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Review Article

Innovative Nanocarrier Strategies for Enhanced Docetaxel Delivery in Cancer Therapy

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Abstract

Docetaxel (DTX) and several other taxanes are one of the most important class of anticancer chemotherapeutic agent. DTX commercially marketed as Taxotere® has higher clinical significance amongst other taxanes owing it a wide range of clinical applications. Although its broad range of applications and wide commercial use, its clinical use limited due to associated undesired side toxicity. Recent developments in nanotechnology has emerged with novel ways to overcome the limitations of DTX. Numerous nanocarrier system offer enhanced efficacy of DTX by utilizing EPR effect, tumor vascular hyperpermeability, reduced lymphatic drainage and raised interstitial fluid pressure in tumor cells. Furthermore, these systems can be actively transported via targeting over expressed receptors in tumor cells or via targeting tumor endothelium. This review covers a range nanocarrier based formulations of DTX used for *in-vitro* and *in-vivo* evaluation for several types of cancer. Although nanoformulations such as polymeric nanoparticles, lipidic nanoparticles or inorganic nanoparticles significantly enhance the solubility, efficacy and bio-distribution of DTX, important obstacles of nanoformulations such as quality control, stability (physico-chemical and physiological), industrial-scale manufacturing and technology, *in-vivo* fate (metabolism, excretion, and chronic toxicity) still remain a concern. Numerous supporting data and regulatory guidelines should be established regarding these concerns to make DTX nanoformulations applicable widespread clinically.

Keywords: Docetaxel; Nanocarriers; EPR effect; Cancer therapeutics; Cancer drug resistance.

Highlights

- DTX stabilizes microtubules, disrupting cell division and promoting apoptosis in cancer cells, and also inhibits angiogenesis to limit tumor growth.
- Delivery methods of DTX (oral, IV, transdermal, inhalation, rectal) face challenges such as poor solubility, bioavailability, and stability, requiring advanced formulation techniques.
- Various nanocarrier systems enhance docetaxel (DTX) solubility, efficacy, and bio-distribution using mechanisms like the Enhanced Permeability and Retention (EPR) effect.
- Challenges like quality control, stability, large-scale manufacturing, and in-vivo fate need more research and regulatory guidelines.

Introduction:

Docetaxel (DTX) is a semi-synthetic derivative of parent compound 10-deacetylbaccatin-III originally obtained from the bark portion of *Taxus brevifolia*. Due to limitation such as expensive process and low yield, it was later efficiently synthesized by French pharmacist in 1988 discovered needle like crystals from the extracts of *Taxus baccata* and consequently improved the precursor yield[1–7]. DTX structurally consist of hydroxyl functional group at 10th position owing DTX more aqueous solubility than other taxanes. DTX is a potent anti-mitotic chemotherapeutic agent responsible for reversible high-affinity binding to tubulin in the microtubule. The above process favors polymerization of microtubule followed by stabilization which impedes mitosis and tumor proliferation. DTX is also cell cycle inhibitor specifically inhibiting G2/M phase which makes it feasible for broad-spectrum anti-tumor chemotherapy viz, breast cancer, non-small cell lung cancer, prostate, and ovarian cancers etc. Additionally, it also has radiation sensitizing and immunosuppressant properties[1,8–13].

Cancer is categorized as one of the most deadly disease accounting for about million deaths around the world. According to WHO, the global cancer crisis has reached up to 20 million newly diagnosed patients with 9.7 million deaths in 2022[14]. It is also estimated the cancer burden worldwide would rise rapidly and exponentially in the upcoming future, due which there is an ever-increasing demand for cost-effective therapy with improved patient compliance. Currently available

options for cancer treatment have been categorized as chemotherapeutics, hormonal therapeutics, and immunomodulation. Chemotherapeutics are often preferred with an adjuvant to radiation and surgery pose a high degree of non-compliance. They also pose increased risks such as damaging healthy cells, immunosuppression, reoccurrence (metastasis) leading to decreased life expectancy and quality of life[14–17].

Various chemotherapeutic small molecules are commercially available such as Doxorubicin, Daunorubicin, Fluorouracil, Taxanes etc. Amongst taxanes, DTX being potent and broad-spectrum anticancer drug having high synthetic yield has gained considerable attention in the late 20th century[18,19]. DTX has few limitations to mention such as poor aqueous solubility, low oral bioavailability, ototoxicity, neutropenia, and hypersensitivity etc. The aforementioned limitations can be attributed to either drug alone or solvent used for solubilizing the drug[20,21]. However, classical anticancer formulations have the major drawback of toxicity and non-selectivity which causes unequal distribution and uptake by healthy cells. In order to overcome the aforementioned drawbacks, researchers have come up with a nanotechnology-based strategy called carrier-mediated targeted delivery. The above approach mainly consists of drug embedded in nanosized carrier enhancing its delivery with maintaining or enhancing its efficacy, improving site-specific delivery, reducing dose and toxicity of the drug[22,23]. Nanotechnology offers a variety of potential carriers such as polymer-based carriers, micellar systems, lipid-based carriers, inorganic nanocarriers etc, which ideally impart good water solubility with efficient stability and prolonged systemic circulation[24].

Targeting approaches can be classified as passive (involving weak/noncovalent/labile drug carrier interaction) and active (strong/covalent drug carrier interaction which can only be cleaved at a specific target). Nanocarrier based drug delivery approach has been quite successful and several FDA approved anticancer nanoparticulate systems such as Doxorubicin liposomes (Doxil®), Paclitaxel nanoparticles (Abraxane®), etc[25–28]. The current review overviews range of nanocarriers under preclinical and clinical development stages for delivery of DTX.

Mechanism of action of DTX:

The mechanism of action of DTX invloves disrupting the process of cell division, ultimately leading to the inhibition of cancer cell growth[29]. The initial stage entails the stability of microtubules. The crucial cellular constituent in all eukaryotic cells consists of microtubules, which also play a role in the proliferation and spread of cancer cells, depending on many vital cellular processes such as cell signaling, division, trafficking, and migration. Microtubules are cylindrical hollow filaments with a diameter of 25nm. They are formed by the noncovalent linkage of αβ-tubulin heterodimers. Microtubules display "dynamic instability" in cells and in vitro, which is a non-equilibrium behavior defined by alternating periods of growth and shortening. This occurs through the addition or removal of tubulin subunits at the ends of the microtubules[30]. Microtubules play a key role in several processes during mitosis, such as aligning chromosomes during metaphase and separating them during anaphase. These microtubules are sensitive to low-concentration medications that hinder their capacity to change and move, which is important for proper cell division[31].

DTX interacts with microtubules, enhancing their stability and thereby interfering with the cell division process. This disruption occurs because microtubules are essential for the formation of the mitotic spindle, which is responsible for separating chromosomes during cell division. DTX inhibits microtubule disintegration, resulting in cells being unable to complete cell division and becoming stranded in the mitotic phase for an extended period of time[32]. Cells exhibit an inability to undergo the process of division, resulting in the inability to produce two daughter cells. DTX-induced mitotic arrest elicits a biological response that ultimately results in apoptosis, a form of programmed cell death[33]. Cells that are unable to divide properly due to DTX's action undergo programmed cell death, reducing the growth of cancerous cells[30].

DTX not only inhibits cell division but also inhibits angiogenesis. Angiogenesis is the biological mechanism through which new blood vessels are formed, playing a crucial role in the proliferation and dissemination of malignancies[32]. Tumors necessitate a supply of blood in order to proliferate. By impeding angiogenesis, DTX might effectively restrict the tumor's capacity to obtain essential nutrients and oxygen, hence impeding its growth[29]. The mode of action of DTX specifically targets the proliferation of cells, a trait commonly observed in cancer cells. By interfering with the process of cell division and triggering cell death, it aids in the treatment of several forms of cancer.

Challenges in DTX Delivery

Oral administration of DTX (DTX) faces various obstacles, such as its low solubility in water (0.025 µg/mL) and limited ability to pass through cell membranes (1 cm/s×10^{-6}), which hinder absorption. Additionally, its high log P value (4.1) and extensive metabolism by CYP450 enzymes in the liver decrease its availability in the body, making oral delivery particularly challenging. Gastrointestinal enzymes and P-glycoprotein (P-gp) transporters reduce bioavailability by pre-systemic metabolism and export. DTX exhibits a high degree of protein binding (98%) and is susceptible to enzymatic breakdown in the acidic stomach environment. Being classified as a class II drug, it stimulates ATPase, which enhances the removal of substances and decreases their availability in the body. These challenges necessitate the use of sophisticated formulation procedures to ensure optimal oral administration[20].

The intravenous (IV) formulation of DTX presents various difficulties, mostly due to its limited water solubility. This necessitates the utilization of intricate solvent systems during administration, hence increasing the complexity of the treatment. Taxotere®, a

commercial medicine, is formulated with two vials containing DTX, Tween 80, and 13% (w/w) ethanol. Before usage, it must be diluted and used within 4 hours due to stability issues, which raises questions about its clinical safety. In addition, the administration of DTX can result in unanticipated and severe hypersensitivity reactions, which are partially caused by the presence of polysorbate 80, despite the use of prophylactic measures such as dexamethasone pretreatment. This emphasizes the necessity for alternate formulations. Moreover, the administration of DTX is frequently linked to unforeseeable acute hypersensitivity events, partially caused by the existence of polysorbate 80, despite the use of preventive measures such as dexamethasone pretreatment. An additional noteworthy concern is the accumulation of fluid in the body, which adds complexity to long-term treatment. In addition, the solvent system, specifically polysorbate 80, adds to toxicities associated with the vehicle. Despite efforts to create formulations without polysorbate in order to reduce negative effects, many of these initiatives have not been successful in achieving desired outcomes in clinical settings due to multiple challenges, such as insufficient drug containment, complicated preparation techniques, and inadequate long-term stability. Conquering these obstacles is crucial for enhancing the safety and effectiveness of DTX in cancer therapy[34].

Transdermal administration of DTX encounters various notable obstacles, mostly attributed to the stratum corneum (SC), the outermost layer of the skin. This layer works as a formidable barrier, characterized by its "brick and mortar" structure, which hinders the penetration of drugs. To successfully penetrate both the lipophilic stratum corneum (SC) and the deeper dermal layers, effective transdermal formulations need to achieve a delicate balance between hydrophilic and hydrophobic qualities. This is particularly challenging when dealing with DTX, which has a large molecular weight and low skin penetration properties. Several approaches, such as employing nanocarriers and chemical permeation enhancers, have been investigated to improve the penetration of substances through the skin. High Permeation Vesicles (HPVs), which utilize nanocarriers and a combination of permeation enhancers and new formulations such as elastic liposomes, have demonstrated potential in significantly improving penetration through the stratum corneum (SC). In addition, the combination of microneedle pretreatment with elastic liposomes has shown to enhance DTX skin permeability. However, the task of achieving a reliable and effective transdermal distribution of DTX is still difficult due to the intricate characteristics of the skin's barrier qualities[35,36].

