CHAPTER II

LITERATURE REVIEWS

2.1 Nicotine

Nicotine is a naturally occurring alkaloid found in a wide variety of plants. However, the principal source of nicotine exposure is through the use of tobacco. Tobacco leaves contain 2-8 % of nicotine combined with malate or citrate. Nicotine is the most important and also the most harmful substance in cigarettes and other tobacco products. The predominant effects of nicotine consist of an increase in pulse rate, blood pressure, plasma free fatty acids, and mobilization of blood sugar.

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, volatile, hygroscopic liquid, oily liquid with an unpleasant pungent odour and a sharp burning persistent taste. Nicotine can mix with an equal amount of water. However, it divides into organic solvents. Thus, it can easily be extracted from aqueous solutions by solvent extraction. It is a strong base and has a boiling point of 274.5°C at 1 atm. Of its two stereoisomers, s-(-)-nicotine is the more active and is the more prevalent form in tobacco. It is also absorbed through the skin. Nicotine free base is readily absorbed through mucous membrane and intact skin, but the salts are not. Absorption of nicotine through the skin is important during nicotine replacement therapy [Yildiz, 2004].

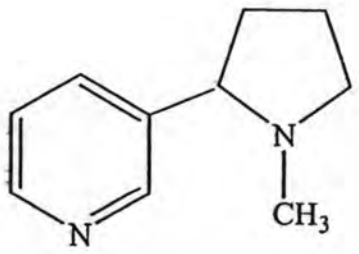


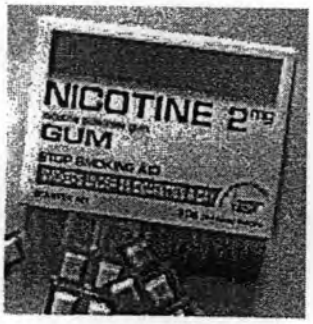
Figure 2.1 Structure of nicotine (1-methyl-2-(3-pyridyl-pyrrolidine)), $C_{10}H_{14}N_2$.

Solubility	:	Soluble in water, alcohol, chloroform, ether, kerosene, light petroleum, and fixed oils.
Storage	:	Store in airtight containers and protect from light.
Adverse effects	:	Nicotine is a highly toxic substance and is acute poisoning. Death may occur within a few minutes due to respiratory failure arising from paralysis of the muscles of respiration. The fatal dose of nicotine for an adult is from 40 to 60 mg.

2.2 Nicotine therapy

Nicotine has been shown to be the drug in tobacco that causes addiction. The nicotine withdrawal syndrome is primarily characterized by craving, irritability, frustration, anger, anxiety, poor concentration, restlessness, weight gain, and decreased heart rate. Pharmacotherapeutic intervention can be classified into four group therapy that replaces nicotine, antagonizes nicotine, provides symptomatic treatment for nicotine withdrawal, and deters smoking [Sugibayashi, *et al.*, 1994].

Nicotine replacement therapy (NRT) is the use of nicotine delivery methods intended to replace nicotine obtained from smoking or other tobacco usage. It was first investigated in the late 1960s and has been shown to be safe and effective in helping people stop using cigarettes. These products are intended for use in smoking cessation efforts to help deal with withdrawal symptoms and cravings caused by the loss of nicotine from cigarettes. Several forms of NRT have been commercialized, including chewing gum, inhaler, nasal spray, sublingual tablet, lozenge, and nicotine patch [Blank, 2002].



a) Nicotine gum

b) Nicotine inhaler

c) Nicotine spray

d) Nicotine sublingual tablet

e) Nicotine lozenge

f) Nicotine patch

Figure 2.2 Nicotine therapy [Online] Available from: www.nysmokefree.com.

2.2.1 Nicotine gum

Nicotine gum is a type of chewing gum that delivers nicotine to the body. For its proper performance the gum has to be alternatively chewed and left in the mouth until complete depletion of the nicotine. Two forms of this device are available, containing 2 or 4 mg of nicotine. A smoker will have to chew one gum approximately every two hours in order to attenuate the nicotine craving during the treatment period.

Nicotine chewing gum is currently available in market as an aid to smoking cessation but there are a number of problems associated with its use. These include adverse effects such as gastric disturbances, and problems for people with dentures.

2.2.2 Nicotine inhaler

The nicotine inhaler is a thin, plastic cartridge that contains a porous nicotine plug in its base. By puffing on the cartridge, nicotine vapor is extracted and absorbed through the lining of the mouth. This is a nicotine (10 mg) impregnated plug, that is inserted into a cigarette-like tube or mouthpiece. Adverse effects reported are mild mouth and throat irritation and coughing. The use of this device is not very popular.

2.2.3 Nicotine nasal spray

The nicotine nasal spray is available as a prescription drug. This consists of a nicotine solution contained in a small bottle fitted for insertion into the nostril. It is designed to deliver nicotine in a more rapid manner than the nicotine patch or gum, which makes the spray more similar to smoking a cigarette in terms of nicotine delivery to the body. The most common side effects are nasal and sinus irritation, watery eyes, throat irritation, sneezing and coughing. This device is expensive, and its use is very limited.

2.2.4 Nicotine sublingual tablet

Nicotine sublingual tablet which delivers 2 mg of nicotine, is placed under the tongue until it dissolves and the nicotine is absorbed through the oral mucosa. This is a doubling of the stop rate and excellent help of withdrawal symptoms and craving. Though the method of delivery is similar to nicotine gum, the sublingual tablet avoids the problem of proper use associated with the gum. Common side effects include irritation in the throat or under the tongue. The tablet form of nicotine is available without a prescription in many countries, but it is not available in the United States.

2.2.5 Nicotine lozenge

The nicotine lozenge is an oral variety of NRT. The lozenge comes in the form of a hard candy, and releases nicotine as it slowly dissolves in the mouth. Like the nicotine gum, the nicotine lozenge delivers nicotine to the brain more quickly than the patch. The most common side effects of lozenge use are soreness of the teeth, indigestion, and irritated throat.

