CHAPTER-II

LITERATURE REVIEW
2. Literature review

Breast cancer represents a major ongoing public health problem as the most common non-cutaneous malignancy among U.S. women (Grobmyer et al. 2012). It is the second leading cancer worldwide after lung cancer, about one fifth of the cancer patient suffers from the breast cancer, and it is the leading cause of cancer death in women. The global burden of breast cancer exceeds all other cancers and the incidence rates of breast cancer are increasing (Jemal et al. 2010).

Over the last several decades the incidence of breast cancer has increased globally (Hortobagyi et al. 2005; Anderson et al. 2008; Porter et al. 2008). The incidence rate of breast cancer greatly increased in Asian countries (Green et al. 2008). In Asia, breast cancer incidence peak shows among women in their forties (Agarwal et al. 2007), whereas in the United States and Europe, it shows among women in their sixties. In India about 50% of all breast cancer patients belong to premenopausal (Agarwal et al. 2007).

Tamoxifen was approved by the FDA in 1977 for the treatment of metastatic breast cancer. The recommended daily dose of Tamoxifen is 20-40 mg (http://www.pdrhealth.com/drugs/tamoxifen-citrate/)

Tamoxifen is widely used in the treatment of breast cancer and as a preventative agent after its surgery (Owens et al. 2002). Tamoxifen has both a pro- and antiestrogenic effect on the nuclear estrogen receptors (ER), modifies the function of the plasma membrane, the microsomes, the proliferative and antiproliferative factors as TGF or cyclins, et cetera (Kangas et al. 1986; Noguchi et al. 1993; Maas et al. 1995; Clemons et al. 2002). As a “selective ER modulator” (SERM), Tamoxifen significantly influences the activity of ER (Lonard et al. 2002).
It has been used in the management of breast cancer for over 30 years. Since its introduction for the treatment of advanced breast cancer, its indications have increased to include the treatment of early breast cancer, ductal carcinoma in situ, and more recently for breast cancer chemoprevention (Clemons et al. 2002). Tamoxifen has a good tolerability profile and moreover, unlike many other endocrine therapies, it is efficacious in both pre- and postmenopausal women. It is the combination of efficacy and tolerability that allows Tamoxifen to maintain its position as the hormonal treatment of choice for most patients with oestrogen-receptor positive breast cancer.

Cho et al. (2008) and Chidambaram et al. (2011) have reported in their review article that cancer nanotherapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, low therapeutic indices and multidrug resistance. To improve the biodistribution of cancer drugs, nanoparticles have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream. They are also able to carry their loaded active drugs to cancer cells by selectively using the unique pathophysiology of tumors, such as their enhanced permeability and retention effect and the tumor microenvironment. In addition to this passive targeting mechanism, active targeting strategies using ligands or antibodies directed against selected tumor targets amplify the specificity of these therapeutic nanoparticles. Drug resistance, another obstacle that impedes the efficacy of both molecularly targeted and conventional chemotherapeutic agents, might also be overcome, or at least reduced, using nanoparticles. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multi drug resistance, resulting in the increased intracellular concentration of drugs. Multifunctional and
multiplex nanoparticles are now being actively investigated and are on the horizon as the next generation of nanoparticles, facilitating personalized and tailored cancer treatment.

Various chemotherapeutic agents are used for the treatment of cancer which may be used alone or in combination with other forms of therapy. Multidrug resistance is a challenge in cancer chemotherapy which can be significantly reversed by delivering drug through solid lipid nanoparticles, polymeric nanoparticles, mesoporous silica nanoparticles, nanoparticulated chemosensitizer, nanoparticulated poloxamer and magnetic nanoparticles. Hydrophobic nature of chemotherapeutics leads to poor aqueous solubility and low bioavailability which can be overcome by nanocrystals, albumin based nanoparticles, liposomal formulation, polymeric micelles, cyclodextrin and chitosan based nanoparticles.

Nanotechnology has been firmly focusing in to the area of drug delivery. Drug delivery through the nanotechnology are continuously improved and maximize therapeutic activity and minimize undesirable side-effects and toxicities. Safari et al. (2014) in their review article described the advanced drug delivery systems based on micelles, polymeric nanoparticles, and dendrimers. Polymeric nanoparticles, carbon nanotubes and many others demonstrate a broad variety of useful properties.

