Development and Characterization of Docetaxel Encapsulated pH-Sensitive Liposome’s for Cancer Therapy

Introduction

Cancer continues to be a major life-threatening disease. This disease is the second leading cause of death in the world. The most limiting factors in treatment of cancer are mutation and drug resistance in the cancer cells, poor selectivity and immunosuppressive action, side effect of the anticancer drugs, and low penetration in solid tumor. There are about 25 lakhs (2.5 million roughly one every 400 person or one in 80 families have cancer) cancer patients in India. Every year about 85,0000 new cancer cases are diagnosed in India resulting in about 58,0000 cancer related death every year. India has the highest number of the oral and throat cancer cases in the world. Every third oral cancer patient in the world is from India. In males -- Oral, Lungs and Stomach cancers are the three most common causes of cancer incidence and death. In females -- Cervical, Breast and Oral cancers are the three main causes of cancer related illnesses and death. Compared to developed countries overall there are less cancer cases in India but this could be due to under diagnosis and under reporting. At the same time regional, ethnic, dietary and socio-economic factors might also results in difference in the cancer susceptibilities and the incidence.

The clinical use of most conventional chemotherapeutics is often restricted, due to inadequate delivery of therapeutic drug concentration to the tumor target tissue or due to serious toxic effects on normal organs. In attempts to improve therapy with these anticancer agents and lessen the coupled side effects, Drug Delivery System (DDS) have been introduced, with the objective of meeting four key requirements for tumor-targeted drug delivery. The key factors are “Retain (drug while in circulation), Evade (the body’s defenses), Target (tumor tissue and vasculature) and Release (drug specifically in tumours)”. Several DDSs have been introduced: namely liposomes, microparticles, polymeric conjugates, micelles and nanoparticles, to facilitate effective chemotherapy with anticancer agents.

Liposomes are used as carriers for drugs and antigens because they can serve the purpose of solubilization, protection, directing potential, can prolong the drug action and can target the drug
to certain targets. Liposomes can lead to tissue specific therapeutic effects, upon interaction with target cell. Various approaches have been proposed for tissue specific targeting like immuno liposomes, immuno liposomes containing prodrugs, antibody dependent enzyme prodrug therapy etc. An advantage of using particle carriers, such as liposomes, is that drugs can easily become encapsulated, either dissolved in the aqueous phase or in the lipid phase, without the requirement of a covalent linkage between drug and carrier. Liposomal surfaces may be easily modified with specific targeted ligands, such as monoclonal antibodies, sugar residues or proteins.

Several strategies have been proposed, to accomplish site-specific triggered release in tumor tissue. New liposomes strategies consist of constructs capable of stimuli-sensitive release: such liposomes are designed to go through structural changes in response to physicochemical stimuli, thus allowing more controlled release of the encapsulated drug. These approaches include the use of pH-sensitive liposomes triggered by characteristics acidic milieu of solid tumors.

Taking advantages of the altered pH gradients in tumor extracellular environments and in its intracellular compartments, pH-sensitive liposome have been designed to prove the concepts of specific cancer cell targeting, enhanced cellular internalization, and rapid drug release. Especially promising is the concept of intracellular drug delivery by the pH-sensitive liposomes because it offers an efficient means of overcoming the multidrug resistance, one of the major causes for cancer treatment failures and also increases the intracellular delivery of the drug.

Docetaxel (Taxotere®) is a second-generation taxane derived from the needles of the European yew tree, Taxus baccata. The synthesis of Docetaxel starts from 10-deacetylbaaccarin III, a non-cytotoxic constituent of European yew tree needles.

Docetaxel acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. It promotes the assembly of tubulin into stable microtubules and inhibits their disassembly, causing inhibition of cell division and eventual cell death. Docetaxel shows 1.9-fold higher than paclitaxel affinity for microtubule. The clearance of Docetaxel depends on the cytochrome P450 (CYP) 3A isoforms, notably CYP3A4 and CYP3A5, and the membrane transporter P-glycoprotein (ABCB1).
Currently Taxotere® is marketed by Sanofi Aventis with global sales of more than 2.9 billion dollars. It is clinically effective against advanced breast, ovarian and non-small cell lung cancer. Docetaxel shows very low water solubility, and presently the only available formulation for clinical use consists of a solution (40 mg/ml) in a vehicle containing high concentration of Tween 80®. This vehicle has been associated with several hypersensitivity reactions and has incompatibility with common PVC intravenous administration. It interferes with the normal binding of Docetaxel to serum proteins in a concentration dependent-manner and can modulate the pharmacokinetics of Docetaxel in vivo.

A major problem of Tween 80® in Taxotere® includes high rates of allergic and/or immune reactions, severe pain at injection sites, serious and potentially permanent damage to blood vessels at or near the site of injection, and for that reason, the FDA has requested the manufacturer of Docetaxel (TAXOTERE®) to include a "black box" warning in the approved label for this product. However, the severe adverse reaction of this drug is not due to the drug itself, but to the excipient polysorbate 80 used in its formulation. In order to eliminate the Tween 80®-based vehicle and in the attempt to increase the drug solubility, alternative dosage forms have been suggested, including liposomes and cyclodextrins. Therefore there is a need for the development of alternative dosage form of Docetaxel devoid of Polysorbate 80.