CHAPTER I
INTRODUCTION

Dexamethasone, a synthetic glucocorticoid, has an outstanding characteristic of being efficient therapeutic drugs for the treatment of brain tumors, eye diseases, ocular disease and diabetic macular edema (Gómez-Gaete *et al*, 2007). According to John D. Heiss and his colleague, the clinical use of dexamethasone supported a suppression of brain tumor–associated cerebral edema (Hempen *et al*, 2002). Beside, dexamethasone has been integrated into microspheres and liposomes in order to suspend and suppress the inflammatory reaction at the site of implantable devices such as glucose sensors (Zolnik *et al*, 2008). A recent literature has shown that dexamethasone-loaded composite system, which applied to the glucose sensor tip reduced inflammation and could efficiently improve their function and lifetime (Ju *et al*, 2010). However, dexamethasone can cause serious side effects. According to Christina Hempen, the most frequent side effects were an increase in serum glucose level, peripheral edema, psychiatric disorders, and Cushing's syndrome when the dosage of dexamethasone at the beginning and during the course of radiation therapy (RT) is median 7–12 mg/day, followed by the end of RT is median 1–6 mg/day within 23 and 7 weeks for patients with primary and secondary brain tumors, respectively (Hempen *et al*, 2002). Thus, the considerable desire for local delivery of dexamethasone in order to minimize the exposure of the whole animal body to the high concentrations of drug needed to obtain an appropriate concentration around implants and to avoid the side effects of chronic use (Makadia *et al*, 2011) (Kim *et al*, 2006).

The local treatment strategy of dexamethasone can be conducted on drug delivery system (DDS) by biodegradable and biocompatible polymer. One of these polymers is poly (D,L-lactide-co-glycolide) (PLGA), which is a FDA-approved biodegradable polymer (Mittal *et al*, 2007). Furthermore, PLGA is highly biocompatible and has been researched and used as delivery carrier for proteins (Ravivarapu *et al*, 2000), macromolecules and especially drugs (Makadia *et al*, 2011). According to T. Hickey and his colleague, they were able to develop dexamethasone loaded PLGA particles, which continuously released drug over 30

days for a suppression of acute and chronic inflammatory reactions (Hickey *et al*, 2002). PLGA is aliphatic polyester based on lactic acid and glycolic acid. The ratio of lactic acid to glycolic acid can be varied in order to control the rate of polymer degradation (Mittal *et al*, 2007, Anderson *et al*, 2012). For instance, PLGA degraded approximately 2 months for the ratio 50/50 of lactic acid to glycolic acid; in contrast, PLGA degraded roughly 5 months for the ratio 85/15 of lactic acid to glycolic acid (Graves *et al*, 2004). Besides, there are many factors affecting the rate of polymer degradation, which is referred to sustained release of drug, including the molecular weight (Park *et al*, 1995), the type of drug (Acharya *et al*, 2010), the initial of drug loading, and the temperature of system (Makadia *et al*, 2011). As for example, the different size of PLGA spheres affected significantly the drug loading efficiency, the release profiles and the quantity of the released drug (Fredenberg *et al*, 2011). In order to improve the efficiency of drug delivery system, the PLGA nanoparticles loaded with magnetite nanoparticles has been widely researched.

The magnetically guiled particles as drug carriers are the new technology for the local treatment. The magnetic particles will be retained within a specific organ by applying an external magnetic field (Okassa *et al*, 2005). For this reason, magnetite (Fe_3O_4) nanoparticles, particularly, loaded PLGA sub-micro particles have been received great attention due to their immense in a variety of applications in Nano biotechnology. Iron oxide, a superparamagnetic nanoparticle (SPION), is suitable to be used as the magnet inside PLGA nanoparticles because it is not only have highly magnetic responsibility and biocompatibility, but also low cytotoxicity (Dong *et al*, 2011). Previous literature by Müille and his co-worker, they synthesized polylactide (PLA) and poly(D,L-lactide-co-glycolide) (PLGA) loaded with the various amounts of magnetite. Their experiment showed that the cytotoxicity of the PLA and PLGA magnetite-loaded particles is quite low qualifying them as potential formulation for intravenous injection with regard to the toxicological acceptance (Makadia *et al*, 2011). Furthermore, J. Cheng and his colleague studied magnetite loaded PLGA microparticles for oral delivery of insulin. The application of an external magnetic field could force magnetite loaded PLGA microparticles in the intestine. The efficacy of this method was confirmed by showing reduced glucose

levels for up to 12 hours post-administration (Cheng *et al*, 2008.). The technique of preparation of superparamagnetic iron oxide loaded PLGA sub-micro particles is double emulsion technique (W/O/W). According to our previous experiment, the double emulsion technique (W/O/W) was successfully used for synthesize PLGA nanoparticles containing superparamagnetic iron oxide nanoparticles by using OA-coated magnetite nanoparticles dispersed in the oil phase. In addition, Fe_3O_4 was homogenously distributed throughout the PLGA particles both in terms of a given particle and across different particles (Bootdee *et al*, 2012).

The aim of this study was to synthesize superparamagnetic iron oxide PLGA nanoparticles. Besides, the relationships between molecular weight of PLGA and an encapsulation efficiency and the drug-released profile were investigated in order to find the suitable molecular weight for sustained drug release. Moreover, in this study, the effects of an initial mass of dexamethasone on encapsulation efficiency and a drug-released profile were also examined.