Engineered nano materials ranges between 1 and 100 nm have novel optical, electronic, and structural properties that are not available either in individual molecules or bulk solids such as, clusters of atoms, molecules, and molecular fragments into small particles. The concept of nanoscale devices has led to the development of biodegradable self-assembled nanoparticles, which are being engineered for the targeted delivery of anticancer drugs and imaging contrast agents. Nanoconstructs should serve as customizable, targeted drug delivery vehicles capable of
delivering large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. Such “smart” multifunctional nanodevices hold out the possibility of radically changing the practice of oncology, allowing easy detection and then followed by effective targeted therapeutics at the earliest stages of the disease. Sinha et al. (2006) in their article briefly discussed about the use of bioconjugated nanoparticles for the delivery and targeting of anticancer drugs.

Researchers have are developed polymeric nanoparticles to deliver various kinds of anticancer drugs such as docetaxel, paclitaxel, doxorubicine etc. to the specific site of action to reduce the side-effects (Pradhan et al. 2013; Koopaei et al. 2014; Gupta et al. 2014; Guo et al. 2015).

A variety of methods have been used to prepare polymeric nanoparticles. Those methods include solvent evaporation, nanoprecipitation and multiple emulsifications etc (Sinha et al. 2013; Rudra et al. 2010; Sahana et al. 2010; Astet al. 2006; Horn et al. 2001; Birnbaum et al. 2000).

Memisoglu-Bilensoy et al. (2005) developed nanospheres and nanocapsules of β-CDC6, (amphiphilic β-cyclodextrin modified on the secondary face with 6C aliphatic esters) were prepared by nanoprecipitation technique directly from inclusion complexes of TMX and β-CDC6 (1:1 molar ratio). Blank and loaded nanospheres and nanocapsules were characterized by particle size distribution, zeta potential, drug loading and in vitro drug release. Particle sizes were between 250 nm and 300 nm for different formulations of nanospheres and nanocapsules. Zeta potential which was around −18 mV for blank particles and between +12 and +15 mV for Tamoxifen-loaded particles. Average entrapped drug quantity was found to be around 150 μg/mL for particles prepared from inclusion complexes and this was double the loading value for conventionally prepared particles. Pre-loaded formulations showed a significantly slower drug
release profile extended up to 6 h while formulations loaded conventionally displayed rapid and complete drug release within an hour. Cytotoxic efficacy of TMX loaded nanospheres and nanocapsules were determined against MCF-7 cells and TMX incorporated in amphiphilic β-cyclodextrin nanoparticles was found to be cytotoxic and effective against this cell line.

Ravikumara et al. (2011) reported in their study they had developed TMX-loaded chitosan nanoparticles (TMXL-ChtNPs) and TMX-free chitosan nanoparticles (TMXF-ChtNPs) were prepared by an ionic gelation (IG) method. The physicochemical properties of the nanoparticles were analyzed for particle size, zeta potential, and other characteristics using photon correlation spectroscopy (PCS), zeta phase analysis light scattering (PALS), scanning electron microscopy (SEM), Fourier transform infrared (FTIR), and differential scanning calorimetry (DSC). The variation in particle size was assessed by changing the concentration of chitosan, pentasodium triplyphosphate (TPP), and the pH of the solution. The optimized TMXL-ChtNPs showed mean diameter of 187 nm, polydispersity of 0.125, and zeta-potential of +19.1 mV. The encapsulation efficiency (EE) of TMX increased at higher concentrations, and release of TMX from the chitosan matrix displayed controlled biphasic behavior. Those TMXL-ChtNPs tested for chemosensitivity showed dose- and time-dependent antiproliferative activity of TMX. Further, TMXL-ChtNPs were found to be hemocompatible with human red blood cells (RBCs) and safe by in vitro cytotoxicity tests, suggesting that they offer promise as drug delivery systems in therapy.

Patel et al. (2011) formulated and evaluated chitosan nanoparticles of TMX for cancer therapy. Nanoparticles of TMX were prepared with chitosan using ionic gelation method. The concentration of the polymer chitosan was selected based on the results on preliminary
screening. The nanoparticles prepared were evaluated for morphology, drug loading efficiency, in vitro drug release and in vitro anticancer activities. The particle shape and morphology of the prepared TMX nanoparticles was determined by SEM analysis. The amount of TMX entrapment in the nanoparticles was calculated by the difference between the total amount of drug added to the nanoparticle and the amount of non-entrapped drug remaining in the aqueous supernatant. A diffusion cell was used to monitor TMX release from the nanoparticles. The formulations FM-1 showed good drug release from the polymer. The percentages of cumulative drug release after 3, 4, 5, 6, 7 and 8 hours were 40.54, 48.68, 56.26, 65.84, 71.42 and 78.03% respectively.