Administering DTX through the lungs has the benefit of directly getting the medicine to the lower parts of the lungs by breathing, avoiding the drug's initial breakdown in the liver and digestion in the stomach. However, there are still a number of obstacles that need to be addressed. It is crucial to ensure that drug particles are of an optimal size to effectively reach the deep lung. Additionally, it is important to preserve the stability and bioavailability of the drug inside the respiratory system. Creating formulations that consistently administer the proper amount directly to lung tissues without inducing local irritation or harm poses a substantial obstacle. Moreover, achieving optimal absorption of inhaled nanoparticles in the deep lung tissues necessitates precise adjustment of their aerodynamic properties. Efficient techniques like spray-drying and freeze-drying are crucial for transforming drug-loaded nanoparticles into a desiccated powder that is suited for inhalation, hence maintaining their stability and functioning. The delivery mechanism must also enable the translocation of DTX over the air-blood barrier in order to access the systemic circulation and target organs, including potential brain metastases. To achieve a sustained release profile that extends the duration of the drug's effect while limiting high concentrations and toxicity, it is necessary to meticulously design and test the nanoparticle carriers[35, 37].

Administering DTX rectally has the advantage of avoiding the liver's first metabolism, which may enhance the drug's bioavailability. Nevertheless, this approach encounters certain obstacles, such as the need to provide uniform and thorough absorption across the rectal mucosa and the necessity to prevent local irritation in order to assure patient comfort. To develop a rectal delivery method for DTX, it is necessary to ensure that the drug remains stable and effective in the unpredictable rectal environment, which is characterized by varying pH levels and enzyme activity. It is crucial to develop formulations that can provide the appropriate amount without causing any harm to the local area. Additionally, it is important to create a delivery system that is both bioadhesive and thermosensitive, meaning it can turn into a gel at body temperature and efficiently stick to rectal tissues. In order to obtain greater systemic bioavailability, it is essential for DTX given rectally to avoid undergoing hepatic first-pass metabolism. Furthermore, it is imperative to attain a consistent release pattern that extends the duration of the drug's effect while reducing the highest levels of concentration to prevent any harmful effects. The formulation should also prioritize patient comfort, mitigating the discomfort typically associated with traditional solid suppositories. Finally, the crucial problem is to guarantee that the formulation offers substantial pharmacokinetic and pharmacodynamic effectiveness while minimizing toxicity when compared to oral or intravenous delivery. The aforementioned problems highlight the necessity for continuous study and advancement in other methods of administering DTX that do not involve injection[35,38].

DTX delivery systems improve the effectiveness of treatment, limit adverse effects, and decrease toxicity, offering substantial benefits compared to conventional formulations. The successful delivery of DTX through nanocarriers relies on two main bonding mechanisms: non-covalent and covalent. These mechanisms require specific properties such as stability until the target cancer cells are reached, selectivity in targeting tumor cells, slow release within these cells, minimal impact on healthy cells, solubility under physiological conditions, and controlled release[39]. Enhancing specificity is

achieved by designing nanocarriers with targeted agents. When choosing a suitable nanocarrier, it is important to address the current limitations and take into account the specific target. The non-covalent approach faces challenges in effectively encapsulating and maintaining stability, whereas the covalent method necessitates prodrugs that can stabilize in the bloodstream, convert efficiently into their active form, and release the drug once they reach cancer cells[39]. The drug delivery strategy of Solid Lipid Nanoparticles (SLNs) has drawbacks, such as a dense lipid crystal structure that hampers the effectiveness of loading drugs and their accessibility for absorption by cells, as well as quick removal by the reticuloendothelial system. Additionally, the drug-loading procedure is intricate due to the requirement of dissolving drug molecules within the lipid matrices employed for SLNs. Although the process of loading drugs into SLN lipid matrices is complex, nanoparticle systems such as SLNs, PMs, and LPHNPs provide a hydrophilic surface that allows for extended circulation and facilitates both active and passive targeting in the bloodstream[39,40]. The merits and demerits of nanocarrier based drug delivery are depicted in Fig. 1.

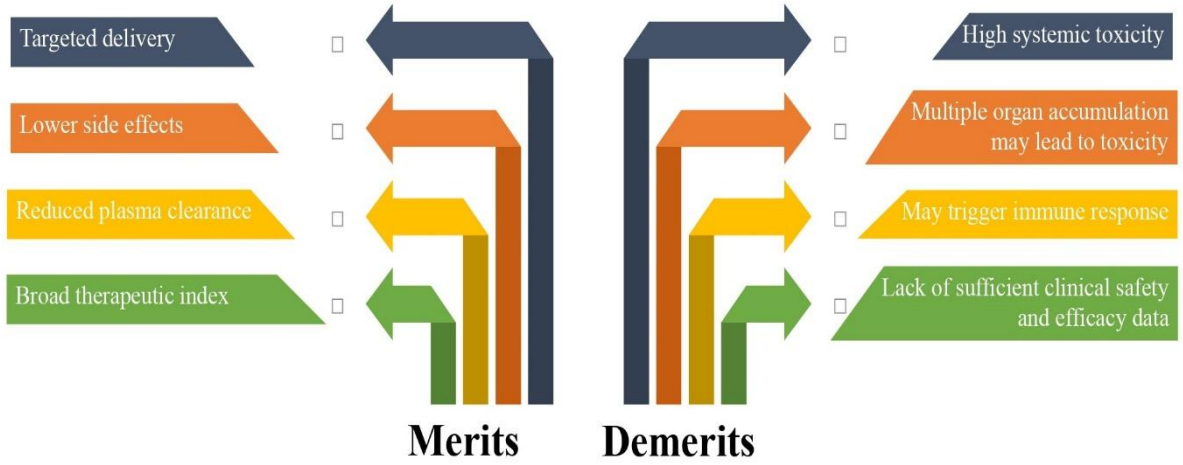

Figure 1: Merits and demerits of nanocarrier based drug delivery

The EPR effect in Nanomedicine Development

The Enhanced Permeability and Retention (EPR) effect elucidates the tendency of macromolecules to collect and persist in solid tumors for a longer duration compared to normal tissue. This phenomenon is frequently employed to rationalize the targeting of nanomedicines to tumors after intravenous injection. While EPR-mediated accumulation is only present in some types of tumors, it is commonly acknowledged as a fundamental characteristic of all solid tumors, forming the basis of a majority of nanomedicine cancer studies. The effectiveness of nanomedicine is impacted by a multifaceted range of parameters, such as the irregular occurrence of the EPR effect in tumors, the dispersion of the delivery system within the tumor, the rate at which the drug is released, and the level of exposure to the released medication in the bloodstream. Optimizing nanomedicine systems requires careful consideration of various parameters, such as the specific delivery method, drug, and tumor features[41].

Mechanism of targeting by nano drug vehicles

The targeting mechanism of nano drug vehicles comprises the utilization of both passive and active targeting strategies as shown in Fig. 2. These methods exploit distinct features of tumor tissues and cancer cells to improve the effectiveness of drug delivery. Passive targeting exploits the distinctive attributes of tumor microenvironments, such as the EPR effect. Tumors frequently stimulate the formation of new blood vessels with enlarged openings in their walls, which enables nanoparticles to enter and gather at the tumor location. Poor lymphatic outflow contributes to the increased accumulation of nanoparticles in tumors, while the diffusion of nanoparticles throughout the tumor is impeded by the elevated interstitial fluid pressure in the tumor microenvironment. In order to address this difficulty, certain nanocarriers are specifically engineered to take advantage of the distinct characteristics of the tumor microenvironment, such as its acidic pH and elevated redox potential, in order to enhance the efficiency of drug delivery[42,43].

Conversely, active targeting refers to the utilization of particular molecules connected to the nanocarriers that bind to cell surface receptors that are excessively produced by cancer cells. This approach improves the precision and effectiveness of delivering drugs to the location of the tumor. Antibodies, peptides, and small molecules are frequently employed to modify the surfaces of nanocarriers, allowing them to selectively bind to particular receptors on cancer cells. This method not only enhances the drug's concentration at the tumor location but also decreases the impact on healthy tissues by limiting non-targeted dispersion[43,44].

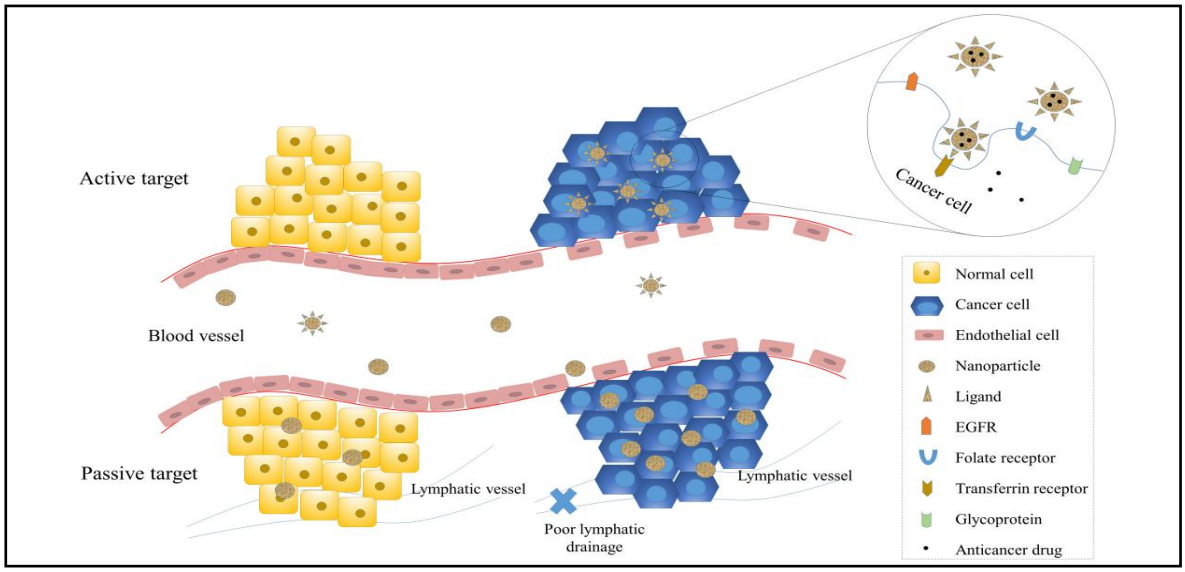

Figure 2: Passive and active targeting of NPs to cancer cells. Reproduced as per creative common attributions license from the source Yao et al., 2020[45]

The Warburg effect is a phenomenon observed in cancer cells, characterized by their preference for producing energy primarily through a rapid glycolysis process followed by lactic acid fermentation in the cytosol. This is in contrast to most normal cells, which generate energy through a slower glycolysis process followed by the oxidation of pyruvate in mitochondria. This phenomenon leads to the secretion of a substantial quantity of lactic acid, which allows cancer cells to flourish in surroundings that have low levels of oxygen and are acidic. Designing medication delivery methods that respond to the acidic conditions of the tumor microenvironment (TME) can effectively target this milieu. These systems exhibit stability under physiological pH conditions but undergo degradation under the acidic pH conditions present in tumors, hence enhancing the targeted delivery of drugs to cancer cells.

Mechanism of Drug Resistance:

Sekino *et.al.* have identified multiple mechanisms that contribute to DTX resistance in prostate cancer. These alterations involve variations in tubulin isotypes, such as βIII-tubulin, which can decrease the ability of DTX to attach to microtubules. Changes in the androgen receptor (AR) pathway, such as mutations and variations, can result in continuous activation and resistance. Genetic rearrangements can cause an increase in the expression of the ERG gene, which in turn can disrupt the normal functioning of microtubules and lead to the development of resistance. Drug transporters, such as ABCB1 and SLCO1B3, have the ability to influence the concentration of DTX within cells. When these transporters enhance the removal of DTX from cells or limit its entry into cells, it can result in resistance to the drug. Cancer stem cells, identified by the presence of CD44 and CD133, have the ability to withstand treatment and contribute to the reoccurrence of the disease. Proteins such as KIF11 and KIFC1, which play a role in the development of the mitotic spindle, can impact resistance by altering the dynamics of microtubules. Furthermore, the upregulation of the PI3K/AKT pathway might lead to resistance by promoting cell survival and proliferation[46].

