

Advancements in the oral delivery of Docetaxel: challenges, current state-of-the-art and future trends

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Abstract: The oral delivery of cancer chemotherapeutic drugs is challenging due to low bioavailability, gastrointestinal side effects, first-pass metabolism and P-glycoprotein efflux pumps. Thus, chemotherapeutic drugs, including Docetaxel, are administered via an intravenous route, which poses many disadvantages of its own. Recent advances in pharmaceutical research have focused on designing new and efficient drug delivery systems for site-specific targeting, thus leading to improved bioavailability and pharmacokinetics. A decent number of studies have been reported for the safe and effective oral delivery of Docetaxel. These nanocarriers, including liposomes, polymeric nanoparticles, metallic nanoparticles, hybrid nanoparticles, dendrimers and so on, have shown promising results in research papers and clinical trials. The present article comprehensively reviews the research efforts made so far in designing various advancements in the oral delivery of Docetaxel. Different strategies to improve oral bioavailability, prevent first-pass metabolism and inhibition of efflux pumping leading to improved pharmacokinetics and anticancer activity are discussed. The final portion of this review article presents key issues such as safety of nanomaterials, regulatory approval and future trends in nanomedicine research.

Keywords: anticancer, permeability enhancement, solubility enhancement, P-glycoproteins, efflux pump, first-pass metabolism

Introduction

Cancer incidence is increasing globally and accounts for about 8.2 million deaths worldwide mainly because of poor tumor targeting and severe dose-related adverse effects to other organs or many other complications associated with the disease.¹ Cancer incidence is higher in developing countries that bear 57% of all cases and 65% of all deaths because of a steady increase in population growth rate, repeated exposure to carcinogens, poor hygiene and many other factors.^{2,3} This dramatic increase in the number of cancer patients would need inexpensive and convenient therapies to alleviate their suffering and improve their quality of life.⁴ Current cancer treatment involves intrusive processes starting initially with chemotherapy to reduce the tumor size, followed by surgical procedures to remove the solid tumor and, if required, another course of chemotherapy and radiation for the complete eradication of cancer cells.^{5,6} Most current anticancer agents are administered intravenously (IV), which requires proper supervision by a trained person during the course of therapy and makes the treatment very expensive.^{7,8}

Oral drug delivery is the most convenient way to administer medicine.⁹ But oral administration of cancer chemotherapeutic drugs is limited due to an extensive

first-pass effect,¹⁰ poor solubility,¹¹ efflux transport,¹² low intrinsic permeability of drug limits, bioavailability of drugs and so on.¹³ Despite the aforementioned limitations, the oral delivery of chemotherapeutic drugs is highly desirable in terms of its convenience in synthesis and administration, ease of design, vast variety of formulations and, most importantly, better patient compliance in terms of chronic ailments.^{14–16} The oral route can be used for systemic as well as localized gastrointestinal tract effects. For systemic applications, the oral route is preferred because of the highly absorptive nature of the intestine that provides a large surface of around 300–400 m² for drug adsorption and varying physiological conditions which also facilitate different types of outcomes not associated with other routes of chemotherapeutic administration.^{17,18} The oral administration of chemotherapeutics may be of great importance in the following clinical cases:^{1,19}

1. Maintenance of plasma drug concentration necessary to produce inhibitory effects on cancer cells.
2. Drug release could be controlled in a better way compared to other routes.
3. Enables chronic treatment, especially with cell cycle-specific agents, such as signal transduction inhibitors, which may result in improved pharmacodynamics compared to intravascular administration.
4. Improved patient compliance as it avoids needles related to discomfort, hazards and special care.
5. Pharmacoeconomics is another prime consideration for many patients, which could be addressed by using oral delivery.

The majority of available anticancer drugs, including “taxanes” (Paclitaxel and Docetaxel [DTX]), belong to the biopharmaceutical classification system class IV, and their clinical use is limited due to their extreme hydrophobicity, low water solubility, low bioavailability and high toxicity.^{20,21} In the past two decades, many types of cancers have been efficiently treated by taxanes, that is, DTX and Paclitaxel, as they can disrupt microtubule function and cause cell apoptosis and death.²²

The delivery of hydrophobic drugs has always been a challenge and it is still a hot research topic since they cannot reach the intracellular environment by crossing the cell membrane because of the surrounding aqueous environment in tissues and organs, whether given orally or IV.^{23,24} Molecular drug discovery and development are expensive and intense processes taking over a decade and over US \$5 billion on average.²⁵ In contrast, designing new drug delivery systems for existing drug molecules with established efficacy is a much more beneficial research area in terms of both time- and

cost-effectiveness. Pharmacological properties of a drug can be greatly improved by selecting an appropriate carrier system based upon the route of administration.²⁶

Taxanes share the largest sales volume of around US \$3.5 billion of the presently available anticancer drugs.²⁷ Thus, development of an oral formulation for DTX would be a great achievement from the patient’s perspective of “chemotherapy at home”.^{28,29} The present review is designed to highlight the various challenges encountered in the oral administration of DTX and nanomedicine-based strategies to address these challenges.

Challenges in the oral delivery of DTX

DTX is a semisynthetic taxane (Figure 1A) prepared by the chemical modification of an inactive precursor obtained from the needles of the European yew tree (*Taxus baccata*).³⁰ It acts by disrupting the microtubule network that blocks cell cycles in the late G2 and M phases, thus inhibiting cell replication as shown in Figure 1B.³¹ DTX has been proven to be better in efficacy as compared to Paclitaxel.³² The drug has a clinically significant antitumor activity against a range of tumor types and is approved for the treatment of breast cancer,³³ ovarian cancer,³⁴ non-small cell lung cancer (NSCLC),³⁵ head and neck carcinoma,³⁶ gastric cancer³⁷ and prostate cancer³⁸ at doses ranging from 60 to 100 mg/m² administered at 1 hour infusions every 3 weeks.³⁹ Weekly IV schedules of DTX result in similar efficacy and a different toxicity profile with a lower incidence of febrile neutropenia compared to three-weekly schedules. Management of neutropenic infections requires patient hospitalization and treatment with IV antibiotics. The other major side effect is neuropathy that is related to cumulative doses and can potentially limit the number of cycles that can be given.⁴⁰

Bioavailability of the drug after oral administration is the key determinant of any delivery system in order to achieve therapeutic outcomes.⁴¹ Dissolution in acidic gastric fluid and permeation across the enterocytes are the rate-limiting factors that govern oral bioavailability. Generally, these rate-limiting factors can be divided into two main categories: 1) physicochemical properties of the drug molecule (ie, solubility, log *P*, dissolution and stability) and 2) physiological factors associated with the gastrointestinal tract (ie, pH, gastric retention time, absorption window, enzymatic degradation, hepatic first-pass effect and P-gp efflux pumps).^{42,43}

Physicochemical properties of DTX

The most important physicochemical properties of the drug are its aqueous solubility and membrane permeability, which