2.2.6 Nicotine patch

Nicotine patch is a transdermal patch that releases nicotine into the body through the skin. It is usually used as a method to quit smoking. The drug slowly leaches out of the reservoir, travels through the skin, and then into the blood stream. The drug molecules must be small enough to penetrate the skin. It must be nonirritating to the skin and have a low melting point, so it can be incorporated in liquid form. It is developed to deliver precise quantities of a variety of drugs to the skin for a prolonged period of time. Some people who use the patch get a rash on their body where the patch is placed. Skin rashes are usually mild and easily treated. Moving the patch to another area of the body helps [Baker, *et al.*, 1990].

The earliest developed transdermal patches were medicated bandages, usually with the drug mixed into the adhesive, designed to bring a known quantity of drug to a known area of skin for a known time. Such devices do not control the rate at which the drug is released. Controlled release transdermal patches rely for their effects on

delivery of a known flux of drug to the skin for a prolonged period of time, measured in hours, days or weeks. Two mechanisms are used to control the drug flux from the patch. The drug is contained within a drug reservoir, separated from the skin of the wearer by a synthetic membrane, through which the drug diffuses or the drug is held dissolved and suspended in a polymer matrix, through which the drug diffuses to the skin. Patches incorporating a reservoir and membrane will deliver a steady drug flux across the membrane as long as excess undissolved drug remains in the reservoir. The membrane system allow nicotine to exist in the bloodstream at a small but constant level over a long period of time. At high concentration levels, there is a risk of harmful side effects [Venkatraman, *et al.*, 1998].

Therefore, the efficacy of a number of other forms of nicotine delivery has been investigated. The nicotine patch was likely to be useful. It was not inherently more effective than nicotine chewing gum, nicotine inhaler, nicotine spray, nicotine sublingual tablet, and nicotine lozenge but was easier to use. Several technologies have been successfully developed to provide rate control over the release of drugs and their subsequent permeation across the skin. These technologies can be classified into the following 5 basis [Sugibayashi, *et al.*, 1994].

2.2.6.1 Pressure sensitive adhesive (PSA) matrix devices

One of the simplest transdermal drug delivery systems (TDS) is a PSA matrix devices. The PSA can be positioned on the face or the back of the device and extended peripherally. Either way, it must fulfill the following requirements, cause no irritation and no sensitization during its period of contract with skin, provide sufficient adhesion to skin during the dosing interval, and be easily removed without leaving an unwashable residue. The most typical PSAs are acrylic, rubber or silicone adhesive. The drug reservoir itself is the adhesive. Monolitic PSAs, for example, are Frandol®, and Nitro Dur II®.

2.2.6.2 Membrane system

In membrane moderated systems, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In a drug reservoir compartment, the drug

solids are either dispersed homogeneously in a solid polymer matrix, viscous liquid medium to form a paste like suspension, or dissolved in a releasable solvent to form a drug solution. The rate controlling membrane can be either a microporous or a non porous polymeric membrane, for example, is ethylene vinyl acetate copolymer. Surface of the polymeric membrane is coated with a thin layer of a drug compatible, hypoallergenic, PSA polymer. The rate of drug can be tailored by varying the composition of drug reservoir formulation, the permeability coefficient and the thickness of the rate controlling membrane. Several TDS have been successfully developed from this technology and are best exemplified by transderm-Scop®, Transderm-Nitro®, Estraderm®, and Catapres®-TTS.

2.2.6.3 Adhesive membrane system

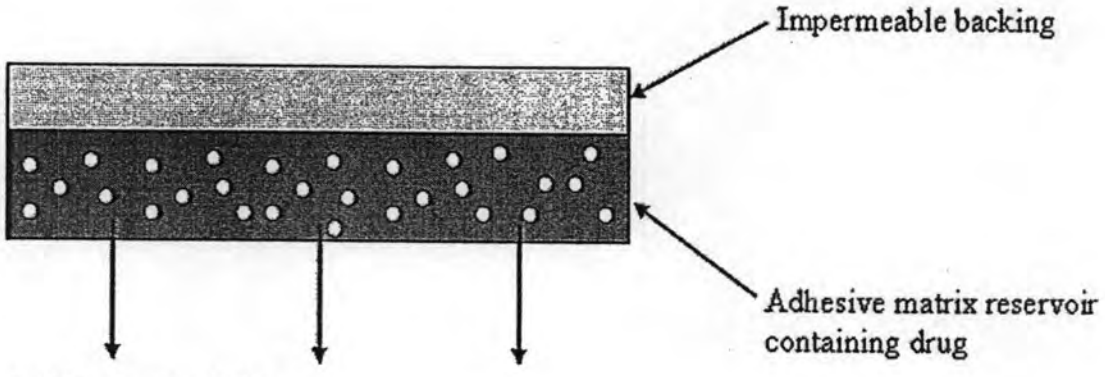
An adhesive layer can be used instead of polymeric membrane or rate control in reservoir devices. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or heating molding onto a flat sheet of drug impermeable backing to form a thin drug reservoir layer. On top of this, a layer of nonmedicated, rate controlling adhesive polymer of constant thickness is spread to produce an adhesive diffusion controlled drug delivery system. Drug release from the Deponit® system composed of several PSA layers is controlled by different diffusivities of the layers.

2.2.6.4 Microreservoir system

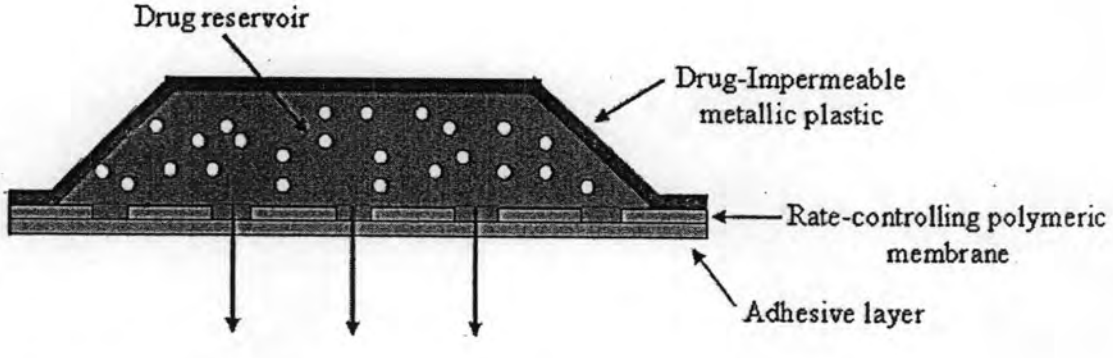
Microcapsule and macrocapsules prepared by polymers and polymeric membranes can be used in types of reservoir devices, such as hollow fibers, porous polymer sheet or filter, and foam as the wall of a capsule. Microencapsulation agents are one of the most important components in this system, and several hydrophilic and hydrophobic polymers are available for this purpose. The microreservoir type is actually a hybrid of reservoir that is formed by suspending the drug particles in an aqueous solution of water soluble liquid polymer. This technology has been utilized in the development of Nitrodisc®. Release of a drug from microreservoir can follow either a partition control or a matrix diffusion control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymatrix.