Galletti *et.al.* identified two primary pathways for DTX drug resistance: Multidrug Resistance (MDR) and tubulin changes. MDR is characterized by the upregulation of drug efflux pumps, such as P-glycoprotein, which hinder the build-up of the drug in resistant cells. This mechanism results in decreased medication efficacy as a result of diminished intracellular drug levels. Modifications in the Tubulin/Microtubule System can result in alterations in the structure or composition of microtubules, which can subsequently decrease the susceptibility of tumor cells to DTX. The modifications influence the dynamic characteristics of microtubules and the interactions between drugs and their targets, ultimately affecting the drug's capacity to interfere with microtubule dynamics and cause cell death[47].

Strategies to overcome drug resistance (using nano drug delivery systems):

Methods to combat DTX drug resistance through the use of nano drug delivery systems encompass augmenting drug transportation, pinpointing particular resistance mechanisms, and strengthening the effectiveness of DTX in cancer cells that have developed resistance. An effective strategy is passive targeting using the enhanced permeability and retention (EPR) effect. This method allows nanoparticles to gather in tumor tissues by taking advantage of the distinctive features of tumor blood vessels. It overcomes resistance to chemotherapy without the need to increase the dosage. By altering the characteristics of nanoparticles, such as their stability, surface charge, and surface functional groups, it is possible to promote their circulation in the body, increase the accumulation of drugs at specific target areas, and overcome drug resistance by limiting their clearance by the reticuloendothelial system and mononuclear macrophages. Different types of nanoparticle carriers can be used to enhance the transportation of drugs. Liposomes, despite occasional instability, can be altered to improve stability and minimize drug leakage. Polymeric nanoparticles, specifically those composed of PLGA (poly lactic-co-glycolic acid), exhibit excellent biocompatibility and have

great drug-loading efficiency, hence facilitating the effective delivery of DTX. Mesoporous silica nanoparticles offer a flexible platform thanks to their expansive surface area and adjustable pore diameters. Stimuli-responsive release mechanisms provide precise medication delivery in response to specific triggers such as light, heat, or pH changes. This reduces the occurrence of hazardous side effects by ensuring that drug release occurs largely at the tumor site[48].

Active targeting strategies entail the modification of nanoparticles with ligands, antibodies, or aptamers that selectively bind to receptors that are excessively expressed on cancer cells. This modification enhances the uptake of nanoparticles and enhances the effectiveness of drugs. An example of this is when nanoparticles that are conjugated with folate target the folate receptor, they can improve the delivery of DTX to tumor cells that are resistant to treatment. In addition, combination therapy employs nanoparticle-based systems to integrate numerous therapeutic drugs, effectively overcoming resistance mechanisms through synergistic effects. An instance of enhancing cytotoxicity against resistant cancer cells can be achieved by combining DTX with P-gp inhibitors or autophagy inhibitors within the same nanoparticle. In addition, nanoparticles have the ability to circumvent efflux pumps such as P-glycoprotein, which are responsible for removing chemotherapeutic medicines from cancer cells. By encapsulating DTX in nanoparticles, it becomes possible to avoid the action of these pumps, resulting in increased drug concentrations inside cells and better therapeutic results. Simultaneously delivering siRNA or miRNA that target ABC transporters, in addition to anticancer medicines, can effectively overcome drug resistance. An example of this is the simultaneous delivery of miRNA-495 and doxorubicin, which has demonstrated effectiveness in reducing the expression of P-gp in cancer cells that are resistant to treatment. Utilizing nanoparticle-based methods that specifically target receptors such as KDR, it is possible to effectively treat resistant malignancies by enhancing the delivery of drugs to the tumor site through the tumor's blood vessels. In addition, the simultaneous administration of Bcl-2-targeted siRNA and chemotherapeutics using nanoparticles can effectively overcome resistance by specifically targeting anti-apoptotic proteins. Nanoparticle-based combination therapies that include NF-κB inhibitors, such as pyrrolidine dithiocarbamate (PDTC) and curcumin, have the ability to increase apoptosis and effectively overcome resistance. Nano drug delivery systems provide a possible method to improve the efficacy of DTX and address drug resistance in cancer therapy by incorporating these strategies[45,48].

Nanocarriers in DTX delivery:

The primary mechanism by which cells internalize nanoparticles is through endocytosis, a process in which the cell membrane surrounds the nanoparticles, forming vesicles that convey them into the cell. This mechanism comprises multiple mechanisms, namely phagocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis, and pinocytosis. Phagocytosis is a frequent occurrence in immune cells, where it entails the process of engulfing opsonized nanoparticles that are identified by certain receptors. Clathrin-mediated endocytosis is a process where clathrin-coated pits are formed to absorb nanoparticles (NPs), which often results in their destruction in lysosomes. Caveolin-mediated endocytosis is dependent on flask-shaped invaginations that contain a high concentration of caveolin proteins. This process is crucial for the control of lipids and the transmission of signals. The efficacy of each pathway is contingent upon the features of nanoparticles, such as their size, shape, and surface chemistry. These properties affect how nanoparticles interact with cell membranes and how they are processed within cells[49]. The complex mechanics have been depicted in Fig. 3.

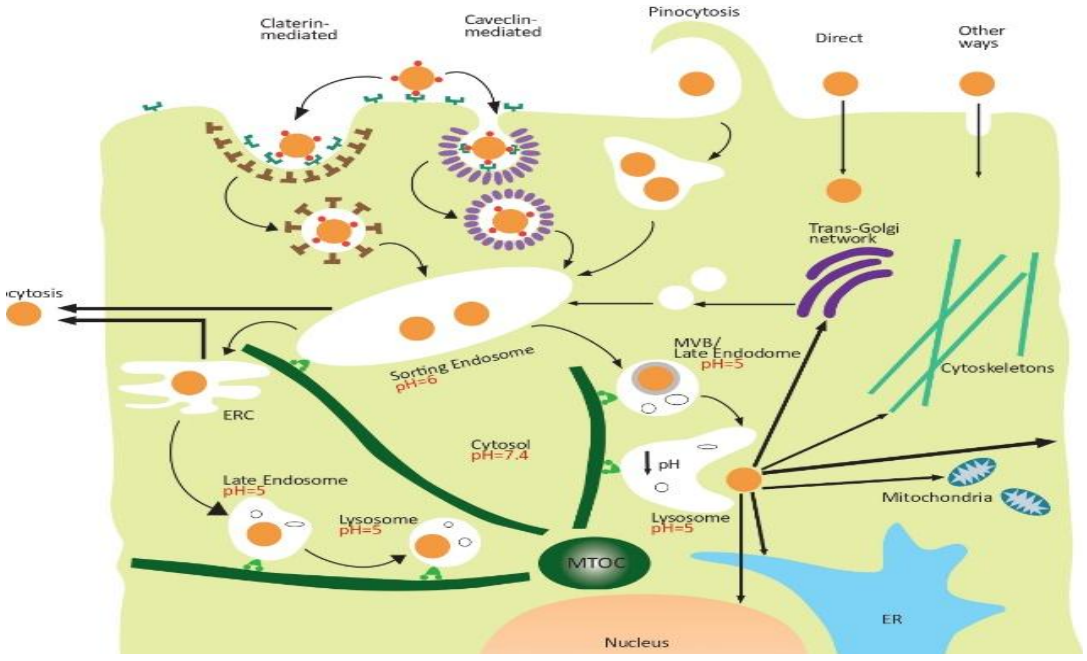

Figure 3: Molecular Mechanism of Nanoparticle Uptake

Several researchers around the world have carried out extensive clinical trials on classical taxane formulations. In spite, very few reports are available for carrier-based formulations of DTX. Different types of polymer-based, lipid-based and inorganic nanocarriers are discussed as follows and also depicted in Fig. 4.

1. Polymer-based nanocarriers:

Since the establishment of drug stability in polymeric nanosystems under physiological conditions, there has been a significant improvement in anticancer efficacy and widespread use of polymeric nanocarriers, especially aqueous soluble polymers in development of drug delivery system[23,49,50]. As described previously, polymeric nanocarrier and DTX in conjugation forms two distinctive types of system viz, Polymer-drug assembly (involving covalent interactions) and polymer nanoparticle (involving non-covalent interactions)[51]. Variety of polymeric nanoparticles have been employed for anticancer drug delivery imparting properties such as (i) good aqueous solubility (ii) biocompatibility (iii) steric protection and (iv) EPR effect[50,51].