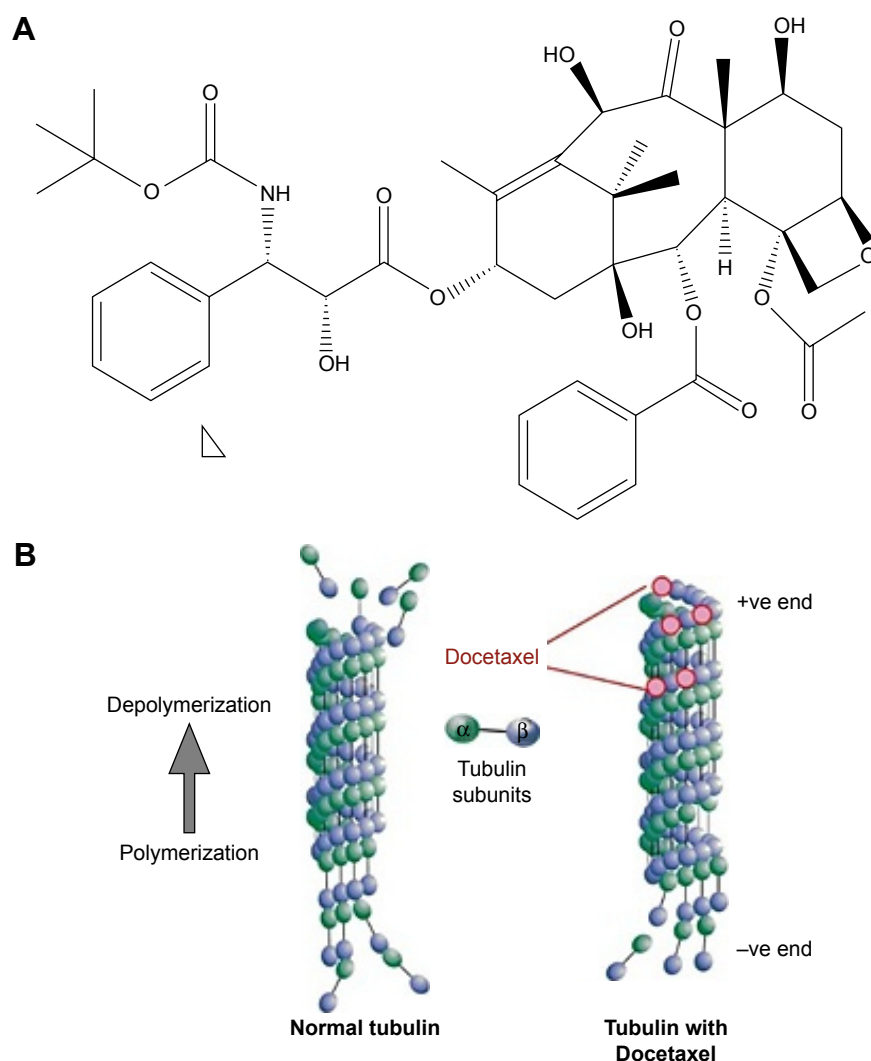


Figure 1 (A) Chemical structure of Docetaxel and (B) graphical representation of the mechanism of action of Docetaxel.

are explained in the Lipinski's rule considering the P_{ka} and $\log P$ -values of the drug.⁴⁴ DTX has a $P_{ka}=10.97$ and $\log P=4.1$, which results in poor aqueous solubility ($0.025 \mu\text{g/mL}$) and low membrane permeability ($1 \text{ cm/s} \times 10^{-6}$).^{1,45} The pharmacodynamics of a drug is fully dependent on its pharmacokinetics (ie, absorption, distribution, metabolism and excretion profile).⁴⁶ The absorption of a drug could be calculated by Fick's law of diffusion, and drugs have been categorized as dissolution rate limited, permeation rate limited and both dissolution/permeability limited accordingly.^{47,48} Poor dissolution and higher $\log P$ -value place DTX in a dissolution/permeability limited category. Similarly, the biopharmaceutical classification system categorizes it as a class IV drug having both low solubility and permeability.^{49,50}

Physiological barriers for DTX

The molecular bases of physiological barriers faced by many anticancer drugs after oral administration are still unknown

and are constantly being investigated. However, two of the most important barriers faced by anticancer drugs, including DTX, are hepatic first-pass clearance by the cytochrome P450 (CYP450) enzyme system and the P-gp efflux pump, which are further explained in the section "Pre-systemic metabolism" and "Transmembrane efflux of drugs".⁵¹

Pre-systemic metabolism

Oral bioavailability is the collective fraction of a drug available systemically after 1) absorption from the gastric mucosa and 2) absorption from the enterohepatic circulation, and 3) the fraction available after the first-pass effect. The gastrointestinal absorption of the drug is affected by a number of factors (ie, metabolism by different metabolic enzymes [amylase, peptidase, lipase and so on], normal flora of the intestine, brush border metabolism [peptidase, alkaline phosphatase, sucrose and so on] and intracellular metabolism carried out by an extrahepatic microsomal enzyme in the

endoplasmic reticulum).⁵² Cytochrome P2A4 (CYP3A4) includes phase II enzymes such as esterases, glutathiones, transferases and so on that are present in enterocytes and act at the gastrointestinal wall, which could also serve as a target for the amide or ester prodrugs. The hepatic first-pass effect by the CYP450 family is the other major contributor for decreasing oral bioavailability.⁵³ DTX is an extensively protein-bound drug, as >98% of it systemically is bound to alpha-1 acidic glycoproteins and albumin.⁵⁴

Transmembrane efflux of drugs

Clinically significant cellular transport systems (such as P-gp, cytoplasmic transport, multidrug-resistant associated protein and fluorochrome efflux) can decrease the oral bioavailability of many drugs which are the substrate of these transporters via an efflux mechanism.⁵⁵

P-gp, a membrane-associated protein belonging to ATP binding cassette transporters, is extensively distributed throughout the intestinal epithelia, hepatocytes, kidneys and capillary endothelial cells forming blood–brain and blood–testis barriers. These P-gps are mainly involved in developing multidrug resistance against many anticancer drugs. P-gp activity is induced by two ways – either by endogenous lipids and peptides or by drugs which are the substrate for it. Depending on the vulnerability, anticancer agents could be divided into three categories. Class I drugs can stimulate P-gp in low concentrations and inhibit it at higher concentrations. On the other hand, class II drugs can cause dose-dependent activation of ATPase leading to lower bioavailability of the substrate drugs and class III drugs can inhibit the activity of ATPase, increasing drug bioavailability.⁵⁶ DTX is a substrate of P-gp and belongs to class II, contributing to its decreased oral bioavailability.⁵⁷ Currently, the development of drug resistance is regarded as a major obstacle to the success of cancer chemotherapy. Due to the presence of drug efflux transporters, pharmacological responses from non-penetrative routes of chemotherapy is at the most moderate.⁵⁸

Current status of the DTX formulation

Taxotere® (Sanofi-Aventis, Anthony Cedex, France) is US Food and Drug Administration (FDA)-approved, IV-administered DTX formulation commercially available. It contains a combination of DTX and Tween 80, a nonionic surfactant from the polyethylene glycol class, to overcome the prime issue of poor aqueous solubility. It was approved for NSCLCs in December 1999, prostate cancer in May 2004, breast

cancer in August 2004, gastric cancer in March 2006 and for head and neck cancers in October 2006.⁵⁹

During clinical trials, DTX was supplied as a sterile solution containing Tween 80 and ethanol (50:50), but the commercially available formulation contains a reduced amount of Tween 80 (26 mg/mg of DTX), which is further diluted with 13% ethanol before injection into the patients. Due to the presence of Tween 80, many cases of mild to severe hypersensitivity were reported along with peripheral edema, weight gain and pericardial effusion with a dose above 400 mg/m².^{60–62}

Tween 80, especially its metabolic product, and oleic acid result in histamine-induced hypersensitivity associated with DTX formulations,⁶³ although pathogen-induced vasoactive substance release is also labeled as a possible mechanism. The association with peripheral edema may be supported by the fact that the vehicle has increased membrane permeability. Lastly, Tween 80 has shown changes in plasma viscosity and red blood cell morphology, which induce cardiovascular side effects of DTX therapy.⁶⁴ Recent studies have also shown the antiangiogenic ability of both DTX and Tween 80 at low concentrations, but the clinically achieved concentration after DTX infusion abolishes the antiangiogenic potential.⁶² Tween 80 also greatly influences the pharmacokinetics of DTX by increasing the concentration of unbound DTX in the plasma, due to formation of Tween 80 micelles, that interacts with alpha acidic proteins.⁶⁵ Also, the higher plasma level of Tween 80 decreases the plasma clearance of DTX, resulting in severe hematology toxicity due to the unbound drug.⁶² All these problems strongly demand for the development of Tween 80-free formulations for DTX with improved pharmacokinetics and pharmacodynamics of the drug.

