Objectives of the present work

- Cancer is the second largest disease with an annual toll of 6 million deaths. Approximately 5 million persons were diagnosed with cancer worldwide in 2008 and by 2020, WHO estimates that there will be some 20 million new cancer patients in the world. By 2011, approximately 12.7 million cancers were diagnosed and 7.6 million people died of cancer worldwide. This makes invasive cancer the leading cause of death in the developed world and the second leading cause of death in the developing world.

- Treatment of cancer involves chemotherapy, radiation therapy and surgery. Chemotherapy is the treatment of cancer with an antineoplastic drug or with a combination of such drugs into a standardized treatment regimen. The most common side-effects of chemotherapy are myleosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss).

- Therefore, focus is now on the development of novel carriers and defining better therapeutic targets relative to the molecular changes in the cancer cells, their vasculature, and the related stroma. Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy.

- Currently Taxotere® is marketed by Sanofi Aventis with global sales of more than 2.9 billion dollars. 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.

- Problems encountered with Docetaxel also include precipitation of drug at higher concentration since it is insoluble in water and also to prepare its solution, mixture of organic solvents are used.
- Therefore, encapsulation of Docetaxel in pH-sensitive liposomes increases the aqueous solubility of the drug and also increases the intracellular deliver of drug at acidic pH (in the early & late endosomal stage) and avoid the lysosomal degradation of the drug as well as reduces the systemic side-effect.
- The development of Docetaxel encapsulated pH-sensitive liposomes which would target directly to the tumor cells and release Docetaxel at a controlled rate and to overcome the limitations associated with the current drug therapy.
- The research project focuses on the different aspects of pharmaceutical development of pH-sensitive liposomal formulation of Docetaxel; characterization of the liposomal formulation, optimization of cryoprotectant to total solid content ratio for the lyophilization, evaluation of selected optimized formulation for in vitro diffusion study, stability study and in vitro cell cytotoxicity study.