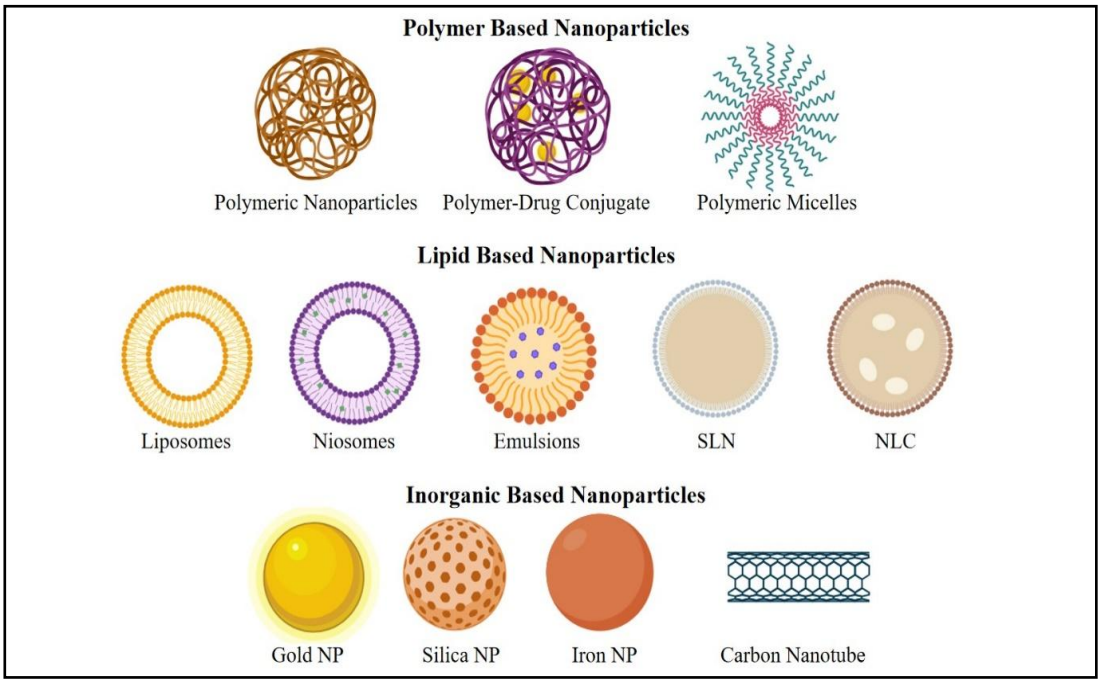

Figure 4: Nanocarriers in DTX Delivery

A. Polymeric nanocarriers: Wang et al., prepared DSPE-PEG2000 and soya lecithin conjugated DTX system for folate targeting. *In-vitro* evaluation of the developed system showed sustain release pattern. The developed system demonstrated reduced toxicity in healthy cells as compared to the marketed formulation. Furthermore, *in-vivo* studies demonstrated enhanced and site-specific tumor exposure in Kunming mice bearing B16 cells when compared to marketed formulation[52]. Ruiz-Gatón et al., prepared a novel DTX loaded pegylated poly (anhydride) NPs for oral bioavailability enhancement. The developed system demonstrated sustained release pattern and prolonged systemic circulation of NPs. Consecutively the developed system revealed enhanced oral bioavailability along with similar biodistribution pattern as that of Taxotere®. Moreover, the clearance of the developed system was found to be similar to that of Taxotere® administered intravenously, which suggests that release of DTX occurs at the epithelial surface followed by systemic circulation[53]. Gao et al., prepared a novel Interleukin 13 (IL-13) functionalized DTX loaded NPs for active targeting of glioblastoma. The developed system revealed the involvement of cytoplasm, endosomes and golgi apparatus in distribution NPs intracellularly. Consecutively the developed system also depicted enhanced cell apoptosis and tumor growth inhibition. Furthermore, *the in-vivo* evaluation revealed enhanced targeted and site-specific delivery of the developed system to glioblastoma cells as compared to non-functionalized NPs[54]. Kushwah et al., prepared a novel self-assembled DTX loaded NPs comprised of modified bovine serum albumin conjugated to anacardic acid and gemcitabine. The developed system was proposed to enhance the anticancer effect by targeted delivery as well as synergism by co-administration of DTX and gemcitabine. The developed system depicted significant enhancement in cellular uptake and apoptosis. Consecutively the developed system also demonstrated a significant increase in AUC and half-life by 6.12 and 6.28-fold as compared to Taxotere®. Moreover, the developed system depicted significant anti-tumor efficacy and safety by reducing nephro and hepatotoxicity[55]. Chu et al., prepared PLA and PLGA loaded DTX NPs using soft-lithography fabrication technique. The developed system was prepared and evaluated by varying drug loading (9 and 20%) of two identical sized, shaped and zeta potential of NPs. The developed system with 9% NP showed approximately 36% reduction in DTX exposure to other organs and increased plasma as well as tumor concentration of DTX by 16 and 39% respectively when compared to 20% NP system Therefore it was observed that 9% DTX NP showed better pharmacokinetics as

compared to 20% DTX NP, these variations depicted drug loading as significant consideration to industrial application[56]. Yu et al., prepared PLA-TPGS embedded DTX NPs using membrane-emulsification technique. The produced nanoparticles showed significantly larger values for area under the curve, half-life, and mean residence time compared to Taxotere®, with approximately 2.23-fold, 13.2-fold, and 8.51-fold increases, respectively. Furthermore, the system demonstrated increased tumor retention time imparting sustain release and enhanced activity against H-22 solid tumor-bearing mice when compared to Taxotere®[57].

Chitosan and Cyclodextrin are the most commonly used oligomers in medication delivery. Chitosan, when used as a nanocarrier, has the advantageous characteristic of being insoluble and stable at neutral and alkaline pH levels. However, its solubility increases in an acidic environment, which can be utilized to release medications specifically in the acidic environment of tumor cells[58–60]. Saremi et al., prepared thiolated chitosan encapsulated polymethyl methacrylate loaded DTX NPs. The developed system depicted sustained release pattern, excellent mucoadhesive properties and imparted enhanced GI permeability. The system demonstrated a consecutive 9-fold increase in half-life and a 10-fold improvement in oral bioavailability compared to free DTX[61]. Ahmad et al. fabricated surface-bound PLGA and chitosan-encapsulated DTX NPs. The in-vitro release profile of the developed system showed an initial burst release followed by a persistent release pattern. The method that was designed showed a significant increase in the amount of drug that can be absorbed via the mouth, up to 5.11 times more than when the drug is used alone. The method demonstrated a five-fold increase in apparent permeability across the rat gut when a third-generation P-gp inhibitor was present. Moreover, the system demonstrated improved cellular absorption in A549 cells, thereby confirming the involvement of P-gp inhibition and nanocarriers in the effective oral administration[62]. Badran et al., prepared novel chitosan encapsulated DTX loaded PLGA and PCL NPs. The developed system depicted sustained release pattern due to chitosan encapsulation. Consecutively, the developed system also showed a highly significant increased cytotoxicity in HT29 colon cancer cell lines as compared to free DTX. Furthermore, the developed system showed better pharmacokinetics by a 4-fold increase in AUC as well as enhanced anti-tumor activity[63].

Cyclodextrin (CD) are excellent nanocarriers for enhanced delivery of hydrophobic drugs due to the presence of hydrophobic core and a hydrophilic shell. Significant improvement has been reported in enhanced aqueous solubility, stability and bioavailability of DTX encapsulated in Cyclodextrin[64,65]. Liu et al. synthesized a new star-shaped β-CD derivative consisting of a CD core and poly(L-lysine) dendron arms. This derivative was used for the simultaneous administration of DTX and MMP-9 siRNA plasmid. The created system demonstrated a notable improvement in cell uptake, apoptosis, and very effective gene transfection in in-vitro trials, when compared to the use of the medication alone. In addition, the new method demonstrated exceptional blood compatibility and decreased potential toxicity in healthy cells[66]. Tao et al., prepared DTX loaded folic acid-CD system for targeted anticancer delivery. The developed system showed increased apoptosis in KB cells. Consecutively, the developed system also demonstrated enhanced tumor growth inhibition and specific accumulation into tumor sites in KB tumor-bearing mice. Moreover, the developed system depicted less toxicity towards healthy cells and tumor growth suppression which can be attributed to intrinsic mitochondrial-mediated apoptosis induced by the DTX complex[67]. Wu et al. synthesized nanoparticles (NPs) using sulfobutylether-β-cyclodextran and chitosan. These NPs were used to simultaneously administer DTX and berbamine. The developed system depicted a controlled release pattern and an augmented intestinal absorption. Consecutively the system demonstrated prolonged circulation of the drug in plasma and significant enhancement in relative oral bioavailability when compared to free DTX. Furthermore, the developed system revealed significant enhancement in cellular uptake, cytotoxicity and apoptosis rate when compared to free DTX[68].

B. Polymer-drug conjugate: Polymer-drug conjugates are the unique drug delivery systems obtained by covalent linkage between drug molecules and polymers. The conjugate systems alongside the drug, comprised of additional functional excipients such as targeting agents, PEG moiety to impart hydrophilicity can be harbored to the polymer thereby resulting into formation of nano-sized freight that are highly site-specific[69]. Murakami et al., prepared a novel PEG and CMC conjugated DTX NPs known as Cellax. The developed system was evaluated for anti-stromal activity in the orthotopic mouse model and depicted an 82% reduction in α-smooth muscle actin level when compared to plain DTX and Abraxane®. Mice treated with Cellax showed a prompt increase in tumor perfusion and vascular permeability by 70 and 30% respectively when compared to control, plain DTX and Abraxane® groups. Similarly, a significant reduction was observed in tumor matrix and tumor interstitial pressure by approximately 2.5 and 3-fold respectively when compared to control, plain DTX and Abraxane® groups. Furthermore, Cellax treatment significantly affected metastasis of cells causing a reduction in lung nodules by approximately 24-fold when compared to plain DTX and Abraxane®[70]. Kushwah et al., prepared dual drug loaded polymer-drug conjugate (PDC) of DTX and Gemcitabine. The study aimed at evaluation of modulation in pharmacokinetics and toxicokinetics of the developed system using short chain (lysine and glycine) and long-chain polymers (PEG1000, PEG2000, and PEG3500) to obtain conjugated system. The dual drug conjugate system expressed good physicochemical properties and stability of the system in plasma. Amongst the developed system long chain PDC system depicted increased cellular uptake as well as enhanced cytotoxicity in MCF-7 and MDA-MB-231 cell lines when compared to free drug. Consecutively the developed system (PEG2000 and PEG3500) revealed better pharmacokinetics by significantly increasing the AUC as compared to drug

alone[55]. Furthermore, this system also showed significant tumor growth inhibition and increased survival rate. Moreover, the NPs also demonstrated a significant reduction in hematological toxicity, hepatotoxicity, and nephrotoxicity[55,70]. Kulhari et al. developed a new formulation of Bombesin peptide nanoparticles coupled with DTX for the purpose of delivering drugs specifically to breast cancer cells. The designed system exhibited a sustained release pattern. Furthermore, the proposed system exhibited a notable reduction in IC50 and a twelve-fold enhancement in cytotoxicity in MDA-MB-231 cell lines when compared to free DTX and Taxotere®[71].

C. Polymeric Micelles: Structurally, polymeric micelles consist of an outward-facing hydrophilic corona and an inward-facing hydrophobic core. The hydrophobic core serves as a storage area for drugs, while the steric stability is achieved by the corona, which ensures the overall stability of the system. Polymeric micelle-based nanocarriers have become important due to their increased ability to dissolve substances, extended stay in the bloodstream, small size, and precise delivery to specific targets[72,73]. Wang et al., prepared PCL and PEG-based micellar system for enhanced oral permeation. The developed system was embedded in a pH-responsive hydrogel specifically targeting intestinal release and absorption. The pH-responsive modification of developed system demonstrated sustain release in the intestine. Consecutively the pharmacokinetic study resulted in 10 fold improvement in oral bioavailability vs micelles alone. Furthermore, the system depicted significant tumor suppression with reduced toxicity against 4T1 breast cancer model vis-à-vis i.v. DTX[74]. Varshosaz et al. developed a new polymer, poly (styrene-maleic acid) linked to poly (amide-ether-ester-imide)-polyethylene glycol, for delivering DTX in the treatment of breast cancer. The proposed system exhibited a five-fold increase in cytotoxicity and improved cellular absorption in a human breast cancer cell line compared to free DTX. Furthermore, the proposed system demonstrated greater efficacy in suppressing tumor growth in live organisms, as well as improving survival rates, when compared to the use of DTX alone[75]. Dou et al. synthesized polymeric mixed micelles using monomethylol poly (ethylene glycol)-poly (d,l-lactic acid), d-α-tocopheryl polyethylene glycol 100 succinate, and stearic acid–grafted chitosan oligosaccharide for the administration of DTX. The method that was developed exhibited a slower release from micelles in comparison to free DTX. In addition, the method demonstrated a 2.52-fold higher oral bioavailability and fewer adverse effects compared to free DTX[76]. Guo et al., prepared a novel co-delivery of resveratrol and DTX via polymeric micelles comprised of methoxy poly (ethylene glycol)-poly (d,l-lactide) copolymer to treat breast cancer. The developed system depicted a significantly lower IC50 in MCF-7 cell lines as compared to free drug. Consecutively, the developed system demonstrated sustained release pattern and enhanced cytotoxicity in MCF-7 cell lines. Moreover, the developed system depicted enhanced pharmacokinetics especially AUC by 3 and 1.6-fold of DTX and resveratrol respectively in comparison with drug alone[77]. Guan et al. synthesized polymeric micelles using stearic acid-modified Bletilla striata. The new system demonstrated favorable biocompatibility and cytotoxicity against several cancer cells, such as HepG2, Hela, and MCF-7. Consecutively, the system depicted enhanced cellular uptake as well as apoptosis rate when compared to i.v. DTX. Furthermore, the system was also found to prevent hemolysis indicating significant biocompatibility[78]. Hekmat et al. developed a nanomicellar system of DTX using Tween 20 and 80, resulting in micelles measuring 14 nm in size and achieving a 99% encapsulation efficiency of DTX. The created method significantly enhanced the solubility of DTX by approximately 1,500-fold, resulting in a concentration of 10 mg/mL in micelles compared to 6 µg/mL in water. Consecutively, the system showed good stability in the gastric fluid as well as intestinal fluid along with prolonged drug release when compared to Taxotere®[79]. Song et al., prepared poloxamer-based solid dispersions for oral delivery of DTX. The developed system comprised of poloxamer F68 and P85 used either in combination or alone. Consecutively, the system comprised of F68 alone resulted in the enhanced dissolution of DTX but no improvement in intestinal permeation which consequently, demonstrated the 1.39-fold enhancement in oral bioavailability. However, F68/P85 based system resulted in enhancement in both dissolution as well as permeation which consequently, enhanced the 2.97-fold increase in oral bioavailability and revealed potential desirability for oral delivery of DTX[80]. Zhao et al., prepared vitamin E-TPGS and TPGS-siRNA encapsulated DTX micelles conjugated with Herceptin for multi-drug resistant anticancer treatment. The developed TPGS-siRNA system demonstrated pH-responsive release intracellularly. Consecutively the herceptin conjugated TPGS-siRNA micellar system showed a significant decrease in IC50 as compared to Taxotere®. Furthermore, the system depicted significant synergistic antineoplastic effect in SK-BR-3, NIH3T3, and MCF7 cell lines vis-à-vis with Taxotere®[81]. Lang et al., prepared a novel DTX-loaded micelle for targeted delivery to the tumor microenvironment. The developed system comprises of poly [(^{1,4}-butanediol)-diacrylate-b-N,N-diisopropylethylenediamine]-polyethyleneimine as pH-sensitive polymer and poly [(^{1,4}-butanediol) – diacrylate - b- N, Ndiisopropylethylenediamine] - peptide-polyethylene glycol as matrix metalloproteinase responsive polymer. The developed system depicts enhanced tumor growth inhibition as well as suppression of pulmonary metastasis in comparison to free drug. The created system consistently shown improved effectiveness in inhibiting tumor growth and increased absorption by tumors in mice with 4T1 tumors, in comparison to the free medication. In addition, the system that was created demonstrated notable biocompatibility and decreased toxicity in mice when compared to the medication in its free form[82]. Raza et al. developed dextran-PLGA polymeric micelles to deliver DTX to breast cancer cells without the need for surfactants. The nanocarriers that were created increased the cytotoxicity by nearly 100% in MCF-7 and MDA-MB-231 cells. In addition, the NPs demonstrated significant compatibility with RBCs and altered the