Emerging trends in oral delivery of DTX

Despite the fact that most of the anticancer drugs, including DTX, face challenges after oral administration in achieving optimum bioavailability to produce the desired effects, promising and encouraging results after oral administration have been reported by various scientists. Also, developing Tween 80-free formulations with improved pharmacokinetics, pharmacodynamics and better tumor targeting has led to several new possibilities.¹ Various strategies have been reported with successful increases in dissolution and permeation of DTX after oral administration. A comprehensive review of all these techniques is described in next section.

Coadministration of other agents – beneficial effect of drug interactions

Coadministration of DTX with a molecule showing inhibitory effects on major barriers of oral administration could also improve its oral bioavailability. For example, coadministration of cyclosporine A with DTX has shown a successful increase in oral bioavailability. Oral administration in rat and dog models has shown a 14%–17% increased peak plasma concentration and a 17-fold decreased clearance, thus showing that cyclosporine A can alter the disposition of orally administered DTX.⁶⁶ A clinical study was conducted on cancer patients by administering 15 mg/kg cyclosporine 30 min preceding the oral administration of DTX. The results showed 8% absolute bioavailability without cyclosporine, which significantly increased to 90% with cyclosporine.⁶⁷ A similar effect was shown by piperlongumine on the oral bioavailability of DTX by inhibiting CYP3A4 metabolism and P-gp and by improved cytotoxicity when coadministered. This strategy successfully improved the oral bioavailability 1.68-fold in rats via permeation enhancement and decreased efflux pump activity 0.64-fold.⁶⁸ The inhibition of CYP3A4 and P-gp, major contributors in limiting oral bioavailability of DTX, can significantly improve the oral bioavailability. A research study conducted on mice lacking all genes for CYP3A4 and P-gp showed significant improvement in oral bioavailability. However, this resulted in intestinal lesions with lethal toxicity, highlighting the potential application and serious concerns of this option, especially with drugs having a narrow therapeutic index.⁶⁹ Coadministration of DTX with a cell penetrating peptide has also shown potential in increasing the oral bioavailability of DTX as well. In one study, cyclodextrin-poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) loaded with DTX and an R7 cell penetrating peptide showed increased toxicity against MCF-7 cells and a 9.47-fold increased oral bioavailability.⁷⁰ Therefore, coadministration of DTX with an inhibitor may be a suitable platform to enhance its oral bioavailability.

Nanocarrier-based approaches

The advent of nanotechnology has created much hype and introduced many possibilities in every field. In medicine, it has introduced so many possibilities in therapeutics and diagnostics that it could be named as the future of efficient personalized drug delivery.^{71,72} After decades of multidimensional research in nanotechnology, it has already started to show a great potential for improving drug delivery systems as evident from the increasing number of nanomedicines

gaining FDA and European Medicines Agency approval.⁷³ These engineered nanocarriers can be tuned for their sizes ranging from 1 to 1,000 nm, surface properties such as charge and ligands attached for specific cellular receptors, and shape based upon the features required for carrying a specific molecule to a target site to achieve a desired therapeutic outcome.⁷⁴ NP-based drug delivery systems have significantly improved cancer therapy and reshaped the landscape of the pharmaceutical industry.²⁷

Nanotechnology-based delivery systems are potential solutions for the oral administration of highly efficient chemotherapeutic drugs such as DTX.⁷⁵ These nanocarriers can be prepared with different materials such as polymers, lipids, inorganic materials, metals and proteins or the hybrids of these materials to tune the nanocarriers (Figure 2) for specific purposes.⁷⁶

The nanoscale drug delivery vehicles (eg, liposomes, prodrugs, core-shell polymeric NPs, metallic NPs, solid lipid NPs and so on) have been explored with several advantages noted, which are as follows:

1. Improved bioavailability by overcoming the solubility or permeability of the molecules.
2. Protection of the drug molecule from harsh environments (eg, against enzymatic degradation by lysozymes, proteases in systemic circulation or highly acidic pH of the stomach).
3. Better tumor targeting through surfaces decorated with ligands for specific receptors or using a pH-sensitive polymer releasing drug in a specific environment inside the tumor.
4. Control of drug release patterns to achieve site-specific release and to maintain the required plasma drug concentration.
5. Co-delivery of drug combinations or along with diagnostic agents for magnetic resonance imaging, computed tomography or positron emission tomography to achieve better therapeutic outcomes and improve patient compliance.⁷⁷

Drug–drug interaction in patients receiving oral chemotherapy has been reported, which is a major concern in developing more personalized and target-specific carriers for the oral administration of chemotherapeutics.⁷⁸ Generally, nanocarriers having particle sizes around 300 nm, positive zeta potential and hydrophobic surfaces have preferential uptake from the enterocytes.⁷⁹ Many research groups have explored these properties for the oral administration of DTX. Different mechanisms of increased oral bioavailability of

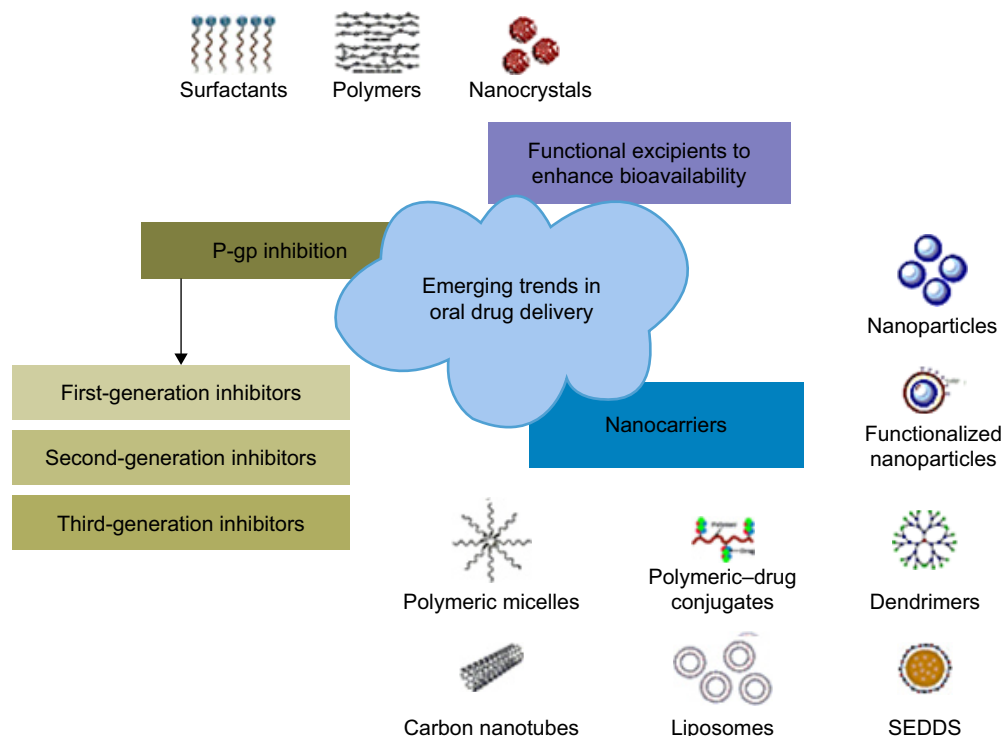


Figure 2 Nanotechnology based emerging trends reported for the oral delivery of anticancer agents.
Abbreviation: SEDDS, self-emulsifying drug delivery systems.

