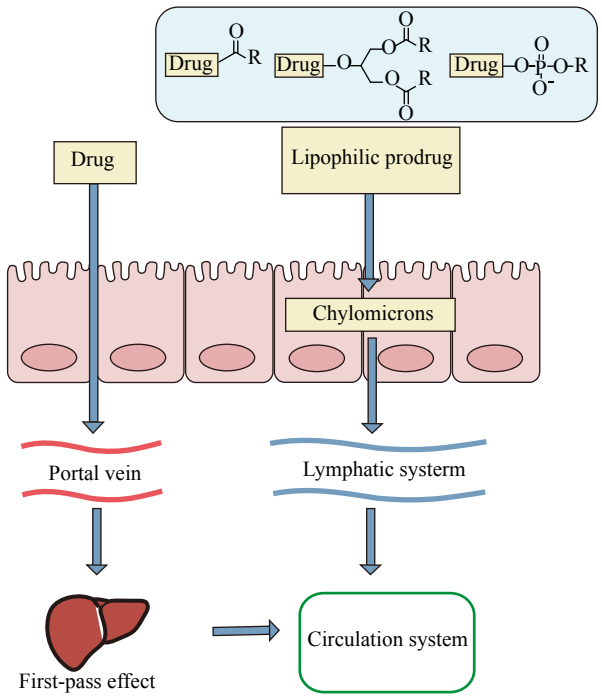


**Fig. 4 Schematic representation of the lymphatic transport of lipophilic prodrugs**

*Surface-modified solid lipid nanoparticles*

In solid lipid nanoparticles (SLNs), drugs are wrapped into the lipid core and the outer carriers consist of natural or synthetic lipids such as lecithin, triacylglycerol and so on. It has been reported that the lipid core of SLNs can stimulate chylomicron formation and facilitate lymphatic uptake, bypassing the hepatic first-pass drug metabolism [74, 75].

Cho *et al*. prepared the SLNs of DTX, modified by D-alpha-tocopheryl polyethylene glycol 1000) succinate (TPGS 1000) on the surface to enhance the lymphatic transport [36]. The SLN group exhibited a significantly larger amount of PTX covered from the mesenteric lymph nodes compared with the oral Taxotere group. In the subsequent pharmacokinetic study, the *AUC* of the SLN group was 12.9 ± 2.25 against 3.85 ± 0.907 $\mu g \cdot mL^{-1} \cdot min$ of the taxotere group and the relative bioavailability of DTX SLNs reached up to 3.55-fold increase in comparison with oral taxotere. These results may be attributed to the improvement of oral bioavailability by reduction of the first-pass effect of SLNs. However, SLNs still have some disadvantages such as low drug loading and being unstable in the body.

## Thoughts on the Future Development of Oral Taxane Formulations

In recent years, with the increased focus on oral delivery, a huge amount of oral taxane formulations have emerged. Some of them has been on the market or under clinical trials, including Liporaxel®, Oraxol®, ModraDoc001 and ModraDoc006, and Tesetaxel and their information is summarized in Table 2. These promising oral taxane formulations are expected to realize transformation from intravenous to oral treatment in chemotherapy, which also means "chemotherapy in home". As shown in the results of clinical trials, oral taxane formulations solved the restrictions of oral absorption of taxanes and efficiently increased the oral bioavailability, which provided feasible strategies for oral administration. However, the oral formulations under clinical trials still have some limitations: (i) There are some safety issues with these formulations. For example, mucosal adhesion of Liporaxel® may cause some damages to the gastrointestinal tract, and the use of ModraDoc006 may cause adverse reactions like nausea, vomiting, and fatigue; (ii) the oral formulations have resolved only one or two aspects of the restrictions for the oral delivery of taxanes, not completely solve the problem of poor oral absorption and (iii) these formulations were designed to improve the oral absorption of taxane drugs, without taking considerations of the release of drugs in the tumor site, which may cause toxicities for other tissues and reduce anti-tumor efficiency.