pharmacokinetic profile by boosting bioavailability by a factor of 16 compared to free DTX[83]. Guo et al., prepared novel polymeric micelles comprised mPEG and PLGA disulfide conjugated with DTX and verapamil for treatment of multi-drug resistant tumor cells. The developed system depicted enhanced *in-vitro* cell apoptosis and increased anti-tumor efficacy. Consecutively, the developed system also demonstrated prolonged *in-vivo* circulation and improved drug accumulation in tumor cells[84]. Wu et al., prepared a novel reduction-sensitive mixed micelle comprised of mPEG-PCL conjugated to DTX and Doxorubicin as amphilic prodrugs for synergistic anticancer treatment. The developed system depicted enhanced cellular uptake and cytotoxicity *in-vitro* as well as efficient accumulation in MCF-7 cells and significant tumor growth inhibition as compared to pure drug. Furthermore, the developed system showed an advantage over the pure drug such as prolonged systemic circulation, controlled release of the drug, and reduced non-specific distribution to normal organs, in turn, lowering toxicity[85]. Li et al., prepared a novel alpha lipoic acid stabilized DTX-IR780 micelles assisted Fluorescence and Photoacoustic imaging in breast cancer therapy. The system that was created demonstrated substantial cellular absorption and cytotoxicity, as well as the suppression of tumor development by the combined use of photothermal therapy and chemotherapy in breast cancer cell lines, surpassing the effects of the drug used in its unbound form. Moreover, in-vivo investigations demonstrated improved accumulation of the created system in the tumor cells and higher effectiveness in treating cancer compared to the unbound medication. Furthermore, the combination of photothermal and chemotherapy greatly enhanced the effectiveness in inhibiting tumor growth[86]. The details of various nanosystems have been depicted in Table 1.

Table 1: Preclinical development of DTX nano-formulation

Nano-formulation	Carrier/system	Outcomes	Ref
Polymeric NPs	Poly(n-butylcyano acrylate)	Enhanced *in-vitro* and *in-vivo* performance in comparison with free drug.	37
	Poly(ethylene glycol)-Poly (lactide-co-glycolide acid)	Augmented *in-vitro* cell uptake and cytotoxicity in BT-474 (HER2-positive) cells vis-à-vis free drug.	87
	Poly (caprolactone)-Poly (ethylene glycol) (PEG-PCL) and Poly (lactic acid)-Poly (ethylene glycol) (PEG-PLA)	Increased drug retention *in-vitro* and *in-vivo* as compared to drug alone.	88
	Poly(lactide-co-glycolide acid)-TPGS, montmorillonite	Amplified *in-vitro* cytotoxicity and oral delivery in rodents in comparison with plain drug.	89
	Poly(ethylene glycol)-b-poly(ε-caprolactone)	Improved cytotoxicity and superior tumor growth inhibition in prostate and breast cancer induced in experimental animals as compared to free drug.	90
	Poly(lactide-co-glycolide acid), lecithin, folic acid and Poly(ethylene glycol)	Increased cytotoxicity in HTB-43 cells and enhanced anticancer efficacy in mice vis-à-vis free drug.	91
	Poly(ε-caprolactone) and Pluronic F68	Heightened cellular uptake and cytotoxicity in MCF-7 TAX30 cell lines in comparison with plain drug.	92
	Poly(lactide-co-glycolide acid)	Enhanced cytotoxicity in T47D cells marked increase in pharmacokinetics and anti-tumor efficacy.	93
	Heptakis (2-O-oligo(ethyleneoxide)-6-hexadecylthio-)-β-cyclodextrin	Enhanced cell apoptosis and cytotoxicity in Hep-2 cancer cell lines.	94
Polymer-drug conjugate	N-(2-hydroxypropyl) methacrylamide HPMA	Enhanced anti-tumor efficacy in rodents with no toxicity to healthy cells.	95
	Low molecular weight chitosan	Enhanced cytotoxicity in NCI-H358 and U87MG cell lines. Augmented pharmacokinetic profile with superior anti-cancer efficacy in mice.	96

	Acetylated CMC and PEG	Enhanced pharmacokinetics and anti-tumor efficacy.	97
	Hyaluronic acid	Enhanced tumor uptake and prolonged circulation in *in-vitro* and *in-vivo* respectively.	98
	Hydrophobically modified glycol chitosan	Enhanced pharmacokinetic profile with significant augmented anti-tumor efficacy and reduced side toxicity in mice bearing A459 lung cancer.	99
	Thiolated chitosan	Enhanced permeation, cellular uptake and high cytotoxicity in MCF-7 and Caco-2 cancer cell lines.	100
	D-α-tocopheryl polyethylene glycol succinate 2000 and folic acid	Enhanced targeted delivery, cellular uptake and cytotoxicity in MCF-7 cancer cell lines.	101
Polymeric micelle	MPEG-PLA and Pluronic P85	Enhanced *in-vitro* and *in-vivo* performance.	102
	Octreotide modified Poly(ethylene glycol)-b-PLA	Enhanced *in-vitro* activity and *in-vivo* anti-tumor efficacy devoid of non-specific toxicity.	103
	Poly(N-isopropylacrylamide-co-acrylamide)-b-poly(DL-lactide)	Enhanced NP accumulation in tumor as well as improved anti-tumor efficacy with reduction in side toxicity.	104
	Methoxy-poly(ethylene glycol)-b-poly(D,L-lactide)	Enhanced *in-vitro* anticancer efficacy in breast, lung and ovarian cancer cell lines. Improved pharmacokinetic profile and increase anti-tumor efficacy in mice, rats and beagle dogs with good bioequivalence and less side toxicity.	105
	D-α-tocopheryl poly(ethylene glycol) 1000 succinate	Enhanced *in-vitro* cytotoxicity in C6 brain glioma cell lines and *in-vivo* biodistribution.	106
Liposomes	Transferrin, methoxy-poly(ethylene glycol) and 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine	Enhanced targeted cytotoxicity and prolonged half-life with good pharmacokinetic profile.	107
	D-α-tocopheryl poly(ethylene glycol) 1000 succinate and Poly(ethylene glycol)	Enhanced *in-vitro* activity and significant improvement in anti-tumor efficacy.	108
	Folate-poly (Poly(ethylene glycol)-cyanoacrylate-co-cholesteryl cyanoacrylate)	Enhanced cell uptake and apoptosis in MCF-7 and A-549 cell lines. Enhanced pharmacokinetic profile and anti-tumor efficacy suggested higher uptake in tumor cells with reduced non-selective uptake by healthy organs.	109
	D-α-tocopheryl polyethylene glycol 1000 succinate mono-ester	Enhanced cellular uptake and cytotoxicity in MCF-7 cell lines.	36
	Cholesterol-folate-Poly(ethylene glycol)	Enhanced cytotoxicity in MCF-7 along with superior pharmacokinetic profile. Significant augmented anti-tumor efficacy and tumor accumulation.	110
	Glycyrrhetinic acid functionalized DTX-liposomes	Enhanced cell uptake and anti-cancer efficacy as well as superior pharmacokinetic profile.	111
Emulsion	Capryol 90 (oil), Cremophor EL (surfactant), and Transcutol (co-surfactant)	Enhanced *in-vitro* permeation and *in-vivo* oral bioavailability.	112
	Soya oil and Miglyol 812, along with soybean lecithin, Pluronic F68 (poloxamer 188), glycerol, oleic acid, and vitamin E	Enhanced pharmacokinetic profile along with reduced toxicity in healthy cells.	113

	Soybean oil and Miglyol 812 (medium chain triglyceride). Surfactants-soybean lecithin and Pluronic F68 (poloxamer 188)	Enhanced pharmacokinetics in beagle dogs. Higher anticancer efficacy was found in mice bearing A549, BEL7402 and BCAP-37 cancer cells. Reduced toxicity was found in comparison to free drug.	114
	lecithin and soya bean oil	Enhanced pharmacokinetics and anti- glioma efficacy alongside significant reduction in hemo-toxicity.	115
	Capryol 90, Vitamin E TPGS, Gelucire 44/14, and Transcutol HP	Enhanced *in-vitro and in-vivo* anticancer efficacy.	21
	Lactose	solid supersaturatable self-emulsifying drug delivery system of DTX enhanced pharmacokinetics and permeation across intestinal lumen in rats	116
SLN	Dioleoylphosphatidyl ethanolamine and lactobionic acid	Enhanced targeting in hepatocellular cancer cell line and superior anticancer activity in rodents.	117
	TGPS 1000 and Tween 80	Better pharmacokinetics with significant reduction in long-term toxicity.	68
	Folic acid functionalized	Enhanced pharmacokinetics and apparent low toxicity.	118
NLCs	Oleic acid-linked DTX	Enhanced pharmacokinetics and enhanced the prodrug loading up to 5-fold.	119
	Lipid nanocarriers modified wit Cysteine	Significant improvement in the penetration of substances in laboratory tests and showed favorable results in the study of how the body processes drugs	120
	Glyceryl monostearate, lecithin, and capric triglyceride	Improved drug solubility, increased entrapment efficiency, and favorable in-vitro release kinetics	121