2.2.6.5 Nonadhesive polymeric matrices

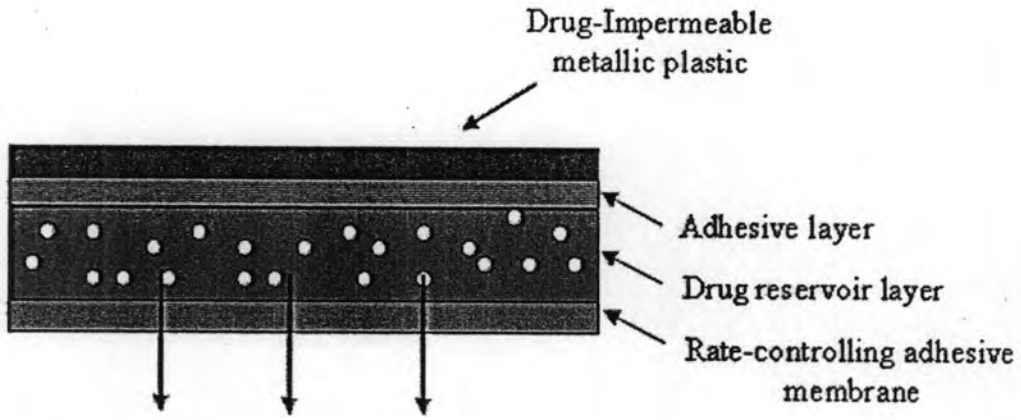
The simplest and least expensive way to control the release of a drug is to disperse it through an inert polymeric matrix. In monolithic systems, the drug is physically blended with polymeric powder, and the medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. This drug reservoir containing polymer disc is then glued onto an occlusive baseplate in a compartment fabricated with a drug impermeable plastic backing. This type of TDS is exemplified by the Nitro-Dur®. The adhesive polymer is usually applied around the circumference to form an adhesive rim around the medicated disc.



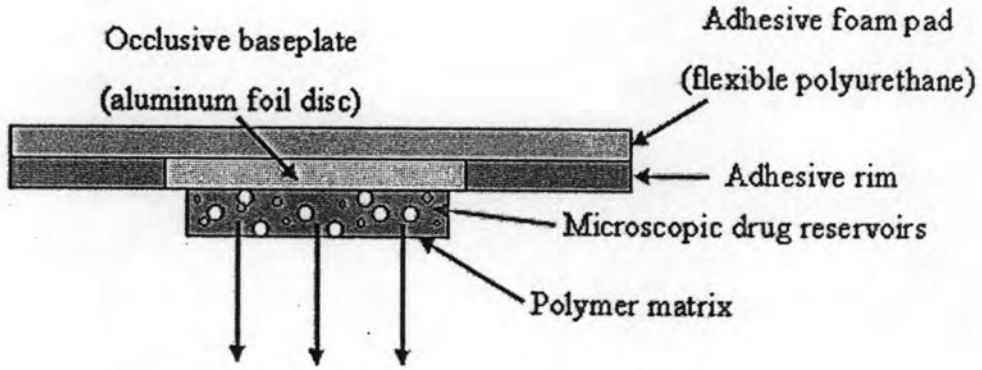
a) PSA matrix device



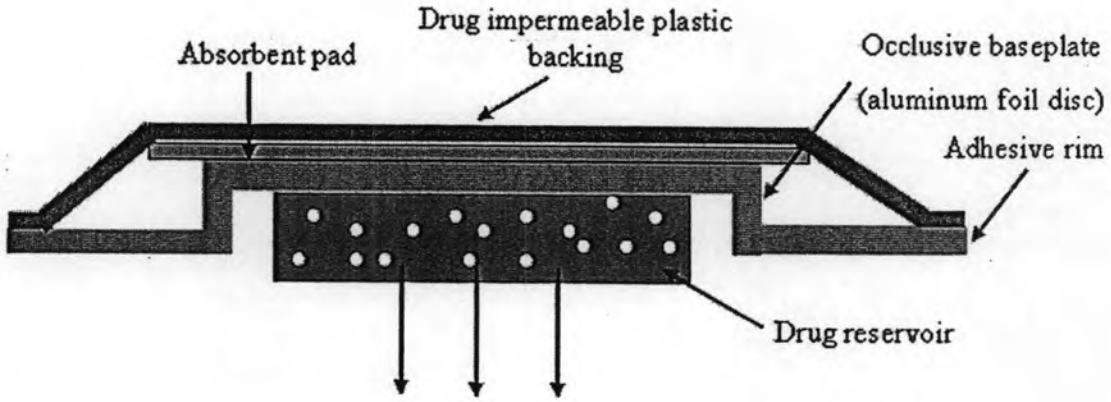
b) membrane-moderated



c) adhesive-controlled TDS



d) microreservoir-type TDS



e) matrix dispersion-type TDS

Figure 2.3 Cross-sectional view of several TDS [Sugibayashi, *et al.*, 1994].

2.3 Biodegradable plastics

These conventional types of plastics are widely used everywhere in the world, since they excel in strength and durability, and can be massively produced at a low cost. On the other hand plastics also have some disadvantages, including long degradation period causing problems in waste disposal. Therefore, there is an environmental need to overcome these disadvantages of plastics derived from petroleum. Bioplastics, plastic derived from plants rather than petroleum and natural gas, represent one approach towards green plastics. They are derived from material, such as corn starch that is degraded under certain conditions after a predetermined length of the time or contain light sensitive functional groups, which can be broken down when exposed to sunlight [Wibowo, *et al.*, 2006].