DTX release have been explored through nanocarriers, including facilitating a paracellular route by modulating tight junctions (through interactions with tight junction proteins), mucoadhesion (either due to electrostatic interactions between the positive surface charges of NP and the negatively charged mucin or a covalent linkage developed between the functional groups at the NP surface and cysteine of mucin), phagocytosis by specialized Peyer's patches (M-cells or mucosa-associated lymphoid tissue), receptor-mediated transcytosis or endocytosis and lymphatic absorption via chylomicron uptake mechanisms from the enterocytes. In addition to this, persorption has been proposed, wherein a carrier-loaded or lepidic formulation permeates through temporary gaps at the cell apex, generated as a result of the migration of the continuously produced intestinal cells in the crypts of Lieberkuhn toward the tip of the villus during digestion.⁸⁰ These mechanisms are shown in Figure 3.

Polymeric NPs

Polymeric nanocarriers have extensively been explored for the oral delivery of anticancer drugs with improved safety profiles. The major advantages of using polymers for drug delivery are their biocompatibility, biodegradability, versatility in linking to different molecules to develop co-block polymers and, most importantly, attachment of functional/targeting

moieties to them. Polymers for oral administration include PLGA, chitosan, gelatin, dextran, alginate and acrylic acid derivatives. The capability to achieve sustained release from the polymeric nanocarriers up to several days is of great interest as it helps to overcome the tissue barriers until it reaches systemic circulation. Similarly, several reports have shown rapid uptake of nanocarriers by the M-cells of immune system or via the lymphatic system, enabling their systemic availability and prolonged release profile.

DTX-loaded polycaprolactone/Pluronic F68 NPs with particle sizes around 200 nm and drug loading up to 69% have been developed with significantly improved cytotoxic potential against MCF-7 breast cancer cells, as compared to IV DTX and Tween 80. The presence of Pluronic F68 not only increased the cytotoxicity of NPs toward cancer cells, but also influenced drug release from the NPs, making it more controlled.⁸¹ PLGA is the most widely used FDA-approved material and is found in different applications in nanomedicine. NPs loaded with DTX were also synthesized with vitamin E-PLGA-succinate derivative, also known as docetaxel-loaded d- α -tocopheryl polyethylene glycol 1000 succinate (TPGS), and montmorillonite for oral delivery. A sustained release of up to 3 weeks after a single oral administration and 21-fold increased bioavailability were achieved as compared to IV DTX and Tween 80. Due to solubilizing and

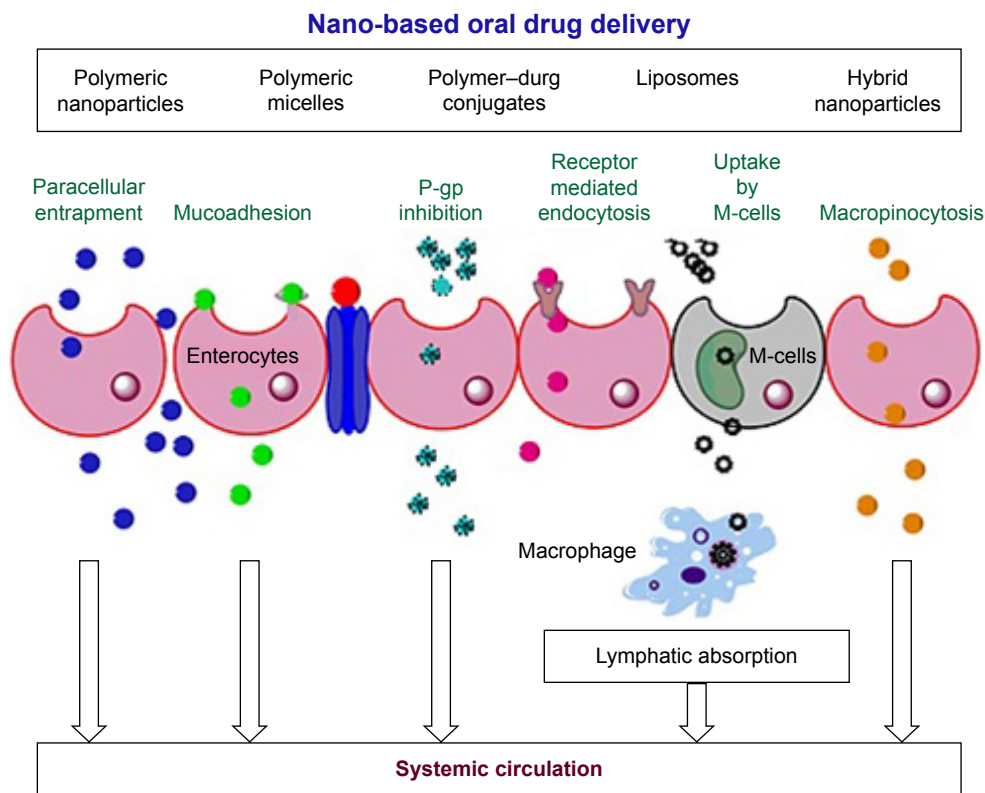


Figure 3 Different cellular mechanisms involved in the cellular uptake and permeation of various nanoformulations across the enterocytes after oral administration.

P-gp inhibiting properties of TPGS, IC_{50} value of DTX was improved four times and the half-life after oral administration was increased 26 times as compared to IV DTX and Tween 80.⁸² Another way to improve oral bioavailability is to enhance gastric retention of the NPs. Accordingly, DTX-loaded nano-carriers were prepared by using polymethyl methacrylate coated with thiolated chitosan, which is a mucoadhesive and enhances permeability from the gastrointestinal tract after oral administration. The *in vivo* pharmacokinetics revealed a 9-fold increase in half-life and 96% increased oral bioavailability as compared to DTX.⁸³ Lecithin has also been reported to successfully increase the oral bioavailability of DTX due to its solubility and permeation enhancing effects. *In vitro* studies showed a sustained drug release and improved permeation on a Caco-2 cell line. The oral bioavailability had a 3.65-fold increase in permeation as compared to a DTX suspension in rats.⁸⁴ Mucoadhesive polymeric NPs were also prepared by using methyl- β -cyclodextrin and poly (isobutylcyanoacrylate) with an outer shell of thiolated chitosan. The synthesized NPs showed a good enhancement for permeation during *in vitro* studies.⁸⁵ Sulfobutylether- β -cyclodextran and chitosan-based NPs were developed for the coadministration of DTX and berbamine. The newly formed NPs showed good drug loading and release kinetics and improved cytotoxicity

against MCF-7 cells. The oral bioavailability of the DTX was relatively improved with significantly improved cytotoxicity. The cytotoxicity of NPs is another major concern which needs to be addressed when designing a carrier. NPs composed of methyl- β -cyclodextrin/polyisobutylcyanoacrylate coated with thiolated chitosan have shown decreased enterocyte toxicity and inflammation followed by oral administration of DTX-loaded NPs as compared to IV DTX and Tween 80.^{86,87}

