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REVIEW OF LITERATURE ON THE COMBINATORIAL DELIVERY OF DOCETAXEL AND NUTRITIONAL SUPPLEMENT FOR THE MANAGEMENT OF SOLID TUMOURS USING NANOCARRIER APPROACH

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Abstract: Over the last decade, the nanotechnology approach has been successfully harnessed for the codelivery of multiple anticancer agents. Nanoparticles offer controlled drug release that can normalize the pharmacokinetics, biodistribution, and stability of chemically dissimilar drugs that may independently have disparate pharmacological behaviors. They can be endowed with long-circulating property that can protect a drug from rapid bio-degradation or bioclearance by evading the RES producing high blood circulation profile and thus enabling transport through biological barriers, preferential drug accumulation to the tumor site via the EPR effect. Stimuli responsive nanocarriers respond to the external or the internal stimuli that can co-release drugs in the same organ, tissue, or cell, resulting in increased therapeutic efficacy with reduced toxicity preventing off-target exposure (Dai et al., 2017; Ma et al., 2013). The increased potency of anticancer drugs is observed at lower effective dosages with the corresponding significant reduction in cancer cell viability or tumor volume compared with two separately administered treatments (Premkumar et al., 2008). The combination therapy can provide maximum effect using nanotechnology approach.
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Introduction:

Docetaxel (DCX) is a second generation taxane, derived from the inactive 10-deacetyl baccatin III, extracted from the European Yew tree (*Taxus baccata*). DCX has better water solubility, pharmacokinetic profile, and anticancer activity than paclitaxel. Current FDA approved DCX products, including Taxotere, are essentially Tween 80/ethanol-based solutions, which unfortunately are associated with various significant side effects. They induce marked hypersensitivity, neutropenia, fluid retention, and alopecia. Hypersensitivity reactions, which are attributed to the Tween 80 in the formulations, can vary from simple skin rash to systemic anaphylaxis and necessitate premedication with corticosteroids. Other problems associated with the Tween 80/ethanol-based DCX formulations include the nonspecific accumulation of DCX in healthy organs, which may lead to systemic toxicity and subsequent discontinuation of therapy.

Nanoparticle-based, Tween 80-free DCX formulations are expected to not only avoid Tween 80-related side effects but also increase the concentration of DCX in tumors due to the enhanced permeation and retention (EPR) effect. Data from many previous studies demonstrate that nanoparticles of 100–200 nm are most successful in tumor vasculature extravasation, although there are disagreements in the literature. The heterogeneous nature of tumor type, size, location, and metastasis may contribute to the disagreements. In order to improve the EPR-related nanoparticles extravasation, nanoparticles should be designed to circulate longer in the blood, while the drug of interest is retained within the nanoparticles. PEGylation is a strategy to render the surface of nanoparticles hydrophilic, thus enabling the nanoparticles to evade early opsonization and circulate longer in the blood. On the other hand, for a drug ined within the nanoparticles, a strong affinity between the drug and the excipient(s) used to prepare the nanoparticles is required.

Solid lipid nanoparticles (SLNs) have been extensively investigated as drug carriers. Advantages of such nanocarriers include high compatibility with lipophilic drugs, ease of fabrication, and controlled release. Various SLN formulations of taxanes have

been previously reported. Heurtault et al. reported the development of a PEGylated lipid nanocapsule formulation (LNC) for paclitaxel using a novel phase inversion-based method. The resultant LNCs were made of an oily medium-chain triglyceride core and stabilized with soybean lecithin as a lipophilic surfactant, and PEG hydroxystearate (Solutol) as a hydrophilic surfactant. Lee et al. applied a high pressure homogenization technique to prepare a SLN formulation of paclitaxel using triglyceryl myristate (trimyristin) and phospholipids. The formulation showed improved *in vitro* activity, but the *in vivo* circulation time and biodistribution profile were not improved, as compared to the market product Taxol. Videira et al. applied a factorial design to optimize formulation parameters to prepare paclitaxel SLN formulations using Compritol 888 ATO (a mixture of mono-, di-, and triglycerides of behenic acid) and Precirol ATO5 (i.e., glyceryl palmito-stearate), and the final optimized formulation demonstrated an improved *in vitro* cytotoxic activity against the murine breast cancer cell line MXT-B2.

The present study aimed at the rational selection of a triglyceride from a list of medium- and long-chain triglycerides for the development of a SLN formulation to ultimately improve the antitumor activity of DCX. Previously it was reported that low melting point triglycerides are excellent solubilizers for DCX, prompting us to hypothesize that high melting point triglycerides will be suitable excipients for preparing DCX-incorporated SLNs. Triglycerides that are solid at body temperature were selected to ensure formulation stability and to avoid droplet coalescence. An oil-in-water (O/W) emulsion-based method was applied, where DCX and all lipid components were dissolved in the oil phase, and the aqueous phase consisted of a 0.1% (w/v) Poloxamer 188 aqueous solution. Finally, the *in vitro* and *in vivo* antitumor activities of the selected formulation were evaluated.

Review of literature:

Passive targeting refers to the preferential accumulation and retention of nanocarriers at the tumor site after systemic administration by virtue of passive diffusion or convection. The phenomenon is popularly known as enhanced permeability and retention (EPR) effect mediated by leaky vasculature and poor lymphatic drainage of tumor. The particle size and the circulation time of nanoparticles influences the efficiency of EPR effect (Maeda et al., 2013; Maruyama, 2011).

