# CHAPTER I

# INTRODUCTION

Melanoma is a type of skin cancer which originates from melanocytes. Melanocytes are found in the epidermis and they contain melanin, the pigment that expresses the human skin color and protects the skin from sunlight damage. The incidence of melanoma and the death rate from melanoma has steadily increased annually. The American Cancer Society estimates that in 2007, approximately 59,940 new cases of melanoma in the United States were diagnosed and almost 8,110 deaths occurred (Jemal et al., 2007). In Thailand, the incidence of melanoma is low. However, the risk of melanoma for Thai people may increase because of increasing in sunlight exposure. There are many factors that can cause melanoma. Sun exposure is the most important risk factor. The others risk factors are unusual moles, skin type (fairer skin is at increased risk), family and personal history of melanoma and weakened immune system. The standard treatment of all stages of melanoma is surgery. After surgery, adjuvant therapy including chemotherapy, radiation, immunotherapy, or the combination of these treatments, may be used to treat later-stage disease and prevent the recurrence of melanoma. Chemotherapy is the use of anticancer drugs, given orally or by injection, which travel through the bloodstream to kill cancer cells. Chemotherapy drugs for the treatment of melanoma may be administered as a single drug or in combination, or in conjunction with immunotherapy, drugs that act on the immune system.

Dacarbazine, or 5-(3, 3-dimethyl-1-triazenyl) imidazole-4-carboxamide, also known as DTIC, was approved by the US Food and Drug Administration for treatment of malignant melanoma. Its mechanism of action is methylation of nucleic acids or direct DNA damage resulting in arrest of cell growth or cell death. When used as a single agent, an approximately 20% objective response rate can be achieved

with median response duration of 5 to 6 months and complete response rates of 5% (Flaherty, 2006). Dacarbazine is administered by intravenous bolus injection or by short term intravenous infusion as a single dose for five days, repeated every 3 or 4 weeks. The plasma concentration of dacarbazine shows a biphasic manner. The initial phase half life is very short, with one study reporting half life as 3 minutes and the terminal phase half life is about 35 minutes. The short half life of the drug may cause cancer cell exposed to the drug for only short time. Thus, the administration by continuous infusion of low concentration may provide more effectiveness than high concentration bolus. Unfortunately, long-term continuous infusion of dacarbazine may fail because of its short stability in aqueous solution (Shetty et al., 1992). The commercial formulation of dacarbazine also contains citric acid and manitol in order to improve drug solubility. After reconstitution, the drug solution has a pH of 3.0 to 4.0 and shows the shelf-life of only 8 hours at room temperature and up to 72 hours at 4°C. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored up to 8 hours at normal room conditions or up to 24 hours at 4°C.

Nanoparticles are solid colloidal particles in size less than 1 micron. Nanoparticles can be divided into two forms, nanosphere which the drug is uniformly dispersed throughout the particles, and nanocapsules which the drug is entrapped in the inner core (Kreuter, 1994). Nanoparticles have been widely used for delivery and targeting of various drugs, especially in cancer therapy (Peppas et al., 2004; Jain, 2005). They increase antitumor drug efficacy while reducing side effects and toxicities. Nanosize range of particles makes them pass more into and accumulate at the required target by passive targeting. In addition, modifying these nanocarriers with targeting moiety, the passage and accumulation may increase by active targeting. Incorporating hydrophilic polymer into nanocarriers makes them escape from rapidly clearance by mononuclear phagocytes system (MPS) and provide them long circulation in blood system, resulting in more chance for drug exposure to the target tissue. In addition, nanoparticles can be used to improve the stability of various agents (Saxena et al., 2004; Perugin et al., 2002). Small particles in nanosize are also suitable for parenteral administration.

Polymeric nanoparticle technology is one of the interesting fields due to their biocompatibility and biodegradability. Several biodegradable polymers were used, the examples of synthetic polymer are poly (glycolide) (PGA), poly (lactide) (PLA), and poly (lactide-co-glycolide) (PLGA) (Hans et al., 2002; Soppimath et al., 2001), and the examples of natural polymer are sodium alginate and chitosan. These carriers can be used to improve the drug stability by reducing direct contact of the drugs to their environment such as aqueous media, temperature and light (Saxena et al., 2004; Perugin et al., 2002). The major advantage of natural polymers includes their low cost and compatibility with the wide range of drugs, with minimal use of organic solvents. Their bioadhesion property, stability and safety are additional advantages. There has been increasing interest in the study of alginate and chitosan for various applications because of their non-toxic, biocompatible and biodegradable nature. These natural polymers have been used for preparation of polymeric nanoparticles. Numerous studies show the achievement when using alginate and/or chitosan nanoparticles to improve drug properties (Sarmento et al., 2006; Ahmad et al., 2006, 2007). Both alginate and chitosan may be used together to form strong complex, resulting in more stable nanoparticles.

In this study, dacarbazine was formulated as nanoparticles using chitosan-coated alginate for stabilized dacarbazine nanoparticles. The size, size distribution, surface charge, morphology and entrapment efficiency were determined. The stability of obtained dacarbazine nanoparticles in aqueous solution was also evaluated.

**Objectives**

The purposes of this study were

1. To prepare chitosan-coated alginate nanoparticles containing dacarbazine.
2. To evaluate physicochemical characteristics and entrapment efficiency of obtained chitosan-coated alginate nanoparticles containing dacarbazine.
3. To evaluate stability in aqueous solution of obtained chitosan-coated alginate nanoparticles containing dacarbazine.