Chitosan-loaded DTX NPs surface modified with PLGA were reported for improved oral bioavailability and tumor uptake.⁸⁸ In this study, the apparent permeability across the rat intestine showed a 5-fold increase in the presence of a third-generation P-gp inhibitor and a 2.2-fold increase without it. Oral pharmacokinetics showed a 5.11-fold increased oral bioavailability as compared to a DTX suspension. The presence of a P-gp inhibitor in formulations improved cellular uptake (A549 cells) as well, confirming the role of P-gp inhibition and nanocarriers in the successful oral delivery of DTX. A similar core-shell system comprising thiolated chitosan shell and polymethyl methacrylate core is reported for the improvement in oral delivery of DTX. Particles with >200 nm size showed 90% entrapment efficiency. The system controlled DTX release for 10 days with an initial burst release. The carrier efficiently transported DTX across

the rat intestine and showed improved toxicity against Caco-2 and MCF-7 cell lines.⁸⁹

Lipid-based nanocarriers

Lipid-based materials have also proven their importance as a drug carrier, including solid lipid NPs (SLNs), liposomes, micro-/nanoemulsions, ethosomes, lipid-based tablets, pro-liposomes, lipopolymeric hybrid nanocarriers and so on.⁹⁰ Of these, liposomes are the only successful carrier approved by the FDA and a number of products are now available in the market.⁹¹ The first anticancer liposomal doxorubicin was approved by the FDA in 1995. Since then, many more liposomal drugs have been evaluated and are in different phases of clinical trials.⁹² The most important feature of liposomes is their ability to incorporate both hydrophilic and hydrophobic moieties and deliver them to the site of action through the extravascular as well as intravascular routes of administration. Liposomes are thermodynamically stable vesicles with an aqueous core surrounded by an amphiphilic phospholipid bilayer.^{93,94} On the other hand, SLNs and nanostructured lipid carriers (NLC) have shown advantages such as higher drug loading, higher permeability and prolonged storage stability, as compared to other lipid-based nanocarriers for the delivery of anticancer drugs. A couple of groups have investigated lipid-based nanocarriers for increasing the oral bioavailability of DTX with promising results. For example, oleic acid-linked DTX prodrug in liquid form was formulated as NLC by mixing with a solid phase lipid that increased the prodrug loading up to 5-fold. These NLC also showed a 4-fold increased bioavailability and significantly improved oral permeability as compared to a DTX solution.⁹⁵

Cysteine-modified lipid nanocarriers for the oral delivery of DTX have been reported with good in vitro permeation enhancement and pharmacokinetic parameters. The permeation enhancement was facilitated by both passive transport and absorption in enterocytes via improved mucoadhesion of the surface cysteine. Oral pharmacokinetics revealed a 13-fold increase in the area under the curve as compared to a DTX suspension.⁹⁶ Another carrier comprising Tween 80 and TGPS 1000 as emulsifiers showed increased oral bioavailability of the DTX-loaded SLN as compared to IV DTX and Tween 80. Bioavailability was further increased with TGPS containing SLNs, possibly due to blockage of P-gp and absorption through the lymphatic system.⁹⁷

Hybrid NPs

Hybrid nanocarriers, composed of two different materials, have been introduced for the delivery of many therapeutic

agents with improved therapeutic outcomes as compared to individual components. The hybrid NPs mostly consist of polymer–lipids, polymer–metal or lipid–polymer hybrid materials.⁹⁸ Hybrid nanocarriers have shown some good results in the oral delivery of cancer therapeutics, including the successful delivery of DTX.

A core–shell system consisting of a polymeric core and lipid shells was functionalized with folic acid for the oral delivery of DTX. The main advantage of the formulation was controlled drug release (about 60%) after 72 hours and a 94% better cytotoxicity against MCF-7 when compared to IV DTX and Tween 80.⁹⁹ A similar hybrid nanocarrier system has been developed by our group for the successful oral delivery of DTX. The nanocarriers consisting of folic acid-labeled polymeric-enveloped nanoliposomes showed high stability and improved in vitro and in vivo properties. The in vitro permeation showed a 9.6-fold increased permeation in the rat intestine and a 13.6-fold increased oral bioavailability as compared to a DTX suspension. Tumor targeting and cytotoxicity were greatly improved against MDA-MB-231 cells, possibly because of P-gp inhibition by thiolated chitosan and better tumor targeting with surface folic acid.¹⁰⁰

Another interesting carrier based on a carboxymethyl chitosan phospholipid bilayer capped mesoporous carbon NP was reported for the oral delivery of DTX with sustained release.¹⁰¹ This hybrid nanocarrier was successful in maintaining a high payload due to an anionic lipid layer and later showed pH-responsive sustained release in gastric media owing to a cationic polymer envelopment. Moreover, the nanocarriers showed improved mucoadhesion. Improved oral bioavailability of DTX was also reported using DTX-loaded nanocapsules prepared from glyceryl tributyrates, oleoyl polyoxyglycerides and PLGA 4000 embedded in Eudragit L and HPMC microparticles. The formulation increased oral bioavailability and C_{max} in minipigs by 10- and 8.4-fold, respectively. The NCs successfully transported DTX across the enterocytes with a reduced biodistribution and plasma release and improved anticancer activity in metastatic lung cancer, compared with IV DTX and Tween 80.¹⁰²

Theranostic nanocarriers

Theranostic nanocarriers are gaining importance in cancer therapeutics as they have the ability to carry a drug molecule along with some diagnostic agent that helps to track disease treatment, perhaps in real time. A couple of theranostic nanocarriers with DTX have been reported in the literature with good results. Theranostic liposomes coated with vitamin E derivatives (TPGS) were designed for the

delivery of DTX along with quantum dots for diagnosis. These targeted liposomes showed better cellular uptake and a 41-fold lower IC_{50} against MCF-7 cells, as compared to IV DTX and Tween 80.¹⁰³ Another study reported a hybrid nano-system with a PLGA core encapsulating superparamagnetic iron oxide NP and DTX within a folate–chitosan shell for magnetic resonance imaging and improved delivery of DTX. The *in vitro* study against folate-positive and -negative cancer cells showed improved uptake by a folate-positive cell line with no effect on magnetic properties and an overall shortened T_2 relaxation time.¹⁰⁴

Emulsions

Emulsion-based formulations are the most common way of efficiently administering lipophilic drugs. To overcome problems such as thermodynamic and kinetic instability, two new types of emulsions have been synthesized, that is, microemulsion and nanoemulsion. Many research groups have reported improved oral bioavailability of DTX by using emulsion-based formulations.