To better solve the restrictions for the oral absorption of taxanes, the combination of multiple oral delivery strategies is a promising method. For example, P-gp inhibition is considered during designing the nano-drug delivery system to avoid efflux by P-gp and increase the poor solubility at the

**Table 2 Summary of oral taxane formulations on the market or under clinical trials**

| Name | Condition | Formulations | Clinical Phase |
|---|---|---|---|
| Liporaxel® | Gastric cancer | PTX, monoolein, tricarprylin and Tween-80 | On the market in Korea |
| Oraxol® | Breast cancer | PTX + P-gp inhibitor (Encequidar) | Phase III |
| ModraDoc001/ModraDoc006 | Solid tumors | DTX, polyvinylpyrrolidone-K30, and sodium lauryl sulphate | Phase II |
| Tesetaxel | Metastatic breast cancer | Tesetaxel | Discontinued |

same time. As mentioned above, HM30181M and PTX were encapsulated into microcapsules with the carriers including hydrophilix ploymers and solvents, to increase the solubility of HM30181M and PTX as well as avoid the efflux effect of P-gp [70]. The co-amorphization of taxanes with a P-gp inhibitor can improve the dissolution and avoid efflux by P-gp. Wei *et al*. prepared a novel preparation of coamorphous DTX and a natural P-gp inhibitor myricetin (MYR) that simultaneously enhanced the dissolution and oral bioavailability of both drugs [76]. Co-administration with intestinal absorption enhancers and P-gp inhibitors can both enhance the intestinal permeability and avoid efflux by P-gp [77]. Besides, the combination of lipid prodrug strategies and lipid-based nano drug delivery system can effectively improve the oral delivery of drugs. The prodrug strategies can increase the lipid solubility of the drugs and avoid drug efflux by P-gp, while the lipid-based nano drug delivery system can further increase drug intestinal solubility by lipid ingestion. Vaskor *et al*. designed a lipophilic prodrug and incorporated it into a self-emulsifying drug delivery system with long chain lipids and lipid-based non-ionic surfactants to maximize drug solubilization in gastrointestinal conditions and facilitate trans-membrane permeation, and hence improved oral absorption [78]. However, the combined strategies at present are too complicated or unstable to scale up, which restrict the application in clinical settings. Therefore, developing a simple and stable strategy that can both solve the restrictions for oral absorption and realize large-scale application is the future development trend.

Studies concerning the oral delivery of taxanes are still in the primary stage. Recently, the research of oral taxanes formulations mainly focuses on the improvement of oral bioavailability, while the process of drug delivery after absorption from the gastrointestinal tract to the tumor site is usually ignored, which results in reduced anti-tumor efficiency and may cause serious toxicities to other body tissues. Therefore, it is also important to realize both efficient oral absorption and on-site tumor-bioactivation. To achieve on-site tumor release, it is a promising method to design drug delivery system which can be stimuli-responsive to the special tumor microenvironment. Taking use of the high reductive environment in the tumor cells, the insertion of reductive-responsive disulfide linkers in prodrug strategy can make taxane release specifically within tumor cells [79]. In light of the acidic environment around tumor cells, Mahmood *et al*. developed an ionically cross-linked chitosan nanoparticle which increased the oral absorption and achieved the specific release in the tumor at the same time [80].

## Conclusion

In this review, we outlined the development of the taxanes and raised the challenges of oral delivery of taxanes. Then, different strategies were introduced according to different problems. In summary, oral administration of taxanes is a promising method for the treatment of cancer with various strategies to increase oral bioavailability. However, the oral formulations of taxanes today still have some limitations, such as safety problems, complicated technology and poor anti-tumor efficiency. Therefore, our current tasks are making full use of the strategies available to deal with the poor oral bioavailability and concentrating on other problems metioned above to develop a formulation that is safe and easy to be prepared, with efficient oral digestion and excellent anti-tumor efficiency.

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