Chapter 1  Introduction

Chemotherapy is well recognized as one of the principal methods in the treatment of cancer, a malignant disease that is listed as one of the major public health threats worldwide (Tomatis et al., 1990; Parkin et al., 2005). In chemotherapy, cytotoxic drugs are administered to the patients to kill the malignant tumour. Chemotherapy is often indicated in treatment of deeply sited tumours and tumour micrometastases in advance stage cancers, whereby in both cases surgery and radiotherapy may play limited roles (NCCP, 2002). Chemotherapy can improve the quality of life and prolong the lifespan of advance stage or disseminated stage cancer patients, and may effect cures in some cancer cases, for example Hodgkin disease, high grade non-Hodgkins lymphomas, germ cell tumours, and leukaemia (NCCP, 2002).

The cytotoxic drugs used in chemotherapy are often of the drug classes that interfere or disrupt the metabolic and proliferative activities of the cancer cells by intoxicating the cells or depriving the cells of their fundamental supplies for living, for example though inhibition of angiogenesis. These drugs are employed with the intention to kill the viable cancer cells found in the primary tumour site as well as the cancer cells that has metastasized to other parts of the body (Bishop, 1999). The anticancer drugs are normally solubilized in an aqueous formulation and administered intravenously or orally to the patients. These drugs can be solubilized in aqueous solution as they are or with the help of a surfactant for the drugs that are insoluble or have poor water solubility. Upon administration, these drugs were distributed rapidly and randomly throughout the body and into the tumour tissue through the tumour vascular network. In such instances, the annihilation of the cancer cells is very much dependent on the drug’s
blood clearance, the amount of the drug distributed into and retained in the tumour tissue interstitium, the rate of the drug uptake by the tumour cells, and as well the presence and rate of the drug’s degradation in the blood. Meanwhile, the rapid and random dissemination of these drugs in the body may reduce the chemotherapeutic drug supply to the tumour tissue and at the same time cause undesirable cytotoxicity to the normal healthy tissue that assume ongoing replication activity, for example the bone marrow tissue, intestinal mucosal lining, hair follicle tissue testicular germinal tissues, and others (Tannock, 1992). Furthermore, some of the surfactants used are toxic to the body tissue as well, for example, the Cremophor EL used to solubilize paclitaxel in aqueous formulation (Li et al., 2002; Weiss et al., 1990). Such cytotoxicity to the normal tissue was found to be responsible for the various adverse effects in patients during chemotherapy, for example bone marrow suppression, stomatitis, abdominal pain, diarrhoea, hair loss, suppression in sperm production, infertility, and others (OCC, 2003), and has limited the use of increased cytotoxic drug doses in the patient to achieve greater anticancer effects.

In spite of its shortcomings, chemotherapy still remains as the one of main options in the cancer treatment. Theoretically, an ideal chemotherapeutic agent should possess characteristics such as long \textit{in vivo} half life, resistance against plasma degradation, can be targeted effectively to the tumour tissue and causes less toxicity to the normal tissues (Chabner & Longo, 2006). One way in doing this is through the improvement and modification of the currently available cytotoxic drugs using polymer - anticancer drug conjugation techniques.

Recently, advances chemical synthesis as well as increased knowledge of neoplasm disease states has led to the development of polymer-anticancer drug
conjugates as a novel class of anticancer agents in chemotherapy. Conjugation of chemotherapeutic drugs to polymers is an attractive approach to solubilize insoluble or poorly soluble anticancer drugs, and to reduce systemic toxicity, enhance tumour targeting and improve the therapeutic index of the anticancer drugs (Duncan et al., 2005). Chemotherapeutic drugs bound to polymers tend to accumulate in solid tumour tissue through enhanced-permeability-retention (EPR) effect (Duncan & Spreafico, 1994). Thus far, preliminary research on copolymer-based anticancer conjugates has progressed rapidly and a variety of conjugate based anticancer drug derivatives, for example poly-(L)-glutamic acid - paclitaxel, poly-(L)-glutamic acid - camptothecin, styrene-copmaleic anhydride - neocarzinostatin and HPMA-doxorubicin have been synthesized and subjected to preclinical / clinical trials (Duncan et al., 2001; Kopecek, 1990; Kopecek & Kopeckova, 1993; Li et al.; 1998, 1999a, 1999b; Maeda, 1991; Maeda & Matsumura, 1989; de Vries et al., 2000). Without doubt, getting better understanding on the polymer drug conjugation techniques and synthesizing more novel polymer - drug conjugates would be of great importance for cancer treatment and continuous generation of advanced antitumour drug classes.

Currently, a great part of the anticancer polymer drug conjugate research and development work have emphasized on the conjugation of the non water soluble drugs or poorly water soluble drugs to the water soluble polymers, with the main intention to increase the solubility of these drugs in the blood and thus the availability of these drugs to the tumour (Table 2.11). Relatively, the use of water soluble anticancer drugs in synthesizing polymer drug conjugates was less explored (Table 2.11). Although water soluble drugs do not have the issue of reduced drug anticancer efficacy due to poor water solubility, conjugation of these drugs to the polymeric carriers is equivalently
important as it may potentially reduce the blood clearance and degradation, non specific toxicity, as well as increase the antitumour efficacy of these drugs.

In this study, we propose to investigate the outcome of applying the polymer drug conjugation strategy to the drugs of the antimetabolite nucleoside analogue class, an anticancer drug class that has good water solubility, using one of its most potent members, that is, gemcitabine as a model. Specifically, the alterations over the water solubility, the aqueous and blood stability, the anticancer efficacy and the non specific tissue toxicity of the model drug after conjugating to a polymer through the simple conventional conjugation methods, for example, esterification, amide bond formation are proposed to be studied. This is because most of the functional groups, for example, -OH and -NH$_2$ on the drug molecules of the anticancer nucleoside class that are responsible for the said characteristics may likely be altered during the conjugation reaction. Also, the possible improvements over the in vivo distribution and the tumour targeting properties of the small molecular size antimetabolite nucleoside upon its conjugation to the polymer were proposed to be investigated. To achieve the above objectives, a novel polymer drug conjugate was proposed to be synthesized by conjugating gemcitabine to a water soluble biopolymer that has been well characterized and frequently employed in PDC synthesis, that is, the poly-L-glutamic acid. Subsequently, the chemical properties and the aqueous and plasma degradation profiles of the synthesized PDC were studied through standard techniques and the anticancer properties of the conjugate were evaluated using in vitro and in vivo breast tumour models. By comparing the results gathered to that of the parent drug, that is, gemcitabine, clues to the mentioned query as well as to the suitability and potential in employing the polymer-drug conjugate strategy to enhance the antitumour efficacy of the rest of the members found in the antimetabolite nucleoside class may be obtained.