Microemulsion

The solubility of DTX has been improved to a 30 mg/mL concentration using the microemulsion technique. The formulation was successfully synthesized with 30 nm particle sizes and remained stable for 24 hours upon a 20-fold dilution. *In vitro* studies showed a very good release profile and permeation enhancement of the formulation as compared to IV DTX and Tween 80. This improvement was further confirmed by a 34.4% increase in oral bioavailability in rats after oral administration owing to P-gp inhibition and increased permeation.¹⁰⁵

Nanoemulsions

Nanoemulsions comprising soybean oil and lecithin were prepared with Pluronic F68 and PEG 4000 as an emulsification system for the oral delivery of DTX. The formulation successfully delivered DTX to MCF-7 breast cancer cells with a 2.8-fold enhanced uptake as well as higher anticancer activity in mice without any toxic effects on the liver and kidney.¹⁰⁶ Another article reports the successful oral delivery and P-gp inhibition by a nanoemulsion of a naturally occurring frankincense oil. The resultant formulation was stable and showed improved uptake and P-gp inhibition in a Caco-2 cell line and low IC_{50} against MDA-MB-231 cells. A significantly higher oral bioavailability of 180-fold resulted in a 19% more antiproliferative effect than IV DTX and Tween 80, suggesting a high potential for formulation development.¹⁰⁷

Self-emulsifying drug delivery systems (SEDDS)

SEDDS form the next generation to emulsions, which rely on the interaction with physiological fluids for the synthesis of micro- or nanoemulsions. The system consists of drugs dissolved in oils and stabilized by surfactants which, upon reconstitution with an aqueous environment and gentle agitation, turn to emulsion as a function of SEDDS composition.

A self-nanoemulsifying drug delivery system (SNEDDS) was prepared by using Capryol 90, Labrasol and Transcutol HP and exhibited 17% increased oral bioavailability, improved antitumor activity and reduced nonspecific toxicity as compared to IV DTX and Tween 80.¹⁰⁸ In another study, spray-dried solid SNEDDS containing colloidal silica were synthesized as an oral carrier for DTX. These SNEDDS produced a nanoemulsion in water and showed 12.5% absolute bioavailability as compared to a clear DTX solution given either via IV or orally.¹⁰⁹ Another approach used to enhance the oral bioavailability of DTX used a solid supersaturable emulsifying drug delivery system. The system showed improved oral bioavailability of DTX in rats, as revealed by an 8.77- and 1.45-fold increased area under the curve as compared to DTX and conventional SEDDS.¹¹⁰ In another study, curcumin-based SEDDS were orally administered with DTX in rats, which showed improved bioavailability 2.4- to 3.2-fold on increasing curcumin concentration. No effect on the clearance of DTX was observed with curcumin, which suggested the inhibition of CYP450 (3A) and P-gp in the intestine.¹¹¹ SEDDS with DTX were synthesized using Capryol 90, vitamin E, Gelucire 44/14 and Transcutol HP with the aim to increase oral bioavailability, block chylomicron flow and improve biodistribution. Oral bioavailability in rats increased by 3.19-fold and cytotoxicity increased by 25-fold as compared to the IV DTX solution.¹¹²

Polymer–drug conjugate

Drug–polymer conjugates provide another possibility of delivering drugs with certain advantages over encapsulation in the polymeric NPs. In this strategy, a drug is conjugated to a polymer by biodegradable chemical bonds to control drug loading and release kinetics. Many natural and synthetic polymers have been explored for conjugation with the drug, leading to cost-effective, biocompatible and biodegradable formulations. By careful selection of the polymer, increased dissolution and permeation have been achieved with improved pharmacokinetics and pharmacodynamics.

Polysaccharides such as dextran, hyaluronic acid, carboxymethylcellulose and chitosan have all shown very good results when conjugated with different drugs of the taxane

family. DTX covalently attached to low-molecular-weight chitosan has shown good antitumor activity in vivo.¹¹³ Pharmacokinetic studies were conducted in mice bearing non-small cell lung carcinoma and a 15-fold increase in half-life was achieved as compared to IV administration of DTX. Moreover, the conjugate also produced low toxicity in terms of weight loss and hematological analysis. In another study, DTX was covalently attached to taurocholic acid linked to heparin, which resulted in self-assembled NPs. The results showed a 6-fold higher oral bioavailability, probably because of bile acid transporter in the small intestine. The formulation also resulted in better cytotoxicity and tumor accumulation of NPs as compared to controls, against MDA-MB-231 and KB tumor models.¹¹⁴ Carboxymethyl chitosan-linked DTX was suggested for improved oral bioavailability and tumor-targeting potential. The formulation indicated improved in vitro properties, and in in vivo conditions, mice bearing B16 melanoma showed improved bioavailability and tumor uptake as compared to DTX solution and a 4-fold decrease in toxicity.¹¹⁵

Micelles

Polymeric micelles are nanostructures composed of an inner hydrophobic core and a hydrophilic corona facing the aqueous environment. The hydrophobic core acts as a drug reservoir and the corona as a steric stabilizer ensuring stability of the system. Polymeric micelle-based nanocarriers have gained much importance recently because of their high solubilizing capacity, improved blood circulation time, small size and targeting ability.¹¹⁶ Their importance and various mechanisms of oral absorption such as membrane permeation, receptor-mediated pinocytosis, inhibition of efflux transporters and mucoadhesion make them a potential candidate for the oral delivery of anticancer drugs.¹¹⁷ Oral delivery of DTX has been reported using different polymeric micelles with some good results.

Polymeric micelles composed of polycaprolactone and polyethylene glycol have been used to increase oral permeation of DTX. The micelle system is further entrapped in a pH-responsive hydrogel for release into the intestinal lumen and subsequent absorption from the small intestine. The in vivo studies showed a 10-fold increased oral bioavailability with the hydrogel-based system as compared to the micelles alone. Better tumor suppression against a 4T1 breast cancer model, along with decreased systemic toxicity was observed as compared to standard IV therapy.¹¹⁸ In another study, micelles formed of beta-casein have been reported for the oral delivery of DTX for gastric cancer.

The nanosized micelles showed good stability and improved physicochemical properties of DTX, leading to increased oral bioavailability.¹¹⁹ DTX was also successfully delivered by co-block polymeric micelles composed of monomethylol poly(ethylene glycol)-poly(D,L-lactic acid), D- α -tocopheryl polyethylene glycol 100 succinate and a stearic acid-grafted chitosan oligosaccharide. The formulation showed good in vitro characteristics and a 2.52-fold increased oral bioavailability as compared to a DTX suspension.¹²⁰ Oral bioavailability of DTX has been successfully improved by micelles composed of stearic acid-modified *Bletilla striata* (an orchid species native to China, Japan, Korea and so on). The formulation showed good biocompatibility and cytotoxicity against different cancer cells including HepG2, Hela and MCF-7. The results indicated a 2- to 4-fold increased toxicity as compared to IV DTX.¹²¹