Biodegradable polymers obtained from renewable resource can provide a wide range of different and interesting applications such as packaging, biomedical applications, production of fibers, and agriculture uses.

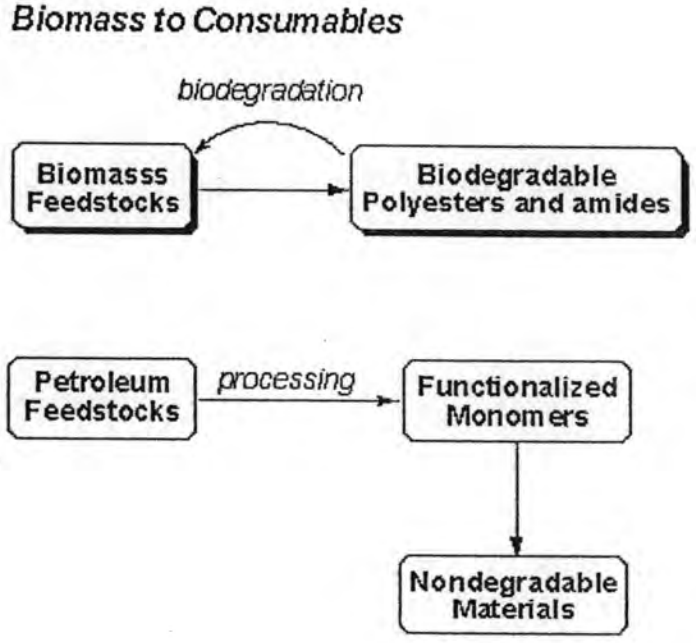


Figure 2.4 The production and disposal of nondegradable materials pose significant problems with increased global population.

The well-known biodegradable polymer are poly(α-esters) such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA). These have been shown to be nontoxic and biocompatible both as polymers and regards their degradation products. These polymers have a range of pharmaceutical and biomedical uses based on their characteristics and physicochemical properties such as surgical fixation, control drug delivery and more recently as tissue engineering scaffolds [Saha, *et al.*, 2006].

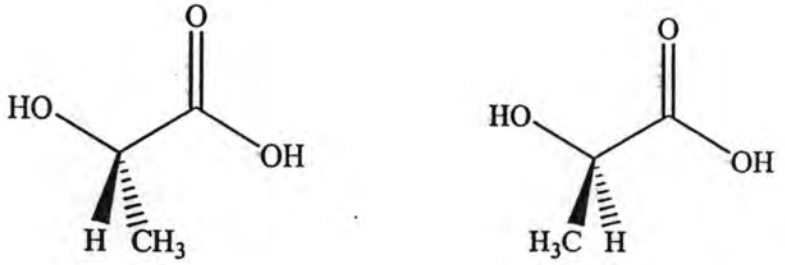
Controlled delivery is the most important and useful application of these polymers. Micro- and nanoparticles of polyesters are an important of delivery systems because of their hydrolytic degradation and low toxicity. The most important properties of these particles are release rate of the drug and the degradation rate, which can be desired [Grodzinski, 1999].

2.3.1 Polylactide

Polylactide (PLA) has been widely studied for use in biomedical applications due to its bioresorbable and biocompatible properties in human bodies. More recently, PLA has proved to be a cost effective alternative to commodity petrochemical with advantages. It can be obtained from renewable agricultural resource, its production consumes carbon dioxide and provides significant energy savings, recyclable, compostable, and mechanical properties can be modified to large extent through control of PLA chains [Murariu, *et al.*, 2007] The basic constitutional unit of PLA, lactic acid (2-hdroxypropionic acid), has been first introduced as 1780 as a sour component of milk. Ever since PLA has found its applications in food, pharmaceutical, and cosmetic industries. Now there are emerging uses as a potential feedstock for the biodegradable polymer industry. The properties and applications of lactic acid, its derivatives and polymer have been discussed. The various routes to polymerization and the companies presently involved in lactic acid production have been covered [Narayanan, *et al.*, 2004].

Lactic acid is a chemical compound that is derived from several biochemical processes. It is a carboxylic acid with a chemical formula of $C_3H_6O_3$. It has a hydroxyl group adjacent to the carboxyl group, making it an alpha hydroxy acid (AHA). In solution, it can lose a proton from the acidic group, producing the lactate ion [Hyon, *et al.*, 1997].

Lactic acid, a colorless liquid organic acid, is chiral and has two optical isomers. One is known as L-(+)-lactic acid or (*S*)-lactic acid and the other, its mirror image, is D-(-)-lactic acid or (*R*)-lactic acid. L-(+)-Lactic acid is the biologically important isomer. It is miscible with water or ethanol.



a) L-lactic acid b) D-lactic acid

Figure 2.5 Structures of lactic acid [Altaf, *et al.*, 2007].

Lactic acid is produced from renewable resource such as corn, potato and sugar beets, and the material is biodegradable thus making it ideal for industrial use. This is fermentation product of lactose (milk sugar) by *Lactobacillus*. This bacterium are also found in the mouth [Swift, 1993].

The commercial process for chemical synthesis is based on lactonitrile. Hydrogen cyanide is added to acetaldehyde in the presence of a base to produce lactonitrile. This reaction occurs in liquid phase at high atmospheric pressures. The crude lactonitrile is recovered and purified by distillation. It is then hydrolyzed to lactic acid, either by concentrated HCl or by H_2SO_4 to produce the corresponding ammonium salt and lactic acid. Lactic acid is then esterified with methanol to produce methyl lactate, which is removed and purified by distillation and hydrolyzed by water under acid catalyst to produce lactic acid and the methanol [Narayanan, *et al.*, 2004].

