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Therapeutic Delivery

What are the unexplored facts about nanomicelles formed from docetaxel clinical injection?

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"our studies have demonstrated that current clinical formulations of docetaxel with Tween-80 and ethyl alcohol formed nanosized micelles when the clinical dilution was made with 0.9% saline or 5% dextrose using a nonsolvent precipitation technique."

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Docetaxel is the main active ingredient of docetaxel injection concentrate and is a semisynthetic diterpene derived from the genus *Taxus baccata* (European yew) [1]. It has a broad spectrum of antitumor activities compared with other drugs currently in use. Docetaxel was found to be 1.3- to 12-fold superior to paclitaxel in terms of therapeutic effect. The drug showed significant and consistent antitumor activities in metastatic, non-small-cell lung and breast cancers. Docetaxel has a major problem with low aqueous solubility when administered as an intravenous injection. To overcome this, docetaxel concentrate was developed using a mixture of Tween-80 and ethanol [2].

Docetaxel injection has been packaged as a set of two vials since 1995 and is also available in a one-vial presentation since 2010, maintaining the same docetaxel to Tween-80 ratio as that of two vials. The first vial (concentrate) of formulation contains docetaxel in Tween-80 and the second vial contains ethanol (95% v/v) as diluent.

The one-vial injection was launched so that the risk of precipitation of the drug during the dilution would be reduced with better storage stability. It was also reported that refrigerated storage could extend the physical and chemical stability of the injection for up to 7 days [3]. On the market, it is available in anhydrous and trihydrate states. Docetaxel is also approved for the treatment of patients with advanced breast cancer in about 90 countries and advanced non-small-cell lung cancer in 70 countries [4]. Docetaxel is a highly lipophilic anticancer drug (log p value = 4.1) with low membrane permeability (1 cm/s $\times$ 10^6) and is categorized as a class IV drug [4,5].

The delivery of lipophilic drugs has always been a challenge when administered intravenously as they cannot cross the cell membrane to target cancer cells because of the surrounding aqueous environment in tissues and organs [6,7].

Taxotere® is the US FDA-approved, commercially available docetaxel formulation. To overcome docetaxel's solubility problem and to make it suitable for intravenous administration, docetaxel is solubilized in Tween-80, a nonionic surfactant under the class of polyethylene glycols. It was approved for non-small-cell lung carcinoma in 1999, for breast cancer in 2004, prostate cancer in 2004, gastric cancer in 2006 and for head and neck cancers in 2006 [8,9].

The recommended dose of docetaxel concentrate is 60–100 mg/m^2, depending on the stage and type of cancer and administered intravenously over a time period of 1 h, once every 3 weeks. Docetaxel is available in the concentration of 20 mg (1 ml) or 80 mg (4 ml) (anhydrous) [10].

Prior to use of the formulation, docetaxel should be at room temperature and then 6 ml of ethanol (95% v/v) is added to the concentrate and the vial is rotated gently for premixing and allowed to stand for 5 min. The solution should be clear and homogenous and then injected into the infusion bag containing 0.9% saline or 5% dextrose for

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administration to cancer patients [11]. The aim of this editorial is to discuss and report the unexplored facts about the docetaxel formulation (docetaxel concentrate) as a nanomedicine, which has not been revealed yet.

Docetaxel nanomedicine: micelle forming drug concentrate of Tween-80

Recently, our studies have demonstrated that current clinical formulations of docetaxel with Tween-80 and ethyl alcohol formed nanosized micelles when the clinical dilution was made with 0.9% saline or 5% dextrose using a nonsolvent precipitation technique. The micelles formed were in the size range of 10–40 nm, had a polydispersity index of 0.2–0.5, and the micelles were stable over a period of 24 h when analyzed by laser light scattering method [3,12].

Tween-80 micelles can enhance the water solubility of docetaxel from 10- to 500-fold [13]. The micelles were formed by a simple, two-step procedure, no sophisticated instrument was required and it was cost effective and easy.

Micelles are amphiphilic self-assembled structures which have a hydrophilic shell and hydrophobic core. Micelles have advantages such as possessing a self-hydrophilic structure on the surface and a smaller dimension (less than 50 nm) which prevents opsonization and leads to prolonged circulation.

Tween-80 is a synthetic nonionic surfactant used in drug delivery systems as a solubilizer, stabilizer or emulsifier and is considered the safest surfactant. Chemically, Tween-80 is composed of fatty acid esters of polyoxyethylene sorbitan which is structurally similar to polyethylene glycols [14,15].

Opsonization is the biological process that creates a barrier for nanocarriers. After intravenous administration, any nanocarrier that comes into contact with an opsonin – a bivalent protein in the blood, will be recognized as a foreign material and the opsonins bind to it and communicate the same with immune cells. This process activates the macrophages by forming vesicles around the nanocarrier by which these particles will eventually be get degraded by fusion with a lysosome [16].

To evade opsonization and prolong circulation, Tween-80 is utilized in this docetaxel injection, which leads to nanomicelles formation [17]. The nanomicelles that formed are uniform in size, highly suitable for parenteral administration and can be quickly prepared prior to administration in no time.

Nanomicelles of docetaxel concentrate may produce favorable pharmacokinetics and maximize efficacy with fewer adverse effects, including enhanced drug delivery to tumors by passive targeting. In one study, Muthu *et al.* prepared vitamin E TPGS micelles of docetaxel for cancer chemotherapy, which demonstrated enhanced cytotoxicity by few folds in comparison to that of control formulations.

The enhanced cellular uptake and cytotoxicity of nanomicelles observed may be due to the nonspecific absorption of micelles by absorptive mediated endocytosis and p-glycoprotein inhibition [18]. In the future, nanomicelles are likely to be developed, which are able to target molecular biomarkers of different cancers for early cancer diagnosis and therapy [19,20].

Conclusion

In this editorial, the unexplored facts about current clinical formulation of docetaxel composed of Tween-80 and ethyl alcohol were revealed. It was demonstrated that micelles are formed when the dilution is made in 0.9% saline or 5% dextrose. The quick formation of docetaxel micelles by a nonsolvent precipitation technique prior to administration is simply amazing in which micelles were usually in the narrow size range of 10–40 nm with a polydispersity index of 0.2–0.5. Moreover, the micelles structure is quite stable over a period of 24 h at room temperature. Therefore, it can be concluded that the advantages of nanotechnology, such as its simplicity and cost–effectiveness, can benefit patients and an increase in formulations in the future will provide effective therapy of life-threatening diseases and decrease the healthcare costs.

The production of docetaxel micelles from docetaxel concentrate requires introducing docetaxel concentrate into an aqueous system. Indeed, this simple process for developing nanomedicine requires facile processing prior to clinical drug administration. Alternatives to Tween-80, including several nonionic surfactants (e.g., Spans, vitamin E TPGS, Cremophors [EL and RH] and Pluronic block copolymers) have been reported to inhibit the p-glycoprotein drug efflux pump. Among these surfactants, Vitamin E TPGS was reported as a potent p-glycoprotein inhibitor. Therefore, inhibition of p-glycoprotein by anticancer, drug loaded, vitamin E micelles may be an effective way to improve the cellular uptake and anticancer efficacy of multidrug-resistant tumors [12,18].

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