A nano-in-micro vector-based carrier was investigated for the improved oral bioavailability of DTX.¹²² In this study, biotin-modified micelles containing DTX were encapsulated in alginate microparticles targeting the intestinal permeation and a sodium-dependent multivitamin transporter for improved oral bioavailability. The formulation was characterized for various parameters and proved its stability for drug loading and release. A significantly improved oral bioavailability of 24.7-fold as compared to DTX and an 84.6% improved anticancer activity against sarcoma 180 was achieved with this dual targeting vector. DTX-loaded micelles in pH-responsive hydrogels were also reported to increase oral pharmacokinetics. The in vitro characterization of the formulation showed controlled release in the intestinal media due to pH responsiveness and improved cytotoxicity against a 4T1 breast cancer model. Oral administration showed a 10-fold increased bioavailability with enhanced antitumor effects, indicating a very good oral delivery potential of the formulation.¹¹⁸ A nanomicelle formulation was also reported for the improved solubility and oral bioavailability of DTX. Micelles comprising Tween 20 and 80 resulted in 14 nm micelles with a 99% encapsulation of DTX. The formulation showed prolonged release in gastric fluid with a decreased IC₅₀ compared with IV DTX and Tween 80. The formulation dramatically improved the solubility of DTX around 1,500 times, that is, 10 mg/mL in micelles as compared to 6 μ g/mL in water.¹²³ Another group reported methoxy poly(ethylene glycol)-poly(lactide) micelles with different size ranges to study the effect of the size of administration and distribution. The results indicated an 84.4% improved oral epidermoid tumor inhibition and cell penetration of DTX-loaded pH-responsive micelles.¹²⁴

Proniosomes

Niosomes are lamellar structures composed of nonionic surfactants with additives to improve their characteristics. Due to the disadvantages associated with their lamellar structures, the dry powder forms of niosomes, termed as proniosomes, have been prepared, which show niosomal dispersion upon rehydration in aqueous solution. Proniosomes are relatively stable and cheaper with improved features as compared to liposomes and other nanocarriers.¹²⁵ Proniosomes are studied for their transdermal delivery, oral delivery, buccal delivery and IV delivery of various classes of drugs. TPGS-modified proniosomes have also been studied for the oral delivery of DTX with improved antitumor activity. The developed formulation was stable in terms of particle size and potential with homogenous synthesis.¹²⁶ Later, an *in vitro* study showed improved permeation across a Caco-2 cell monolayer. Oral pharmacokinetics showed a 7.3-fold improved absolute oral bioavailability compared to a DTX solution and significantly higher antitumor efficacy in MCF-7-bearing mouse model.¹²⁷

Solid dispersion

Solid dispersions of DTX have been prepared to overcome the limitations of low aqueous solubility. In *in vitro* studies, Soluplus solid dispersion showed up to 93-fold increase in DTX solubility.⁵⁰ A poloxamer F-68/F-85-based solid dispersion has been reported to improve the oral bioavailability of DTX. The formulation is based on a mixture of Poloxamer F68 and Poloxamer F85, and showed a 2.97-fold improved bioavailability as compared to Poloxamer F68 alone, thus showing that F85 has a better potential as a permeation enhancement excipient in the formulation.¹²⁴ Another attempt to improve pharmacokinetics by using solid dispersion was made by using DTX with PVP-K-30 and sodium lauryl sulfate. The capsule-filled solid dispersion was tested in a Phase I clinical trial using ritonavir as a pharmacokinetic booster and was compared to IV DTX and Tween 80. The results showed no significant difference in pharmacokinetics, except for higher and more variable exposure to DTX after oral administration of Taxotere, which showed a major advantage with low intraindividual variability and the absence of ethanol and polysorbate in the formulation.⁴⁹

Toxicity concerns

Local toxicity associated with modified drug delivery systems, especially with nanocarriers, is a serious concern in the oral delivery of anticancer agents (DTX). The whole production cycle of the nanomedicine is different from conventional

pharmaceuticals in terms of production, distribution, clinical administration and waste disposal. Therefore, there is a prime need of intensive *in vitro* and *in vivo* toxicity profiling of oral administration. Despite all the advancements in the recent past, scientists are still struggling to clearly describe the toxicokinetic of these nanomedicine formulations and little research efforts have been put in this area to date.¹²⁸ The *in vitro* cytotoxicity screening of the polymers and other biomaterials cannot predict cytotoxicity, hemocompatibility and biocompatibility of such nanomedicines.¹²⁹ In addition to this, toxic effects may be encountered due to large surface area, high absorption capacity, the aggregation state and surface coating of the NPs.¹³⁰ Therefore, nanotoxicological evaluations of these new carriers should involve collaborations of scientists from cellular biology, molecular biology, pharmacology, chemical engineering, biotechnology and toxicology. Recently, Giardiello et al have reported accelerated oral nanomedicine discovery of human immunodeficiency virus drugs from miniaturized screening to clinical production. This process facilitated the synthesis and optimization of a miniaturized library of nanomedicines that are screened for physicochemical properties, *in vitro* and *in vivo* pharmacological evaluation and pilot-scale production of batches for clinical applications. This strategy is also applicable for multiple drug-loaded nanomedicines.¹³¹

Regulatory aspects

According to the above discussion, nanomedicine-based approaches have shown promising results in the oral delivery of DTX as summarized in Table 1. Although different regulatory agencies, such as the FDA, have established programs for accelerated approval of oncology products, the toxicity data of newly developed drug delivery systems are insufficient and may hinder the regulatory affairs for their approval and commercialization.¹³² Therefore, an early dialogue between the regulatory agencies and manufacturing will ensure successful exploration of health, safety and environmental aspects of the nanomedicine development process. In addition, a diverse library of reagents, experiments and equipment are available for the same purpose. This has created difficulty in interpretation and comparison of results reported by different authors. Therefore, uniformity in experiments is needed and standardized protocols must be developed for reproducible and, hence, more trustable science.¹³³ Nevertheless, new technologies including instruments, methods and techniques must be designed to meet the ever-increasing and unmet needs of nanomedicine safety assessment. Multidisciplinary studies including material