$$CH_3CHO + HCN \longrightarrow CH_3CHOHCN$$

acetaldehyde hydrogen cyanide lactonitrile

a) Addition of Hydrogen Cyanide

$$CH_3CHOHCN + H_2O + H_2SO_4 \longrightarrow CH_3CHOHCOOH + 1/2(NH_4)_2SO_4$$

lactonitrile sulphuric acid lactic acid ammonium salt

b) Hydrolysis by H_2SO_4

$$CH_3CHOHCOOH + CH_3OH \longrightarrow CH_3CHOHCOOCH_3 + H_2O$$

lactic acid methanol methyl lactate

c) Esterification

$$CH_3CHOHCOOCH_3 + H_2O \longrightarrow CH_3CHOHCOOH + CH_3OH$$

methyl lactate lactic acid methanol

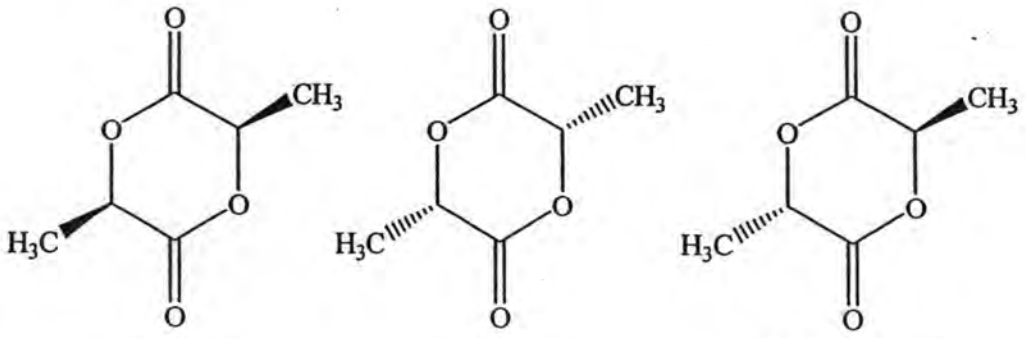
d) Hydrolysis by H_2O

Scheme 2.1 The chemical synthesis method produces a racemic mixture of lactic acid [Narayanan, *et al.*, 2004].

Lactic acid has many pharmaceutical and cosmetic applications and formulations in topical ointments, lotions, anti acne solutions, humectants, and dialysis applications, for anti carries agent. Calcium lactate can be used for calcium deficiency therapy and as anti carries agent. This biodegradable polymer has medical applications as sutures, orthopaedic implants, controlled drug release etc. Polymers of lactic acids are biodegradable thermoplastics. These polymers are transparent and their degradation can be controlled by adjusting the composition, and the molecular weight. Their properties approach those of petroleum derived plastics. Lactic acid esters like ethyl/butyl lactate can be used as green solvents. They are high boiling,

non-toxic and degradable components. Poly L-lactic acid with low degree of polymerization can help in controlled release or degradable mulch films for large-scale agricultural applications [Narayanan, *et al.*, 2004].

Lactide is a cyclic dimer produced from the dehydration of lactic acid. It has extensively use in many fields such as surgical sutures, bone fixation, and drug delivery systems. When lactide is prepared from racemic lactic acid, the three isomers that result are D-lactide, L-lactide and *meso-* lactide. The meso isomer can be removed, but D and L-lactide are enantiomers that comprise the racemic form, *rac* - lactide. When *rac*-lactide is polymerized with simple catalysts, an amorphous polymer results from an essentially random incorporataion of D and L- lactide units in the growing chain. Since the properties of the racemic polymer are not suitable for most practical applications, commercial processes presently utilize L-lactide produced from L-lactic acid. Poly(L-lactide) and poly(L-lactic acid) (both tremed PLLA) are biodegradable aliphatic polyester synthesized from ring opening polymerization of L-lactide or polycondensation of L-lactic acid, respectively, producing high molecular weight PLLA and low molecular weight PLLA from the respective synthesis technique [Loo, 2006].

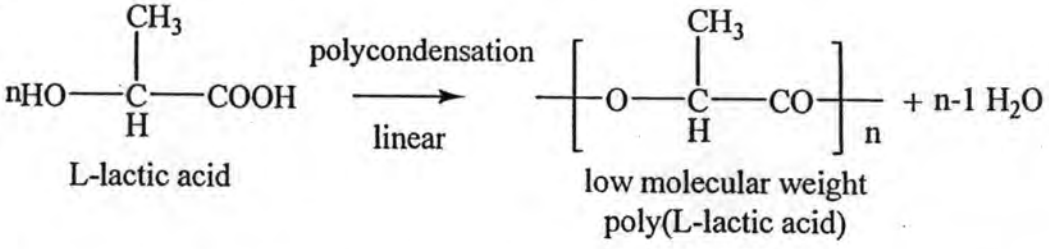


a) D-lactide b) L-lactide c) Meso-lactide

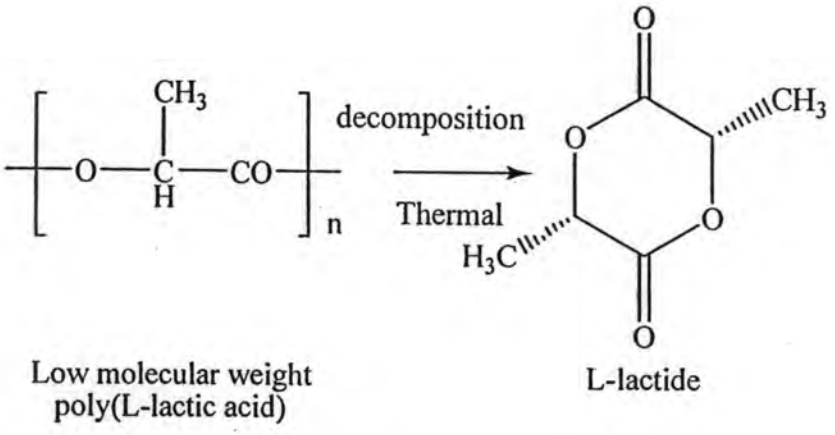
Figure 2.6 Structure of lactide. [Online] Available from: http://www.cem.msu.edu/~smithmr/Lactide.htm.