2. Lipid-based nanocarriers:

A. Liposomes: These systems are categorized as either unilamellar or multilamellar based on the quantity of lipid bilayers they include. Water-soluble medications can be enclosed within the watery compartments, whereas lipophilic or amphiphilic substances can be confined between the layers of lipids[122]. Several liposomal DTX formulations are currently undergoing evaluation in both preclinical and clinical trials. NeoPharm, Inc. conducted a Phase I clinical trial to investigate the effectiveness of a new delivery system called liposome-encapsulated DTX (LE-DT). The trial focused on determining the maximum tolerated dose, dose-limiting toxicity, pharmacokinetics, and anti-tumor effects of LE-DT in patients with advanced cancers[123]. Yang et al., prepared DTX and vascular endothelial growth factor (VEGF) siRNA loaded dual peptide modified cationic liposomes. The developed system depicted enhanced binding ability and internalization of the drug into glioma cells. Consecutively, the developed system depicted enhanced anti-tumor activity and significant tumor targeting in U87 MG tumor-bearing mice as compared to drug alone. The enhanced antitumoral activity of the developed system observed mainly due to the avert opsonization as well as blocking the non-specific RES uptake. Furthermore, the developed system provides an effective strategy for brain-targeted drug delivery of DTX and siRNA in synergism along with tumor growth inhibition[82]. Sonali et al., prepared DTX encapsulated in transferrin conjugated TPGS liposomes for brain targeting. The developed system depicted a slow and sustained release pattern. Consecutively, the *in-vivo* evaluation revealed better pharmacokinetics and superior brain targeted potential of the developed system depicting enhanced site-specific delivery in comparison with Docel™. Moreover, the developed system also showed 8.91-fold enhanced anticancer efficacy and reduction in non-selective toxicity when compared with Docel™[36]. Fan et al., prepared a novel prodrug-modified cationic liposome for DTX and gemcitabine targeted delivery in CD44-overexpressed triple negative breast cancer. The developed system depicted enhanced cell uptake in the MDA-MB-221 cell line. *In-vitro* studies revealed that the developed system demonstrated significantly enhanced apoptosis, cytotoxicity and suppressed wound healing. Consecutively, the developed system depicted selective accumulation in tumor cells. Moreover, the developed system also showed enhanced anti-proliferation as well as anti-tumor efficacy and devoid of systemic toxicity[124]. Kushwah et al., prepared a novel anacardic acid functionalized stealth liposomes for targeted delivery of DTX in breast cancer animal model. The developed system depicted sustained release pattern and was found stable in accelerated storage conditions. Moreover, the

developed system demonstrated enhanced cellular uptake by 2.88-fold when compared with plain DTX. Moreover, the developed system depicted enhanced tumor growth inhibition and apoptosis in MCF-7 cell line in comparison with plain DTX. Furthermore, *in-vivo* pharmacokinetics of the developed system revealed improved AUC and half-life by approximately 3.7 and 4.5-fold as compared to Taxotere®, respectively. Moreover, the developed system also demonstrated a significant reduction in tumor volume and non-selective toxicity in comparison with Taxotere®[125]. Raju et al., prepared Trastuzumab conjugated TPGS loaded DTX liposomal system. The developed system depicted significant decrease in IC50 with SK-BR-3 cells when compared to free DTX. Consecutively, the system depicted enhancement by 3.47 and 10-fold in half-life and AUC compared to free DTX. Furthermore, the system also demonstrated enhanced cytotoxicity in comparison with free DTX[87].

B. Proniosomes: Niosomes refer to composite structures of nonionic surfactants that have a lamellar structure. Proniosomes, which are dry powder variants of niosomes, have been developed to address the limitations of their lamellar structures and improve stability[126]. Proniosomes exhibit enhanced stability and cost-effectiveness in comparison to liposomes and other nanocarriers, while also showcasing superior characteristics[127]. Liu et al. formulated TPGS-modified proniosomes for the purpose of orally administering DTX. The system that was created demonstrated enhanced entrapment efficiency and a biphasic release pattern characterized by an initial burst release followed by persistent release. Subsequent in-vitro experiments demonstrated enhanced permeability across a Caco-2 cell monolayer. The pharmacokinetics of the system demonstrated a 7.3-fold increase in the amount of drug absorbed when taken orally, compared to the DTX solution. This resulted in much greater effectiveness in inhibiting tumor growth in a mouse model with MCF-7 tumors[128].

C. Emulsions: Zhang et al., prepared a novel lipid emulsion comprised of DTX and linoleic acid conjugate for breast cancer treatment. The developed system showed sustained release pattern in PBS. Moreover, the developed system demonstrated good *in-vitro* cytotoxicity against 4T1 breast cancer cells. Consecutively, the pharmacokinetic study revealed that the developed system enhanced bioavailability and prolonged half-life as compared to plain DTX. Furthermore, the pharmacodynamics of the developed system revealed a good level of tolerance and improved efficacy in mice bearing breast cancer model[129]. Ma et al., prepared a novel anti-tumor synergistic agent Brucea javanica oil, soybean lecithin and PEG comprised DTX loaded microemulsion. The developed system showed superior pharmacokinetics by an increase in AUC and prolongation of half-life as compared DTX alone[130]. Verma et al. formulated a nanoemulsion using lecithin, soybean oil, Pluronic F68, and PEG 4000 to facilitate the oral administration of DTX. The new approach exhibited improved absorption by MCF-7 breast cancer cells, with a 2.8-fold increase, and indicated greater anticancer efficacy in mice without causing any harmful effects on the liver and kidney[131]. Pandey et al., prepared DTX loaded nanoemulsion comprised of acetyl-11-keto-β-boswellic acid for P-gp modulation and oral delivery DTX. The system demonstrated stability against stress conditions as well as under physiological conditions. Consecutively, the system also showed enhanced cell uptake and low IC50 in MDA-MB-231 cells and P-gp inhibition in a Caco-2 cell line. Furthermore, the system depicted significant enhancement of up to 180-fold increase in oral bioavailability consequently improved antiproliferative effect with 19% greater inhibition than Taxotere®[132].

Self-emulsifying drug delivery systems (SEDDS) forms the future generation to emulsions, which can form *in-situ* micro- or nanoemulsion systems. Seo et al., prepared a novel DTX-loaded self-nanoemulsifying drug delivery system (SNEDDS) comprised of Labrasol, Capryol 90, and Transcutol HP. The system that was created demonstrated a 17% increase in the amount of a drug that can be absorbed by the body through the mouth, compared to a solution of the drug. The system exhibited improved anticancer effectiveness and reduced nonspecific toxicity in comparison to Taxotere®[133]. Quan et al. developed spray-dried solid self-nanoemulsifying drug delivery systems (SNEDDS) using colloidal silica as an oral carrier for DTX. The formulated self-nanoemulsifying drug delivery system (SNEDDS) exhibited a 12.5% absolute bioavailability, which was compared to the bioavailability of the DTX (DTX) solution administered intravenously (i.v.) or orally[134]. Valicherla et al. formulated self-emulsifying drug delivery systems (SEDDS) including DTX, which consisted of vitamin E, Gelucire 44/14, Capryol 90, and Transcutol HP. The objective was to increase the absorption of the drug when taken orally and boost its dispersion in the body. The method that was created demonstrated improved permeability and retention in tumors in mice with generated breast cancer. The new method demonstrated a 3.19-fold increase in oral bioavailability and a 25-fold increase in cytotoxicity compared to Taxotere®[21].

D. Solid lipid nanoparticles: Solid lipid nanoparticles (SLNs) have demonstrated benefits such as increased drug capacity, extended storage stability, and enhanced permeability compared to other lipid-based nanocarriers for delivering anticancer medications[135]. Cho et. al., prepared DTX-loaded SLN comprised of TGPS 1000 and Tween 80. The developed system depicted sustain release behavior as compared to Taxotere®. In addition, the method demonstrated improved absorption through the mouth compared to Taxotere®. Furthermore, the use of TGPS containing SLNs significantly boosted the bioavailability, potentially by inhibiting P-gp and facilitating absorption into the lymphatic system[68]. Pawar et. al. developed a new formulation of folic acid functionalized solid lipid nanoparticles (SLN) that include both DTX and curcumin. This formulation is designed for targeted delivery of anticancer drugs. The new approach demonstrated improved cytotoxicity and cellular uptake in the MDA-MB-231 and MCF-7 cell lines. Furthermore, the in-vivo pharmacokinetics of the proposed system demonstrated a substantial increase in

the area under the curve (AUC) and mean residence duration when compared to Taxotere®. Moreover, the created method demonstrated a decrease in the buildup of non-specific DTX in essential organs when compared to Taxotere®[118]. Mosallaei et al., prepared DTX-loaded SLNs. The developed system reported a significant increase in cellular uptake capacity as well as a decrease in cell viability. Consecutively, the system enhanced efficacy, tumor inhibition and survival in C-26-implanted BALB/c mice when compared with free DTX[136]. Naguib et al., prepared trimyristin and PEG-2000 comprised DTX SLN. The developed approach showed a notable increase in the ability to kill cells, improve therapeutic effectiveness, and demonstrate more potent anti-tumor activity in mice injected with TC-01 cells compared to the unbound DTX. Furthermore, the system depicted a reduction in non-selective uptake by vital organs such as kidney, spleen, liver, heart, and lungs[137]. Zhu et al., prepared SLN comprised of DTX and FA-conjugated to the oxidized single-walled carbon nanotubes and encapsulated the same in lipid system. The developed system demonstrated higher permeability and anti-tumor efficacy in MCF cell lines vis-à-vis plain DTX[138].

E. Nanostructured lipid carriers: Nanostructured lipid carriers (NLCs) are upgraded version of SLNs, comprised of a mixture of solid and liquid lipids with imperfect matrix and voids. These novel systems offer merits like enhanced drug loading capacity as well as improved release characteristics[139]. Sun et al., prepared oleic acid-linked DTX prodrug as NLC that enhanced the prodrug loading up to 5-fold. The developed system showed slow release from the matrix. Furthermore, the system demonstrated a fourfold increase in bioavailability and a substantial improvement in intestinal permeability compared to the DTX solution[119]. Fang et al. developed lipid nanocarriers that were modified with cysteine for the purpose of delivering DTX orally. The created technology demonstrated a significant improvement in the penetration of substances in laboratory tests and showed favorable results in the study of how the body processes drugs. The improvement of permeation was aided by both passive transport and absorption in enterocytes through the improved mucoadhesion of the surface cysteine. The oral pharmacokinetics of the proposed system demonstrated a 12.3-fold augmentation in the area under the curve when compared to a DTX solution[120]. Sun et al., prepared a novel oleate prodrug of DTX loaded NLC. The developed system showed sustained release pattern as compared to the DTX system without oleate. Consecutively, the developed system demonstrated the enhanced membrane permeability as well as intestinal bioadhesion in comparison to plain DTX. Moreover, the developed system depicted enhanced bioavailability by 4.04-fold in comparison with plain DTX[119]. Fan et al. synthesized DTX-Nicotinamide conjugated nanostructured lipid carriers (NLCs) using a combination of glyceryl monostearate, lecithin, and capric triglyceride. The proposed system exhibited improved drug solubility, increased entrapment efficiency, and favorable in-vitro release kinetics as per the Weibull dynamic equation. Moreover, the in-vivo permeation investigation demonstrated that the skin permeability in SD rats was greater compared to free DTX[121].