Table 1 Different nano-based approaches used for the oral delivery of Docetaxel

Serial no.	Material	Characterization	Outcomes	References
Polymeric nanoparticles				
1.	Polycaprolactone/Pluronic F-68	In vitro	Increased cytotoxicity and controlled drug release as compared to IV Docetaxel and Tween 80	81
2.	PLGA, vitamin E, montmorillonite	In vitro and in vivo	Improved oral pharmacokinetics with a 21-fold increased oral bioavailability and sustained release over 3 weeks as compared to IV Docetaxel and Tween 80. Also, a 3- to 4-fold increased anticancer activity was observed	82
3.	Polymethyl methacrylate, thiolated chitosan	In vivo	A 9-fold increased half-life and 96% increased oral bioavailability via increased permeation	83
4.	Lecithin	In vitro	The oral bioavailability was increased 3.65-fold as compared to a Docetaxel suspension	84
5.	Methyl- β -cyclodextrin and thiolated chitosan	In vivo	Improved oral bioavailability with a sustained release effect	85
6.	Sulfobutylether- β -cyclodextrin and chitosan	In vivo	A 1,447% increased oral bioavailability and decreased plasma clearance	134
7.	Methyl- β -cyclodextrin, polyisobutyl cyanoacrylate, thiolated chitosan	In vitro	Decreased enterocyte toxicity and inflammation as compared to IV Docetaxel and Tween 80	87
8.	Chitosan, PLGA		A 5-fold increased permeation and 5.11-fold increased anticancer activity against A549	88
9.	Glyceryl tributyrate, oleoyl polyoxyglycerides and PLGA 4000 NC embedded in Eudragit L and HPMC microparticles	In vivo and in vitro	A 10- and 8.4-fold improved oral bioavailability and C_{max} compared with IV Docetaxel and Tween 80. Increased antitumor effect against metastatic lung cancer	102
Lipid-based nanocarriers				
10.	Oleic acid-Docetaxel prodrug	In vivo and in vitro	A 4.04-fold increased oral bioavailability as compared to Docetaxel	95
11.	Cysteine-modified lipid nanocarriers with PEG 2000	In vivo and in vitro	A 13-fold increased AUC as compared to Docetaxel	96
12.	DTGPS 1000, Tween 80	In vivo and in vitro	Increased oral bioavailability as compared to IV Docetaxel and Tween 80 via P-gp blocking and lymphatic uptake	97
Hybrid nanocarriers				
13.	Polymeric core-lipid shell	In vitro	Sustained release and 94% better cytotoxicity as compared to IV Docetaxel and Tween 80	99
14.	Mixed lipid core and folate grafter thiolated chitosan shell	In vivo and in vitro	A 9.6-fold increased permeation and 13.6-fold increased oral bioavailability as compared to Docetaxel suspension	100
15.	Carboxymethyl chitosan, phospholipids, mesoporous carbon NPs	In vitro	Improved mucoadhesion, sustained drug release in gastric pH and improved anticancer activity	101
Theranostic nanocarriers				
16.	Liposomes, TPGS with quantum dots	In vitro	Improved cellular uptake with a 41-fold increased cytotoxicity as compared to IV Docetaxel and Tween 80	103
17.	SPION, PLGA, folate-chitosan	In vitro	Improved cellular uptake and shortened T_2 relaxation time for better imaging	104
Emulsions				
18.	Microemulsion Caproyl 90, Cremophor EL, Transcutol	In vivo and in vitro	A 34.3% increased oral bioavailability as compared to IV Docetaxel and Tween 80. Sustained release over 12 hours	105
19.	Nanoemulsion soybean oil, lecithin, Pluronic F68, PEG 4000	In vitro	2.8-fold increase in cellular uptake and least toxic effect against a MCF-7 cell line	106
20.	Frankincense oil-based nanoemulsion	In vivo and in vitro	182.5-fold increased relative oral bioavailability and 19% increased anticancer activity against MDA-MB-231	107
Self-emulsifying drug delivery systems				
21.	SNEDDS Capryol 90, labrasol, Transcutol HP	In vivo	17% increased oral bioavailability and antitumor activity as compared to IV Docetaxel and Tween 80	108
22.	SNEDDS based on colloidal silica	In vivo	12.5% increased oral bioavailability as compared to a Docetaxel solution	109

(Continued)

Table 1 (Continued)

Serial no.	Material	Characterization	Outcomes	References
23.	Supersaturable self-emulsifying drug delivery system	In vivo and in vitro	Improved oral bioavailability by 8.77-fold and AUC by 1.45-fold as compared to IV Docetaxel and Tween 80	110
24.	SEDDS curcumin	In vivo	2.6- to 4.4-fold increased C_{max} and 2.4- to 3.2-fold improved oral bioavailability	111
25.	SEDDS Caproyl 90, vitamin E, Gelucire 44/14 and Transcutol HP	In vitro and in vivo	A 3.19-fold increased oral bioavailability and a 25-fold increased cytotoxicity	112
Polymer–drug conjugates				
26.	Chitosan–Docetaxel	In vivo and in vitro	15-fold increased half-life as compared to a Docetaxel solution and decreased toxicity	113
27.	Taurocholic acid–heparin–Docetaxel	In vivo and in vitro	6-fold increased oral bioavailability with improved tumor targeting and uptake in MDA-MB-231 cells	114
28.	Carboxymethyl chitosan–Docetaxel	In vivo and in vitro	Improved oral bioavailability and tumor targeting with a 4-fold decreased toxicity	115
Polymeric micelles				
29.	Polycaprolactone, PEG	In vivo and in vitro	10-fold increased oral bioavailability in a pH-sensitive hydrogel and effective at inhibiting tumor growth in a 4T1 breast cancer model	118
30.	β -casein	In vivo and in vitro	Improved oral bioavailability and toxicity	119
31.	Co-block polymeric micelles	In vivo and in vitro	2.52-fold increase in oral bioavailability with sustained drug release	120
32.	Steric acid-modified <i>Bletilia striata</i>	In vivo	2- to 4-fold increased oral bioavailability as compared to IV Docetaxel	121
33.	Co-block mixed polymer biotin-modified micelles in alginate microparticles	In vivo and in vitro	27.4-fold increased oral bioavailability and an 84% increased cytotoxicity as compared to Docetaxel	122
34.	Tween 20 and Tween 80	In vitro	Improved solubility up to 1500-fold with higher anticancer activity against a C26 colon cancer cell line	123
35.	Methoxy poly(ethylene glycol)-poly(lactide)	In vitro and in vivo	84.4% inhibition of an oral epidermoid tumor	124
Proniosome				
36.	TPGS proniosomes	In vitro and in vivo	7.3-fold increased oral bioavailability and increased anticancer activity in MCF-7 tumor-bearing mice model	127
Solid dispersion				
37.	Poloxamer F68/P85	In vitro and in vivo	2.97-fold increased oral bioavailability	124

Abbreviations: AUC, area under the curve; IV, intravenous; NP, nanoparticle; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); SEDDS, self-nanoemulsifying drug delivery systems; SPION, superparamagnetic iron oxide nanoparticles; TPGS, docetaxel-loaded D- α -tocopheryl polyethylene glycol 1000 succinate.

science, toxicology, bioinformatics, molecular biology and medicine are expected to play an important role in the next decade.

Conclusion and future prospects

Given the recent technological advancements and knowledge accumulated over the past decades, we believe that smart targeted drug delivery carriers can be designed for the oral delivery of hydrophobic anticancer drugs such as DTX. Major barriers faced by DTX could easily be addressed using a nanotechnology-based novel drug delivery system by improving dissolution, increasing mucosal permeation, blocking P-gp efflux pump or pre-systemic metabolism leading to improved pharmacokinetics and pharmacodynamics of DTX. It is pertinent from the available literature that the oral administration of DTX will surely improve a patient's quality of life in addition to decreasing the cost of

therapy as well as reducing the overall burden of the health care system, especially in developing countries.

With the dawn of nanotechnology in chemotherapeutics, in particular, for oral delivery, a number of questions need to be addressed and justified. The most important factor is the estimation of the toxicity profile of these nano-based drug delivery systems, although dedicated efforts are being made by numerous researchers in this regard. The results achieved so far using different nano-based delivery systems seem to be very encouraging and promising to increase the oral bioavailability of DTX, along with increasing its pharmacokinetics and improving its toxicity properties manifold. Furthermore, sincere efforts are being made in understanding the cellular interactions of various formulations and the mechanisms of their efficacy and safety profile. Nevertheless, more stringent research attempts are needed for the translation of laboratory success into

product development. This could be achieved by focusing more on the ways to improve drug loading, release kinetics and the use of cost-effective materials and methods. Most of the reported studies have characterized such properties in vitro; yet, extensive in vivo evaluation is needed for better insight of the outcomes. Most importantly, more attempts should be made to explore new targeting moieties that can decrease unwanted side effects, which is a major concern with chemotherapy so far. Also, a detailed toxicological evaluation of these nanocarriers is needed for supporting the efficacy and safety of the formulation to be developed as a safe dosage for commercialization.

Acknowledgments

The authors are extremely thankful to their institutions for providing the necessary facilities and funding for this study.

Disclosure

The authors report no conflicts of interest in this work.

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