Low molecular weight of lactic acid through polycondensation was performed in the absence of any catalyst simply by distilling out water from aqueous solution of lactic acid at high temperatures. Reduced pressure was applied until white solid crystal of L-lactide was formed. Problems associated with condensation

polymerization, such as the need for exact stoichiometry, high reaction temperature, and the removal of low molecular weight byproducts (e.g., water) are excluded in ring opening polymerization [Loo, *et al.*, 2006].



a) L-lactic acid polycondensation to low molecular weight poly(L-lactic acid)

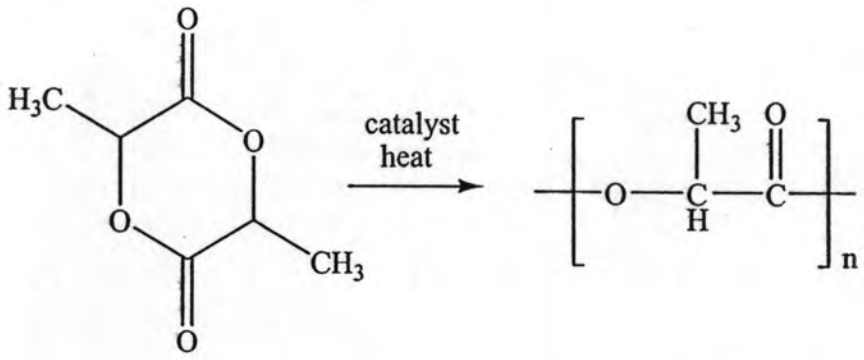


b) Thermal decomposition of low molecular weight poly(L-lactic acid)

Scheme 2.2 Chemical reactions of lactide [Dechy-Cabaret, *et al.*, 2004].

PLA can be prepared by ring opening polymerization (ROP) from the cyclic dimer either L-lactide and D-lactide. The polymer that results from the polymerization of these monomers, poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA), respectively, are both isotactic and semi-crystalline with identical properties. It can be easily produced in a high molecular weight form through ROP using most stannous octoate as catalyst. Due to the chiral nature of lactic acid, PLLA has a crystallinity around 37%, a glass transition temperature (T_g) between 50-80°C and a melting temperature (T_m) between 173-178° C. The polymerization of a racemic mixture L-

and D-lactides leads to the synthesis of poly(D,L-lactide) (PDLLA) which is not crystalline but amorphous.



Scheme 2.3 Chemical reaction of polylactide [Sodergard, *et al.*, 2002].

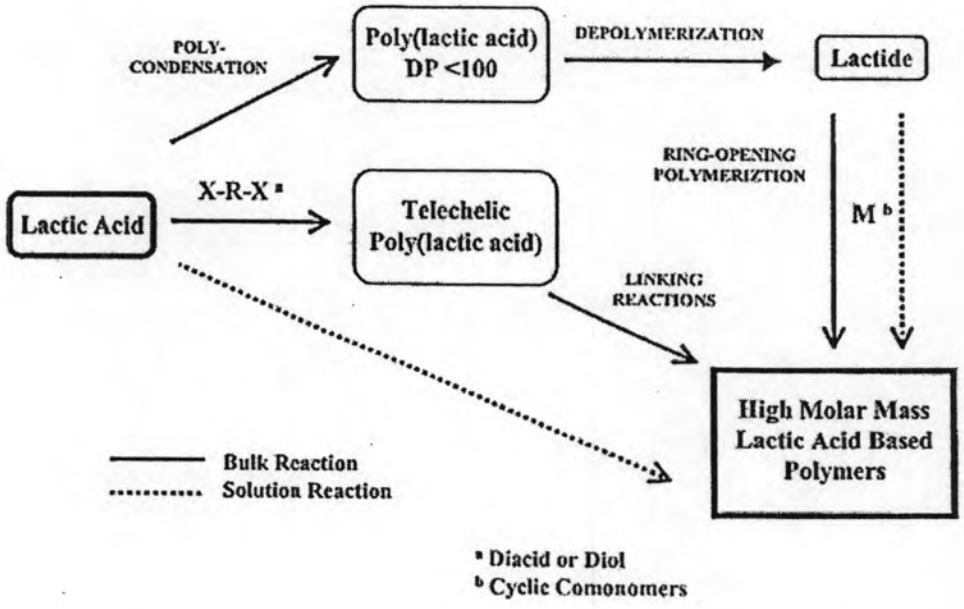


Figure 2.7 Different routes for the preparation of lactic acid based polymers [Sodergard, *et al.*, 2002].

PLA is currently used in a number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices, but it is also evaluated as a material for tissue engineering. Being biodegradable it can also be employed in the preparation

of bioplastic, useful for producing loose-fill packaging, compost bags, food packaging and disposable tableware.

2.3.2 Polyglycolide

Polyglycolide or polyglycolic acid (PGA) is a biodegradable, thermoplastic polymer and the simplest linear, aliphatic polyester. It can be prepepared starting from glycolic acid by means of polycondensation or ring-opening polymerization. Although Glycolic acid or hydroxyacetic acid occurs naturally as a trace component in sugarcane, beets, grapes and fruits, is the smallest α-hydroxy acid (AHA). It is a member of the polyester with a chemical formula of $C_2H_4O_3$. Glycolic acid appears as white crystals that are very soluble in water (0.1 g/ml), alcohols, acetone and ethyl acetate. The crystals also have a slight tendecy to solubilize into diethyl ether and some hydrocarbon solvents. Glycolic acid works as an exfoliating agent because of its high acidity and solubility. When placed on the skin as part of an exfoliating cream or gel, glycolic acid goes under the damaged upper layers of skin and destroys the glue which holds dead skin to the surface. As this dead skin is chemically burned off, the other components carry the individual flakes away and a water rinse neutralizes the remaining acid. The result is a much-smoother skin surface and a more youthful appearance. A secondary benefit of glycolic acid is the ability to draw moisturizers into the newly-exfoliated skin surface. This is why cosmetic counters often sell a complete system of skin care; the rest of the alpha-hydroxy line contains moisturizers and neutralizers to counteract the corrosive actions of glycolic acid. PGA polymerization, although the most common route to synthesize this polymer uses glycolide, the cyclic dimer of glycolic acid as starting material and it has no chiral centre in the molecule and therefore it does not form enantiomers [Baker, *et al.*, 2006].

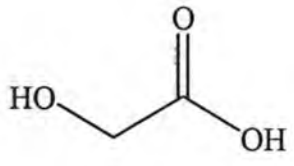


Figure 2.8 Structure of glycolic acid [Altaf, *et al.*, 2007].