The NPs uptake and their clearance by the macrophages is influenced by several physicochemical properties of the NPs such as particle size, surface charge, solubility, and surface functionality (Duan and Li, 2013). Small NPs (generally of particle size 1 μm) suffers with high clearance rate from the physiological environment where they may also aggregate and be retained mechanically by capillaries. Within the particle size range between the two extremes, minimal clearance mechanisms are observed and circulation time is greatly prolonged (Salatin et al., 2015). Considering the surface charges, the negatively charged NPs show a low phagocytic uptake compared to positively charged particles. However, some reports have suggested that the neutral and cationic NPs can reduce the uptake by RES and clear less rapidly than the negatively charged ones. The negatively charged NPs may interact with the cationic sites on the macrophage surface and be recognized by the scavenger receptors, thereby facilitating uptake by RES. Therefore, less positively charged NPs exhibit a promising potential as longcirculating carriers with desirable biocompatibility and biofunctionality (Blau et al., 2000; Duan and Li, 2013). Particle shape is yet another factor affecting the cellular attachment and internalization of NPs. Prolate ellipsoidal shapes exhibit best attachment, but the poorest internalization while the Oblate ellipsoids exhibit both high attachment and high internalization and thereby higher phagocytosis (Duan and Li, 2013)

Chitosan (CS), a derivative of chitin (abundantly found in the exoskeleton of crustacean), is a linear amino-polysaccharide comprising of randomly distributed β (1-4) linked Dglucosamine and N-acetyl-D-glucosamine units. CS behaves as a polyelectrolyte in the acidic media due to protonation of the NH2 functional group on the C2 position of the Dglucosamine repeating units. The pKa value close to 6.5 helps establishing the electrostatic interactions with negatively charged cell membrane in weakly acidic microenvironment of tumors (pH 6.8–7.2) (Huang et al., 2004; Key and Park, 2017). CS can be fine-tuned for achieving the specific degrees of deacetylation (DDA), fractions of protonatable amine (charge), average molecular weights and additional moieties (Alameh et al., 2018). Low molecular weight chitosan (LMW-CS) is a promising polymer for surface modification of NPs, which can impart both stealth effect and electrostatic interaction with cells at mildly acidic pH of tumors (Abouelmagd et al., 2015). CS has also demonstrated anticancer effects by interfering with the tumor cell metabolism and inhibiting the cell growth (Badran et al., 2018). It can

mediate apoptosis and death of bladder tumor cells through caspase-3 activation (Hasegawa et al., 2001).

The chemical modifications such as carboxyl methylation of the hydroxyl group or Pegylation to the CS chain, improve its solubility over a broad pH range and can serve as carrier for enhancing the colloidal stability of some hydrophobic drugs (Key and Park, 2017; Ramya et al., 2012). The LMW-CS functionalized PLGA NPs with a polydopamine layer attenuated the release of PTX in physiologic environment and enabled acid-specific delivery in the tumor microenvironment (Abouelmagd et al., 2015). The pH-sensitive properties of CS are an additional advantage for cancer treatment because the free amine groups may act as a ―proton sponge‖ which help in facilitating the endosomal escape phenomenon. Free amine groups attract H+ ions from the cytosol resulting in osmotic swelling and eventual rupture of an acidic compartment, like an endosome or lysosome. CS polymers have been very efficiently used for the systemic delivery of oligonucleotides (Yang et al., 2015). CS can also function as targeting ligand for specific receptors overexpressed on cancer cells. Rao et al., prepared DOX encapsulated CS-decorated NPs for targeting and eliminating the tumorreinitiating stem-like cancer cells (CSCs), a major cause of cancer recurrence after chemotherapy. The CS on the NPs specifically targeted the CD44 receptors of the CSCs and released the DOX into the acidic TME resulting in improved cytotoxic effects and reduced tumor size in an orthotopic xenograft tumor model (Rao et al., 2015). CS polymers can also be used in photothermal therapies in cancer treatment (Fathi et al., 2018; Yang et al., 2015). The CS micelles loaded with Photosan (a photosensitizer) showed higher fluorescence signals and generated higher ROS levels under laser illumination demonstrating their potential as PDT agents for pancreatic cancer (H. Li et al., 2015). The (poly(N-isopropylacrylamide)-cooleic acid)-g-chitosan ((PNIPAAm-co-OA)-g-CS) copolymer-gold hybrid NPs produced a thermo-responsive release of erlotinib and produced higher cellular uptake in A549 cells (Fathi et al., 2018).

The stimuli-responsive nanomedicines have recently received considerable attention for tumor treatment owing to their very stable or inert nature during the circulation until reaching the tumor tissue or the cells. Reaching the target site, they respond to the respective stimuli such as charge reversal, hydrophobic-to-hydrophilic transition, PEG detachment, size shrinkage, NP disassembly and ligand exposure leading to the enhanced uptake, on-demand drug release, effective endosomal escape and deeper tumor penetration improving the effect of cancer therapy (Crucho, 2015). The stimuli-sensitive nanomedicine exploits the pathophysiological features of the TME in solid tumors or the external forces as stimuli. The internal stimulus includes the acidic pH, high temperature, hypoxic environment, overexpressed enzymes and redox responsiveness due to elevated reductive conditions within the organelles. The widely used external stimuli include hyperthermia therapy, magnetic, ultrasound and photo-responsive therapy. The up-regulated stimuli in the normal tissue or the down-regulated stimuli in the TME could compromise the responsiveness of these type of nanomedicines (Torchilin, 2014).

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