Cancer may be the most feared disease of our time. It is characterized by uncontrolled growth and cell proliferation. At cellular level, the development of malignancy is an ordered, sequential, multistep process involving genetic alterations in the form of rearrangements, mutations and amplification of oncogenes, or deletions / mutations in tumor suppressor genes. The uncontrolled proliferative tendency and immortality endows cancer cells with the capacity to form invasive and metastatic tumors. Cancer therapy is achieved by removal or killing of neoplastic cells. Radiotherapy (RT), chemotherapy (CT), surgery and hyperthermia (HT) are being extensively used for management of cancer. There has been a recent upsurge in interest in the use of hyperthermia as a fourth modality for cancer treatment.

Mammalian cells die after hyperthermia in a time-temperature dependent and cell cycle dependent manner. Heat may be more damaging to tumors than to normal tissues due to the differences in microenvironment: (i) reduced blood flow in tumor tissue results in slower dissipation of heat in tumors as compared to surrounding normal tissues thereby mediating enhanced cell killing, (ii) hypoxic tumor cells have an increased sensitivity to heat, (iii) nutritionally deficient tumor cells with reduced pH are more susceptible to heat. In addition, heat appears to preferentially damage the fragile neovasculature of the tumor.

Heat shows greatest clinical promise when it is used in combination with RT or CT. Elevated tissue temperature of 40-43°C sensitizes the tumor cells to certain chemotherapeutic drugs. In this context, it has been shown that the action of various anti cancer drugs such as bleomycin, melphalan and cis-platin is also enhanced by heat.
treatment. HT shows a synergistic action when combined with RT. It acts as a radiosensitizer by inhibiting repair of sublethal and lethal DNA damage caused by RT. The rationale for combination of HT with CT or RT is its ability to augment the radiosensitivity or chemosensitivity of tumor cells. Hypoxic tumor cells as well as tumor cells in S-phase are radioresistant and may become foci for tumor regrowth if not killed completely. HT, on the other hand, is effective against both S-phase cells and intra-tumor hypoxic cells which are acidic and nutrient deficient.

One of the major obstacles in the successful use of antitumor drugs in the treatment of cancer is their toxicity to normal tissues. Cancer chemotherapy ideally aims at targeting antineoplastic drugs to the tumor with little or no effect on cells of normal tissues. Liposomes are spherical microscopic particles consisting of a lipid bilayer enclosing an aqueous compartment (unilamellar vesicles) or a number of concentric bilayers each enclosing an aqueous space (multilamellar vesicles). These vesicles are currently being tried as vehicles for delivery of pharmaceutical agents. The distribution of liposomes in vivo can be influenced by varying their size, charge, fluidity, and route of administration.

Liposomes serve as attractive targeted drug delivery (TDD) systems to increase the therapeutic index of antitumor drugs. In preclinical studies, the use of liposomal doxorubicin has shown reduced cardiotoxicity and enhanced antitumor therapeutic efficacy. While clinical trials using doxorubicin encapsulated in stealth liposomes are in progress, alternative strategies are being tried for specific targeting of liposomes encapsulated drugs to tumor tissues.
Temperature sensitive liposomes can be designed from synthetic lipids to release an entrapped drug preferentially at temperatures attainable by mild local hyperthermia. Liposomes are known to release their encapsulated water soluble contents quickly near their gel to liquid crystalline phase transition temperature, selective release can therefore be obtained in a locally heated region by injecting liposomes having phase transition temperature (Tm) a few degrees above physiological temperatures. HT increases the therapeutic effectiveness of drug containing liposomes in the treatment of neoplasm by promoting selective drug release at the site of tumor subjected to localized hyperthermia. Temperature sensitive release can be achieved by using miscible mixtures of pure lipids having sharp transition temperatures to adjust the transition temperature to the desired point. For these studies synthetic lipids eg., dipalmitoyl phosphatidyl choline, DPPC (Tm = 41°C), usually in combination with dipalmitoyl phosphatidyl glycerol DPPG (Tm = 41°C) or distearoyl phosphatidyl choline DSPC (Tm = 54°C) are used.

In the present study we report a novel method for preparation of thermosensitive liposomes using natural lipids such as egg phosphatidyl choline (PC) and cholesterol (Ch) in combination with ethanol. Ethanol has a biphasic effect on gel to fluid phase transition of PC bilayers, reducing Tm at low concentrations, which appears to be correlated with induction of fully interdigitated gel phase.

This property of ethanol has been exploited in designing thermosensitive liposomes using PC and Ch in different molar ratios to obtain vesicles that undergo gel to liquid crystalline phase transition at hyperthermic temperature (Tm = 43°C).
The thermotropic behaviour of these liposomal preparations was examined by differential scanning calorimetry (DSC). The size, stability, in vitro cytotoxicity, biodistribution and in vivo uptake of thermosensitive liposomes in tumor tissue was studied. The in vivo efficacy of combination of hyperthermia and thermosensitive liposomes entrapped melphalan was determined in murine melanomas propagated in C57Bl/6 mice. The purpose was to determine whether the therapeutic index of melphalan is increased by TDD effect. These natural lipid derived heat sensitive liposomes are biodegradable, non toxic and more cost effective than thermosensitive liposomes prepared from synthetic lipids for use in multimodality cancer therapy.