CHAPTER-I

1. INTRODUCTION

Cancer is among the most devastating diseases and it is the root cause of more than 25% of deaths in many countries (Pathak and Kathiyar, 2007). As per the World Health Organization (WHO) report, 14.1 million individuals were diagnosed with cancer and 8.2 million deaths occurred from cancer in 2012 globally. If recent trends are seen globally in the future, this number is expected to increase 50% by 2020, according to a current report from the International Agency for Research on Cancer (IARC) (Stewart and Kleihues, 2003). It affects the people at all stages of life with the high risk for most of the cancer types increasing with age. The most commonly diagnosed cancers worldwide are lung, breast, colorectal and stomach cancers and contributed almost 40% of all cases. According to the WHO, the overall age standardized cancer incidence rate is 25% more in men than women. In India, cancer is the third major cause of death accounting for 0.4 million deaths per year, and is therefore a major concern for public health. The incidence rate has been increasing in most part of the world, but there are great difference between developed and developing countries. Incidence rate is higher in more developed countries but mortality is relatively higher in less developed region due to short of early detection and treatment facilities.

The treatment for cancer may include chemotherapy, surgery, radiation therapy, hormone therapy or immunotherapy. The standard treatment of most disseminated cancers is chemotherapy. Several anticancer agents including cisplatin, paclitaxel, etoposide, vinblastine, vincristine, camptothecin, mitoxantrone, 5-fluorouracil, indomethacin etc. are in clinical use worldwide. However, these drugs are associated with different kinds of adverse effects. The occurrence of dose limiting side effects and the development of resistance associated with the use of conventional anticancer drugs often reduce the clinical benefit (Chen et al., 2007), and have shown the urgent need for development of novel drug delivery system, exploration of novel targets for the efficient drug delivery and synergistic combination of antitumor agents to cut short the drug concentration, in order to reduce the toxicity and increase the drug efficacy. Tumor
targeted delivery of conventional therapeutics has emerged as one of the novel approach to overcome the adverse effects associated to it. Targeted drug delivery refers to drug buildup to pathological sites predominantly and preventing their accumulation in healthy tissue, thereby affecting the balance between drug efficacy and toxicity (Torchilin, 2000). Simultaneously, in order to optimize drug therapy, drug delivery systems can modify routes of administration, bio-distribution and elimination of therapeutic candidate.

Cis-diamminedichloroplatinum (II), commonly known as cisplatin, is potentially useful in the treatment of various solid tumors such as testicular, ovarian, cervical, bladder, head and neck, oesophageal and small cell lung cancer (Kelland, 2007). However, its clinical use is hampered due to severe adverse effects including nephrotoxicity, ototoxicity, neurotoxicity, nausea and vomiting (Wang and Lippard, 2005; Pabla and Dong, 2008). Among diverse kinds of adverse effects of cisplatin, nephrotoxicity is a critical obstacle and limits its use and efficacy in the cancer chemotherapy. In order to improve the therapeutic efficacy of cisplatin in the treatment of cancer, various formulations have been investigated including drug–polymer conjugates (Malik et al., 1999), liposomes (Newman et al., 1999), micelles (Nishiyama et al., 2001), disks (Deurloo et al., 1991), microspheres (Hagiwara et al., 1993), and nanoparticles (Moreno et al., 2010). Particulate based delivery systems appear to be a promising option for the cisplatin delivery because they improve the efficacy by more selective and controlled delivery of the cisplatin to the tumor tissue and thereby reducing apparent toxic side effects (Avgoustakis et al., 2002). For cisplatin delivery, three attributes of nanoparticle based formulations are of particular significance; (a) the passive targeting of tumors with nanoparticles has been associated with enhanced permeation and retention effect (Maeda et al., 2001) that could lead to targeted delivery of cisplatin to tumors, (b) sustained release pattern from the nanoparticles could be advantageous because the intermittent administration of cisplatin at sub-therapeutic doses was more effective than after a single high dose to induce apoptosis with cisplatin (Kishimoto et al., 2005) and (c) controlled release formulations exhibited potential for
improving therapeutic efficacy of cisplatin and overcoming the drug resistance (Verrijk et al., 1992; Kim et al., 2008).

In order to reduce nephrotoxicity and, in turn, improve the efficacy of cisplatin, the tumor should be selectively exposed to the cisplatin while exposure to the kidney should be minimized. Recent advances in drug delivery systems hold great promises for improving cancer therapy. Nanoparticles composed of biodegradable polymers can offer the attributes of controlled and site-specific delivery of the therapeutic agent with improved efficacy and lesser adverse effects. On the other hand, targeting agent with the affinity for the receptors over expressed on cancer cells can be explored for site specific delivery of chemotherapeutic agent to the tumor. Another emerging area of research in cancer chemotherapy is drug combination. Conventional monotherapy includes compromised drug accessibility to tumor thereby necessitating a higher dose and repeated treatment, resulting in intolerable cytotoxicity and adverse effect, and resistance to the chemotherapies (Sahoo et al., 2007). For a decade, combination chemotherapy has been in clinical practices that have sorted out the draw backs involved with single agent based chemotherapy.

In this study, various approaches were investigated in order to improve chemotherapeutic potential of cisplatin. First, cisplatin loaded PLGA nanoparticles were developed, characterized and investigated for anticancer potential and toxicity profile. In another approach PLGA-PEG copolymer based nanoparticles were developed for cisplatin and functionalized with HA for the site specific delivery of cisplatin. Subsequently, albumin, a non toxic, biocompatible, hydrophilic and biodegradable polymer, was investigated for drug delivery of cisplatin in the form of nanoparticles and conjugated with folate to confer attribute of site specific delivery. Further, a drug combination strategy for cisplatin was investigated with the aim to improve cytotoxicity in cancer cells and reduce the toxicity in normal cells through the use of a reduced dose. In this approach the combination of cisplatin with pentacyclic triterpenediol (TPD)-an institutional anticancer lead obtained from *Boswellia serrata*, was investigated. This
study comprises investigation of various approaches for the improved chemotherapy with cisplatin.

The objectives of the study include:

- Development and characterization of poly (lactic-co-glycolic) acid (PLGA) particle based delivery system for cisplatin
- Development and characterization of hyaluronic acid functionalized poly (lactic-co-glycolic) acid-poly (ethylene glycol) (PLGA-PEG) based targeted delivery system for cisplatin
- Development and characterization of folate functionalized albumin based delivery system for targeted delivery of cisplatin
- Development and characterization of formulation of in-house anticancer lead (pentacyclic triterpenediol) and investigation of combination potential of this formulation with cisplatin.