Sarmah et al. (2012) studied the antiproliferative action of TMX, on a Jurkat (human T-cell leukemia cell line), by comparing the free drug and TMX loaded guar gum nanoparticles. They have developed a new formulation containing chemically cross-linked guar gum nanoparticles (GG NPs) loaded with TMX by single step (oil in water) emulsion and in-situ polymer cross linking technique was employed to prepare spherical and smooth surfaced nanoparticles in the size range of 200-300nm. Nanoparticle size and shape was confirmed by transmission electron microscope (TEM) analysis. Cytotoxicity on Jurkat (human T-cell leukemia) cell lines as determined by cell growth inhibition after 48 h of incubation has indicated that TMX loaded guar gum nanoparticles were as efficient as the free drug when applied to the cancer cells. From this study the researchers further concluded that the crosslinked guar gum nanoparticles loaded with TMX exhibited sustained release of the drug and delayed apoptosis over a long period of time making it suitable for cancer treatment.

Sarmah et al. (2014) have prepared, characterized and studied the biodistribution of TMX loaded cross-linked guar gum (GG) nanoparticles. Nanoparticles were prepared via a single step emulsion process and particle size was evaluated. The extent of tissue distribution and retention
following oral administration of TMX loaded GG Nanoparticles and TMX tablet in female albino mice was analyzed over a period of 48 hours. Till 48 hours, the particles remained detectable in both mammary and ovary tissue (estrogen receptors). Uptake and retention of TMX from nanoparticles and tablets in mammary gland and ovary tissue changed with time. Results showed that the uptake and retention of nanoparticles were more in the mammary gland between 24 - 48 hours (11.2% at 24 h; 4.65% at 48 h). As mammary gland is the target organ in breast cancer therapy, it may be concluded that the cross-linked GG nanoparticles are capable of releasing drug at the target and minimize the uptake and retention in non-target tissue, the ovary (7.98% at 24 h; 1.9% at 48 h). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with time were measured. Further they reported that no abnormal changes in the liver enzymes were observed. GG nanoparticles may be used as a drug carrier system for treating cancer.

Avgoustakis (2004) has reported that pegaylated biodegradable nanoparticles made of PLA, PLGA evaded phagocytosis and thus extended the range of sites within the body where the nanoparticles reached.

Sahana et al. (2010) prepared TMX nanoparticle, a loaded PLGA (85:15) by multiple emulsification (w/o/w) and solvent evaporation technique. Different parameters such as drug-polymer ratio, polyvinyl alcohol concentrations, and homogenizing speeds were varied at different stages of preparation to optimize the desired size and release profile of drug. The characterization of particle morphology and shape was performed by field emission scanning electron microscope (FE-SEM) and particle size distribution patterns were studied by direct light scattering method using zeta sizer. In vitro drug release study showed that release profile of
TMX from biodegradable nanoparticles varied due to the change in speed of centrifugation for separation. Drug loading efficiency varied from 18.60% to 71.98%. The FE-SEM study showed that biodegradable nanoparticles were smooth and spherical in shape. The stability studies of TMX in the experimental nanoparticles showed the structural integrity of TMX in PLGA nanoparticles up to 60°C in the tested temperatures. So by performing the various in vitro characterization studies they have confirmed that nanoparticles containing TMX could be useful for the controlled delivery of the drug for a prolonged period.

Cirpanli et al. (2010) were formulated Tamoxifen in nanoparticulate carrier systems in the form of PLGA, poly--caprolactone (PCL) and chitosan nanoparticles. The PLGA and PCL nanoparticles were prepared by a nanoprecipitation technique whereas the chitosan nanoparticles were prepared by the ionic gelation method. Mean particle sizes were under 260 nm for PLGA and PCL nanoparticles and around 400 nm for chitosan nanoparticles. Polydispersity indices were less than 0.4 for all formulations. Zeta potential values were positive for TAM loaded nanoparticles because of the positive charge of the drug. Drug loading values were significantly higher for PCL nanoparticles when compared to PLGA and chitosan nanoparticles. All nanoparticle formulations exhibited controlled release properties. These results indicate that TAM loaded PLGA; PCL and chitosan nanoparticles may provide promising carrier systems for tumor targeting.