3. Inorganic nanocarriers:

Inorganic nanoparticles (NPs) are often characterized as substances with diameters ranging from 1 to 100 nanometers. Because of the distinct physicochemical characteristics of the nanoparticles (NPs) and the unique functional molecules attached to their surfaces, they have the ability to readily penetrate and move through tissues, cells, and organelles[140].

A. Gold nanoparticles (AuNPs): Among various types of inorganic NPs, AuNPs, first synthesized and investigated in the mid-19th century by Faraday[141]. These NPs are most widely used in drug delivery and biomedicinal application due to their biocompatible and nontoxic properties can easily modify its surface with functional ligands[142]. Francois et al., prepared PEG-functionalized AuNPs to improve the solubility of DTX. The developed NPs depicted absence cytotoxicity toward either MCF7 or HCT15 adenocarcinoma cells when administered alone. Consecutively, the NPs showed 2.5-fold more cytotoxic than Taxotere against MCF7 cells. Furthermore, the NPs in HCT15 cells displayed IC50 value lower than that of Taxotere[143]. Wan et al., prepared DTX loaded gold doped apatite nanorods in malignant liver cancer treatment. *In-vitro* studies of the developed system demonstrated enhanced apoptosis, cell permeation and cytotoxicity in human liver cancer cells (HepG2). Moreover, *in-vivo* evaluation of the developed system revealed restoration of the normal physiology of the liver with an apparent reduction in non-selective uptake by other vital organs such as lungs, kidneys, and spleen[144].

B. Silicone nanorattles: Silicone nanorattles are mesoporous silicone nanomaterials (MSN) that possess a hollow cavity. Due to their distinctive characteristics such as a substantial specific surface area and pore volume, strong chemical and mechanical durability, and compatibility with living organisms, they play a crucial role in drug delivery systems[145]. Li et al., prepared DTX loaded PEGylated silica nanorattles employed for liver cancer therapy. The developed system depicted substantially lower IC50 in Hep-G2 human liver cancer cells, than that of free DTX. Consecutively, the system also depicted enhanced antitumor efficacy with a 15% increase in tumor inhibition rate when compared with Taxotere on the murine model. Additionally, *in-vivo* toxicity assessment of the system provided satisfactory results in rodents. Furthermore, the system also demonstrated high therapeutic efficacy and low toxicity[146]. Khosravian et al., prepared folic acid functionalized MSNs for targeted delivery of DTX in breast cancer treatment. The *in-vitro* studies of the developed system revealed depicted enhanced cytotoxicity, apoptosis and cellular uptake in MCF-7 cells. Consecutively, *in-vivo* and *ex-vivo* fluorescence imaging of the developed system revealed enhanced tumor uptake and reduced non-selective uptake by other vital organs[147].

C. Carbon-based nanocarriers: Wang et al., prepared single-walled carbon nanotubes (SWCNTs) loaded DTX

to establish synergistic enhancement of chemotherapy and thermal ablation. The developed system demonstrated enhanced *in-vitro* cytotoxicity in PC3 cell lines. Consecutively, the system also depicted higher efficacy in murine S180 bearing mice as well as a significant decrease in tumor volume as compared to free DTX[148]. Arora et al., prepared DTX-tethered multi-walled carbon nanotubes (MWCNTs). The developed system demonstrated faster drug release in acidic pH resembling tumor microenvironment when compared to plain DTX. This property of carbon nanotubes can be substantially exploited for better antitumor activity[149]. Shi et al., prepared DTX conjugated folic acid and amine functionalized C60-fullerenes. The developed system demonstrated enhanced DTX uptake by approximately 7.5-fold higher and significant cytotoxicity in cultured PC3 cells. Consecutively, *in-vivo* evaluation depicted enhanced antitumor activity as well as reduced toxicity in normal cells for murine S180 cancer model *vis-à-vis* the plain DTX[150]. Raza et al., prepared functionalized carboxylated and acylated fullerenes C60-fullerenes conjugated to DTX. The developed system depicted control release pattern as well as prevented hemolysis. Consecutively the system also demonstrated increased cytotoxicity on both invasive and non-invasive cancer cell lines. Furthermore, *in-vivo* evaluation depicted a 4.2-fold increase in bioavailability as well as a 50% reduction in clearance with substantial biodistribution of the drug[151].

D. Iron nanoparticles: Rezaei et al., prepared a novel DTX loaded nanoMIL-100 introduced as Fe based metal-organic framework with the drug loading of 57.2 %. The developed system depicted pH-dependent and sustained release pattern. Furthermore, the developed system showed enhanced cytotoxicity and a significant decrease in IC50 value in MCF-7 cell lines when compared with the free DTX[152].

4. Miscellaneous

A. Dendrimers: Dendrimers consist of 3D structures of uniformly dispersed macromolecules resembling tree-like branches. Every single dendrimer is a spherical nano-sized molecule with high molecular weights. Dendrimer as a vector is highly suitable for drug delivery due to the properties such as monodispersed system, multivalent, host-guest entrapment, numerous peripheral functional groups and interior cavities[153]. Interior architecture of dendritic channel can function as a reservoir for active drug molecules or molecules can be terminally bonded to functional groups present on the surface[154]. Both hydrophilic and hydrophobic drugs can be incorporated in the dendrimeric system and can be potential nanocarriers for anticancer and gene delivery. Nanovector system comprised of dendrimers significantly impart increased aqueous solubility, bioavailability, pharmacokinetics, and pharmacodynamics of API in *in-vitro* as well as *in-vivo*[155]. Benito et al., prepared a novel DTX loaded functionalized dendrimer in association with cyclodextrins as nanocarriers to target lectin binding. The glycodendrimer–cyclodextrin conjugates for DTX delivery demonstrated high drug solubility with efficient delivery at targeted receptors. Consecutively, the developed system suggested the formation of multivalent ligand that might depict the active targeting approach involving drug-receptor interaction with increased binding affinity to lectin[156]. *In-vivo* studies have been reported on dendrimer loaded DTX by Sylvania Platinum Ltd. According to the report, dendrimer-DTX was efficient in the treatment of breast cancer induced in experimental animals with significantly prolonged duration of action vs Taxotere. Significant improvement in aqueous solubility was observed with dendrimer-DTX system concluding necessary measures to develop an appropriate drug delivery system[157]. Gajbhiye et al., prepared DTX loaded Polysorbate 80 conjugated poly-(propyleneimine) dendritic nanoconjugate (P80-PPI) to evaluate its anticancer efficacy. Gamma scintigraphy studies depicted that the developed system was able to reach higher brain concentration via targeted delivery. Consecutively, *in-vivo* studies revealed enhanced anti-cancer activity in tumor-bearing rodents and further depicted highly significant effect on reduction in tumor volume by the developed system as compared to free DTX[158]. Pooja et al., prepared DTX and Paclitaxel (PTX) loaded dendrimer-TPGS mixed micelles. The developed system depicted 20.36-fold increase solubility of DTX. Consecutively, the *in-vitro* release studies of the developed system revealed sustained release pattern in an acidic environment. Moreover, the developed system also depicted enhanced cytotoxicity in A549, MCF-7 and CHO cell lines and showed excellent blood compatibility by preventing hemolysis[159].

Clinical development of DTX

Taxotere® is a marketed brand of the clinical formulation of DTX in Tween 80. Clinical evaluation of Taxotere® has depicted effective decrease prostate-specific antigen (PSA) levels as well as improved symptoms and the survival rate in hormone-resistant prostate cancer patients[4]. It was approved first for non-small cell lung cancer in 1999, and then for prostate and breast cancer in 2004, as well as for gastric, head and neck cancers in 2006[160,161]. However, the adverse effects of Taxotere® include hypersensitivity reactions, cutaneous reactions, fluid retention, cardiac disorders, bone marrow suppression, peripheral neuropathy, fatigue and alopecia[4,162]. The ethanol/Tween 80 solvent required to augment the DTX solubility can be held into account for the hypersensitivity reaction, decreased tumor uptake and increased exposure to other organs[4,163]. Several reports have shown evidence of adverse events from mild to severe hypersensitivity reactions, episodes of pericardial effusion and peripheral edema as well as weight gain which is accountable to Tween 80. Tween 80 along with its metabolite causes histamine-induced hypersensitivity attributed to DTX formulations[164]. Tween 80 causes enhanced membrane permeability consequently leading to peripheral edema. Moreover, Tween 80 has also shown to modulate the viscosity and morphology of blood and its components especially erythrocytes respectively which are likely cause of cardiovascular side effects associated with DTX therapy[20]. Although recent research has revealed the

anti-angiogenic activity of both DTX as well as Tween 80 at low concentrations, the dose of DTX administered clinically after infusion eliminates the anti-angiogenic activity. Apparently, the higher plasma concentrations of Tween 80 reduces the plasma clearance of DTX, leading to severe hemato-toxicity due to the presence of free drug[79,165]. Therefore, there is a need for developing an alternate drug delivery system that evade these challenges and selectively deliver DTX to the targeted cancer cells.

A novel DTX polymeric NP formulation known as BIND-014 was reported for investigational clinical phase I trial in 2010[4,166]. BIND-014 was formulated as a nanocarrier platform designed for precise and targeted drug delivery. The delivery of BIND-014 was directed towards a specific target, the prostate-specific membrane antigen (PSMA). PSMA is a cell-surface protein that is highly expressed in cancer cells and in the new blood arteries that form in or link to several types of solid tumors. BIND-014 consists of DTX contained within a phosphatidylcholine (PC) matrix, which is further encased with PEG and has a PSMA targeting ligand incorporated on the PEG surface. During the initial phase 1 trial, patients with advanced solid tumors were given BIND-014 either every three weeks or weekly (Table 2). The dose levels delivered ranged from 3.5 to 75 mg/m2 for the three-week interval and 15 to 45 mg/m2 for the weekly interval. Good tolerance was exhibited by the patients towards BIND-014 devoid of unforeseen toxicities. Less than 20% of subjects showed common drug attributed side effects such as anemia, neutropenia, alopecia, diarrhea, and fatigue. The BIND-014 exhibited enhanced dose-dependent pharmacokinetics in a linear pattern with a prolonged systemic circulation of NPs when compared to DTX alone[167]. Furthermore, the BIND-014 phase II trial depicted a 30% PSA response, 32% measurable disease response, and about 50% circulating tumor cell (CTC) conversions. The median radiographic progression-free survival was 9.9 months. A novel CTC detection system developed by Epic Sciences detected 89% of CTCs and 61% of which had CTCs with a high level of PSMA expression. After the treatment period, a preferential reduction was observed in PSMA-positive CTCs. Additionally, therapy-related adverse effects such as nausea, neuropathy, neutropenic fever, and fatigue[166].