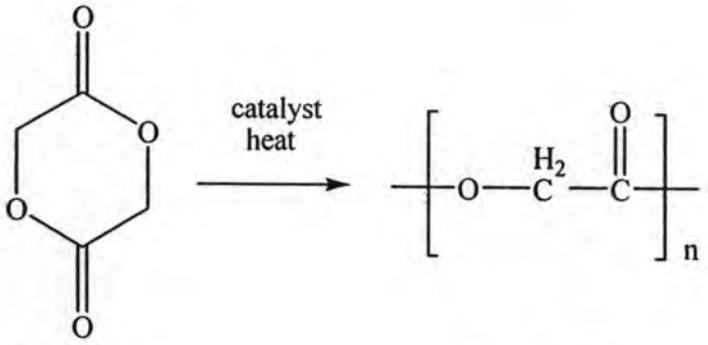
Glycolide can be prepared by heating low molecular weight PGA under reduced pressure, collecting the diester by means of distillation. ROP of glycolide can be catalyzed using different catalysts, including antimony compounds, such as antimony trioxide or antimony trihalides, zinc compounds (zinc lactate) and tin compunds like, stannous octoate (Tin(II) 2-Ethylhexanoate) or tin alkoxides. Stannous octoate is the most common used initiator. The procedure followed for ring opening polymerization is briefly explained by a catalytic amount of initiator is added to glycolide under a nitrogen atmosphere at a temperature of 195°C. The reaction is allowed to proceed for about two hours, then temperature is raised to 230°C for about half an hour. After solidification the resulting high molecular weight polymer is collected [Dobrzynski, *et al.*, 1999].

Figure 2.9 Structure of glycolide [Takahashi, *et al.*, 2000].

PGA can be obtained through several different processes starting with different materials. Polycondensation of glycolic acid is the simplest process available to prepare, but it is not the most efficient because it yields a low molecular weight product. Glycolic acid is heated at atmospheric pressure and a temperature of about 175-185°C is maintained until water ceasesd to distill. Subsequently, pressure is reduced to 150 mmHg, still keeping the temperature is maintained constant for about two hours and the low molecular weight PGA is obtained. The most common synthesis used to produce a high molecular weight form of the polymer is ROP of glycolide [Dobrzynski, *et al.*, 1999].

PGA has a glass transition temperature between 35-40°C and its melting point is reported to be in the range of 225-230°C. PGA also exhibits an elevated degree of

crystallinity, around 45-55%, thus resulting insoluble in water. The solubility of this polyester is somewhat unique, in that its high molecular weight form is insoluble in almost all common organic solvents (acetone, dichloromethane, chloroform, ethyl acetate, tetrahydrofuran), while low molecular weight oligomers sufficiently differ in their physical properties to be more soluble. However PGA is soluble in highly fluorinated solvents like hexafluoroisopropanol and hexafluoroacetone sesquihydrate. Fibers of PGA exhibit high strength and modulus and are particularly stiff [Takahashi, *et al.*, 2000].



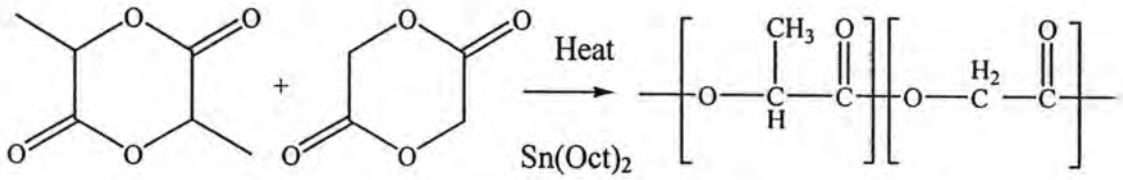
Glycolide Polyglycolide

Scheme 2.4 Chemical reaction of polyglycolide [Takahashi, *et al.*, 2000].

2.3.3 Poly(lactide-co-glycolide)

Biodegradable polymer prepared from poly(lactide-co-glycolide) (PLLGA) is excellent candidates for the controlled release of many pharmaceutical compounds, can either function as a matrix to control diffusion of the drug, followed by polymer biodegradation and elimination of the degradation products from body, or it can participate in and control the rate of drug release by polymer hydration and degradation. By varting the molecular weight and lactide/glycolide ratio [Li, *et al.*, 1997]. This polymer has high biocompatibility, nontoxicity, and easy processability in different forms. PLGA can be synthesized in a wide range of molecular weights by following two processes. Direct polycondensation reaction of lactic acid and glycolic acid which leads to low molecular weight polymers and bulk ring opening polymerization of lactide and glycolide, in the presence of metal catalysts to synthesize high molecular weight polymers [Wu, 2004]. Until recently, two initiators

are presently used industrially to make PLGA polymer by ring opening polymerization of lactide and glycolide, namely stannous octanoate ($Sn(Oct)_2$) and zinc (Zn) metal [Vert, *et al.*, 1998]. $Sn(Oct)_2$ was selected worldwide because it is efficient, configuration respecting, provides fast polymerization and it can produce high yield, molecular weight controlled, and narrow distributed polymers. Moreover, $Sn(Oct)_2$ can avoid transesterification reaction and has lower biologic toxicity [Yuan, *et al.*, 2005]. Zn metal is efficient, nontoxic catalysts, and configuration respecting but leads to rather slow polymerization. Zinc powder itself is a relatively good polymerization catalyst that is used industrially [Vert, *et al.*, 1998]. The catalyst is necessary to start the polymerization. Under mild condition, high molecular weight aliphatic polyesters of low polydispersity can be prepared in short periods of time [Frauenrath, 2005].



