CHAPTER I

INTRODUCTION

1.1 Introduction

Nicotine is an alkaloid found in the members of the solanoceous plant family such as tomato, potato, green pepper, and tobacco. As nicotine enters the body, it is distributed quickly through the bloodstream and can cross the blood-brain barrier. The chemical nicotine is an addictive component in cigarettes. The effects in the whole intact animal or human consist of an increase in pulse rate, blood pressure, and mobilization of blood sugar. The LD_{50} of nicotine is 50 mg/kg in rats, 3 mg/kg in mice, and 40–60 mg can be a lethal dosage for adult human beings. Nicotine is more toxic than many other alkaloids. This makes it an extremely deadly poison material [Yildiz, 2004].

Nicotine replacement therapy (NRT) is widely use for nicotine withdrawal during smoking cessation and relief of cigarette craving. Controlled levels of nicotine are giving to patients through gums, dermal patches, or nasal sprays to treat them off of their dependence [Davaran, 2005]. The first widely used method of nicotine replacement employed nicotine containing chewing gum where nicotine is bound to an ion-exchange resin. The drug is released from the gum by interaction with saliva and is absorbed through the oral mucosa or after swallowing. However, nicotine chewing gum have some unpleasant side effects, including bad taste, nausea, heartburn, and hiccups. Other disadvantages include that chewing gum is probably socially unacceptable to some smokers or under some social circumstances and it is contraindicated for people with dentures or other dental appliances [Berner *et al.*, 1992].

An alternative method for nicotine substitution is the use of a transdermal nicotine patch. Transdermal drug delivery offers a safer and more convenient method of drug administration. Nicotine is well suited for transdermal therapy because it is a

liquid which can penetrate into skin easily, be volatile, highly lipid soluble, and reactive liquid and strong solvent [Davaran, 2005].

The advantages of transdermal nicotine include :

(a) the convenience and increased agreement of once-a-day dosage form,

(b) a more constant plasma level to minimize the undesirable side effect of nicotine, even during period of sleep, so morning cigarette craves might be reduced,

(c) the elimination of the poor taste, irritation and hiccups associated with the nicotine containing chewing gum,

(d) a decrease in the gastrointestinal side effect of the gum [Berner *et al.*, 1992].

The patch helps compensate this craving while the smoker is effort to quit. The drug slowly leaches out of the reservoir, penetrates through the skin, and then into the blood stream. One example of the patches consists of a plastic chamber that contains the drug and covers by a selectively permeable membrane to control the rate at which the drug is delivered. This permeable membrane can be made from a variety of thermoplastics, such as nylon 6,6, polyethylene, ethylene-vinyl acetate, and cross-linked polyvinyl alcohol [Davaran, 2005]. However, the major disadvantage of these thermoplastics is that they are made from crude oil, a nonrenewable resource. Although the plastics can be recycled, the amount of solid waste generated by plastics is becoming a problem. Biodegradable plastics made from renewable resources are using important materials because they help the decrease need on petroleum and reduces the amount of waste material.

A basic requirement for the use of drug delivery systems for human therapy is their biodegradability and biocompatibility. Currently polylactide (PLA) and polyglycolide (PGA) are the most used biodegradable materials. They are the major members of the poly α-hydroxy acids which are one group of the polyesters. The novel drug delivery system consists of biodegradable poly(L-lactic-co-glycolic acid) (PLLGA) nanoparticles. They are used as vehicles for the targeted and controlled delivery of drug. Copolymers of lactide and glycolide are often used as biomaterials and carrier for drug delivery systems because they are low toxicity, excellent

biocompatibility, and biodegradation to nontoxic cleavage product [Grodzinski, 1999]. PLGA nanoparticles provide drug release in a controlled manner so that its concentration is maintained within therapeutic levels for longer periods of time. The polymerization method used in the synthesis of cyclic ester polymers is ring-opening polymerization in the presence of stannous octoate as catalyst [Li *et al.*, 1997]. The properties of copolymers can be controlled by adjusting their molecular weight (Mw) and the molar ratio of lactide to glycolide, that design a practical transdermal patch capable of holding load of nicotine and control release at the appropriate rate.

Rate-controlling of nicotine in commercial nicotine transdermal patch means the control of nicotine diffusion from skin-facing side at a first flux of greater than zero but less than 2 mg/cm^2 in any hour for a first time period of greater than zero but less than 5 hours, then at a second flux between 20 and 800 $\mu g/cm^2$ for a second time period of 7 hours or more [Baker *et al.*, 1990].

In this work, we attempted to synthesize the biodegradable polymer for the purpose of nicotine controlled release system with the release rates similar to those commercially available ones.

Figure. 1.1 The nicotine patch (10 and 15 milligrams of nicotine per patch for slow release into body over a 16 hour period). [Online] Available from: www.pharmcom.com.

1.2 Objectives of the research

1.2.1 To prepare controlled release PLLGA film containing nicotine.

1.2.2 To study factors affecting nicotine releasing of controlled release PLLGA.

1.3 Scopes of the research

1.3.1 Preparation of L-lactide from L-lactic acid by polycondensation and thermal decomposition.

1.3.2 Preparation of PLLGA by ring opening polymerization.

1.3.3 Preparation of PLLGA/PVA film containing nicotine.

1.3.4 Investigation of controlled-release film morphology by Scanning electron microscope (SEM).

1.3.5 Determination of release rate of controlled-release nicotine by UV spectrophotometer.

1.3.6 Study on the factors affecting nicotine releasing of controlled-release film including ratio of copolymer, and quantity of nicotine.