Table 2: Clinical trials of DTX nano-formulation

Brand name	Formulation	Indication	Clinical phase	Ref
ABI-008 (Celgene)	DTX nanoparticles (nab-DTX)	Metastatic castration-resistant prostate cancer	NCT00477529 (Phase II)	168
ANX-514 (Mast Therapeutics)	DTX liposomes	Advanced solid tumor	NCT00664170 (Phase I)	169
ATI-1123 (Azaya Therapeutics)	DTX liposomes	Solid tumor, non-small cell lung cancer, and lung cancer	NCT01041235 (Phase I)	170
BIND-014 (BIND Therapeutics)	PSMA targeted DTX PEG-PLGA or PLA-PEG particle	Prostate, metastatic, non-small cell lung, cervical, head and neck, or KRAS positive lung cancers	NCT02479178 (Phase II) NCT02283320 (Phase II) NCT01812746 (Phase II) NCT01792479 (Phase II) NCT01300533 (Phase I)	166
CPC-634	Polymeric drug conjugate DTX nanoparticles	Ovarian cancer and solid tumor	NCT02380677 (Phase II)	171,172
CriPec (Cristal Therapeutics)	DTX micelles	Solid tumors	NCT02442531 (Phase I)	173
CRLX301 (Cerulean)	Cyclodextrin based nanoparticle DTX Conjugate	Dose escalation study in advanced or metastatic solid tumors	NCT02380677 (Phase I/II)	174
DEP® Starpharma	Dendrimer based DTX	Advanced solid cancers, including lung (small cell and non-small cell), prostate, pancreatic, gastro-oesophageal, breast, cervical, renal and brain.	UK-MHRA EudraCT Number: 2019-004332-36 (Phase I/II)	175
Docecal (Oasmia Pharmaceutical)	DTX micelles	Breast cancer	EudraCT Number: 2012-005161-12 (Phase II/III)	176

DTX-PM DOPNP201 (Samyang Biopharmaceuticals)	DTX micelle	Head and neck cancer and advanced solid tumors	NCT02639858 (Phase II) NCT02274610 (Phase I)	177
DTX PNP and Taxotere (Samyang Pharmaceuticals)	Polymeric nanoparticles of DTX	Advanced solid cancer	NCT02274610 (Phase I)	178
LE-DT (Neopharm, Inc)	DTX liposomes	Pancreatic cancer	NCT01151384 (Phase I/II)	123,168
MM-310 (Merrimack Pharmaceuticals)	EphA-2 targeted Liposomal DTX	Advanced breast, lung, and prostate cancer	NCT03076372 (Phase I)	179
MNK-010 (Mallinckrodt Inc.)	DTX liposomes	Advanced solid tumors	NCT02040558 (Phase I)	180
Nanoxel-PM™ (Samyang Pharmaceuticals)	DTX polymeric micelles	Triple negative breast cancer	NCT02982395 (Phase I)	34
NDLS (Jina Pharmaceuticals Inc.)	Nanosomal DTX lipid suspension	Operable Triple negative Breast cancer	NCT03671044 (Phase II/III)	181–184
NKTR-105 (Nektar Therapeutics)	DTX-PEG conjugates	Advanced solid cancer	Phase I	185
SGT-53/DTX (SynerGene Therapeutics)	Liposomal DTX	Advanced solid tumors	NCT00470613 (Phase I)	186

Belani et al. reported a phase III study involving a novel combination of cetuximab with carboplatin and DTX for advanced NSCLC patients. The results revealed that the novel combination demonstrated moderate anticancer efficacy for patients with the advanced stage as well as an acceptable toxicity profile[4,187]. Furthermore, the phase II and III clinical trials for the capecitabine and DTX combination in patients with metastatic breast cancer depicted a synergism when compared to single agents co-administered[4,188].

A novel DTX loaded liposome (LE-DT) was developed by NeoPharm, Inc. The DTX loaded liposomal-based drug delivery system has been investigated in clinical Phase I to evaluate the pharmacokinetics, maximum tolerated dose, dose-limiting toxicity and anti-tumor effects in patients with advanced tumors. Sylvania Platinum Ltd (SPL) developed a novel dendrimer-based DTX NPs. A preclinical report on SPL's dendrimer-DTX showed enhanced anti-cancer efficacy in treating breast cancer as compared to Taxotere® with prolonged action than Taxotere®. Furthermore, SPL has gained approval to conduct a PhaseI/II clinical trial to establish the safety and bio-equivalence with Taxotere®[1].

Nano Aqualip Technology has created a lipid solution called NDLS, which is based on nanocarriers and consists of lipids that have been deemed safe by the USFDA and are generally regarded as safe (GRAS). The NDLS (Doceaqualip) demonstrated enhanced stability and pharmacokinetics, as well as safeguarding DTX from the surrounding tissue environment. The therapeutic effectiveness of NDLS was evaluated in comparison to Taxotere® in patients with locally advanced or metastatic breast cancer who had previously experienced treatment failure with chemotherapy[181,189]. Patients in the NDLS group did not receive corticosteroids as premedication, but, the safety outcomes of NDLS were similar to those of Taxotere®. No instances of severe allergic responses such as bronchospasm or facial edema were reported with NDLS. The febrile neutropenia seen was in line with the published incidence for Taxotere®. DTX has demonstrated efficacy in treating recurrent or metastatic breast cancer, including HER2 positive/negative individuals and those with metastatic triple negative breast cancer. NDLS is the sole authorized and accessible NDDS (Nanoparticle Drug Delivery System) of DTX in India[181].

Toxicity and Safety of DTX Nano Formulations (Regulatory Concerns)

DTX nanoformulations are created to improve the transportation of the drug and reduce the harmful effects on the body that are often caused by traditional formulations. Nevertheless, these nanoformulations present distinct toxicity and safety concerns that require meticulous deliberation. An important consideration is the influence of particle size and surface characteristics on the behavior of nanoparticles. When an illustration, nanoparticles that are harmless when they are 100 nm in size may acquire toxicity when their size diminishes. Moreover, these nanoparticles have the capability to form clusters or break apart inside the body, which might have a substantial impact on their safety characteristics. Nanoparticles have distinct distribution and accumulation patterns compared to conventional medications, sometimes resulting in their accumulation in specific organs such as the liver and spleen, which can induce toxicity specific to those organs. Thorough assessments are required to fully comprehend the long-

term safety of solid lipid nanoparticles (SLNs) containing DTX, notwithstanding their potential in lowering systemic toxicity. An additional worry pertains to the possible activation of the immune system by nanoparticles, particularly those that consist of polymers or antibodies capable of stimulating immunological responses. Regulatory agencies stress the importance of conducting a comprehensive evaluation of the immunogenicity of these formulations[1].

Several investigations have documented the distinct hazard characteristics of various DTX nanoformulations. Solid Lipid Nanoparticles (SLNs) have shown the ability to decrease the overall toxicity of DTX in animal models by enhancing the targeted delivery of the medicine to the tumor site, while minimizing unintended side effects. Nevertheless, SLNs still require thorough in vivo experimentation to validate these advantages in human beings. Another variant, mesoporous silica nanorattles, containing PEGylated DTX, has demonstrated reduced toxicity and increased anticancer efficacy in vivo when compared to conventional DTX formulations. While these nanoparticles have the advantage of providing controlled medication release and enhanced biodistribution, it is necessary to conduct additional research to determine the long-term effects and potential toxicity of the silica material used. PEGylated liposomes and TPGS-coated liposomes have been found to improve the solubility and bioavailability of DTX. In addition, they exhibit increased cytotoxicity against cancer cells in laboratory tests. However, there are still uncertainties regarding the stability, large-scale production, and potential long-term toxicity of these materials that have not been fully investigated[1,190].

Regulatory bodies face considerable difficulties when assessing the safety of nanomedicines because of their unique characteristics. The FDA presently evaluates nanomedicines individually, as there are no specific regulatory criteria in place for these items. Detractors contend that the current rules for conventional medications are insufficient in evaluating the safety of nanoformulations. The evaluation procedure for nano-oncological products entails a thorough examination of the potential risks and benefits. Due to their unique characteristics, nanomedicines are frequently categorized as New Molecular Entities (NMEs), which requires the submission of new drug applications that involve thorough preclinical and clinical assessments to guarantee both safety and effectiveness. It is necessary to revise ethical norms and safety laws in order to specifically address the distinct dangers associated with nanomedicines. These concerns include potential immunological reactions and unforeseen toxicity that may not be evident in animal experiments but become apparent during human trials. Regulatory authorities emphasize the significance of establishing rules that effectively reconcile patient safety with the therapeutic advantages of nanomedicines[1,190]

Conclusion

The study reveals that the use of advanced nanocarrier techniques has significantly enhanced the delivery and effectiveness of DTX (DTX) in cancer treatment. Conventional DTX formulations, like Taxotere®, have demonstrated clinical effectiveness but are hindered by problems such as limited capacity to dissolve in water, low availability in the body, and notable side effects, including hypersensitivity reactions and the accumulation of fluid over time. The restrictions primarily arise from the solvents employed to dissolve DTX, such as polysorbate 80, which enhance its toxicity. To tackle these issues, nanocarrier systems, such as polymeric nanoparticles, lipidic nanoparticles, and inorganic nanoparticles, have been created. These carriers improve the ability of DTX to dissolve and remain stable, resulting in improved distribution in the body and decreased harmful effects. Nanocarriers utilize the increased permeability and retention (EPR) effect to selectively accumulate in tumor tissues, taking advantage of their leaky blood vessels and inadequate lymphatic drainage. This precise delivery method not only enhances the amount of DTX at the specific location of the tumor but also decreases the amount of exposure to healthy tissues, thereby diminishing any adverse effects. In addition, nanocarriers can be designed to selectively target cancer cells by attaching ligands or antibodies that can identify and bind to certain receptors that are excessively expressed on tumor cells. By actively targeting, the precision and efficacy of DTX delivery are further enhanced.

Preclinical and clinical evaluations have demonstrated that these formulations utilizing nanocarriers can achieve a continuous release of DTX, enhance its distribution throughout the body, and improve its effectiveness in treating different forms of cancer. However, there are still significant obstacles to overcome in the field of nanocarrier systems, including the need to provide quality control, stability, and scalability. Furthermore, it is essential to have a more comprehensive understanding of the in-vivo destiny of these nanocarriers, encompassing their metabolic processes, elimination from the body, and potential long-term harmful effects, in order to facilitate their extensive use in clinical settings. In summary, the advancement of nanocarrier-based DTX formulations signifies a substantial progression in cancer therapy, providing a superior and less risky substitute for traditional DTX therapies.

Future Prospects

The study proposes numerous areas for further research and development to fully exploit the potential of nanocarrier-based DTX delivery systems. Future research should prioritize enhancing the stability and scalability of these formulations to guarantee consistent performance and enable large-scale production in industrial settings. Furthermore, extensive in-vivo investigations are required to have a deeper understanding of the long-term destiny, metabolism, and possible toxicity of these nanocarriers. Further improvements in targeting techniques, such as the integration of numerous targeting ligands and the investigation of novel biomaterials, have the potential to enhance the precision and effectiveness of these systems. In summary, the ongoing advancements in

nanotechnology and drug delivery offer significant potential for enhancing the effectiveness of cancer treatment with DTX and other chemotherapy drugs.

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Omkar Kolhe: Conceptualization, literature search, data collection, manuscript drafting, preparation of figures and tables, and revision of the manuscript.
Mukesh Ratnaparkhi: Supervision, critical review, scientific editing, guidance in manuscript structuring, and final approval of the version to be published.

Abbreviations

DTX: Docetaxel

Enhance Permeation and Retention

P-gp: P-glycoprotein

SLN: Solid Lipid Nanoparticles

NLCs: Nanostructured Lipid Carriers

TME: Tumor Microenvironment

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