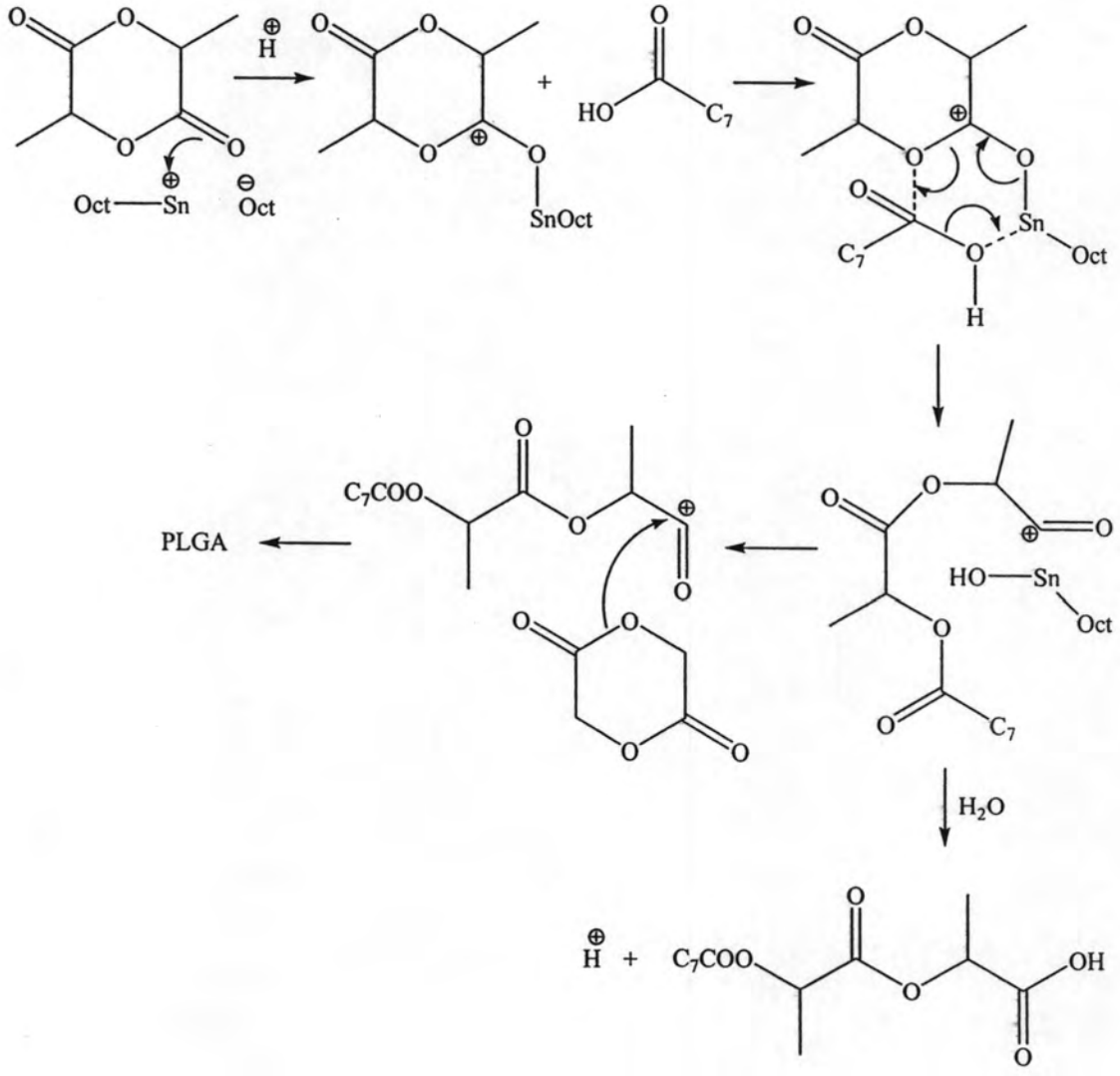
Lactide Glycolide PLGA

Scheme 2.5 Chemical reaction of PLGA [Li, *et al.*, 1997].

Many types of drug delivery devices based on PLGA include microspheres [Wu, 2004], implantable rods [Fukuzaki, *et al.*, 1991], fibers [Wu, 2004], films [Sampath, *et al.*, 1992], tablets [Murakami, *et al.*, 2000], pellets [Marcotte, *et al.*, 1989], beads, nanoparticles [Wu, 2004], and others.

Biodegradable aliphatic polyesters have become a very important of material in a wide range of biomedical and pharmaceutical application. The developments which have taken place in the controlled ring opening polymerization of cyclic esters via called coordination insertion mechanism, the propagation is thought to proceed by coordination of monomer to the active species, followed by insertion of the monomer into the metal-oxygen bond by rearrangement of the electrons [Rutot, *et al.*, 2001]. The catalyst and mixture of monomers were added to the reaction. The molar ratio of the lactide/glycolide was 50/50, 70/30, and 90/10. Polymerizations were carried out in

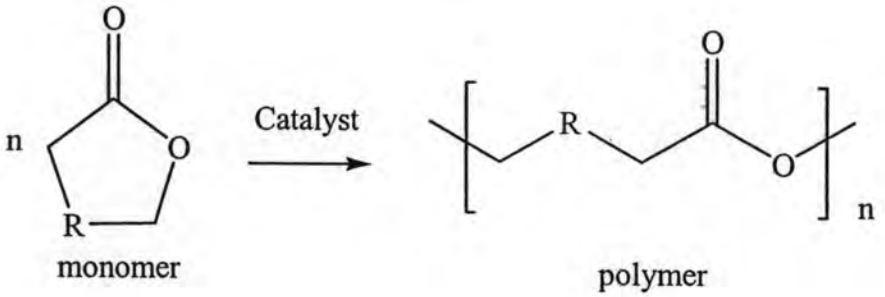
bulk under dry nitrogen with rigorous exclusion of moisture. Reaction temperatures and times ranged from 120-140°C for 24-72 hours. The product was dissolved in a small amount of dichloromethane and precipited in an excess of methanol [Li, *et al.*, 1997].



Scheme 2.6 Mechanism of PLGA proposed to account for the characteristics of stannous octoate [Vert, *et al.*, 1998].

2.4 Ring opening polymerization

Polyesters can be prepared by two different approaches, by the polycondensation of hydroxycarboxylic acid or by the ring opening polymerization (ROP) of cyclic esters. The polycondensation technique is less expensive than ROP, but it is difficult to obtain high molecular weight polymers. Polyesters are formed when cyclic esters are reacted with a catalyst or initiator. Scheme 2.7 presents the reaction pathway for ROP of cyclic ester.



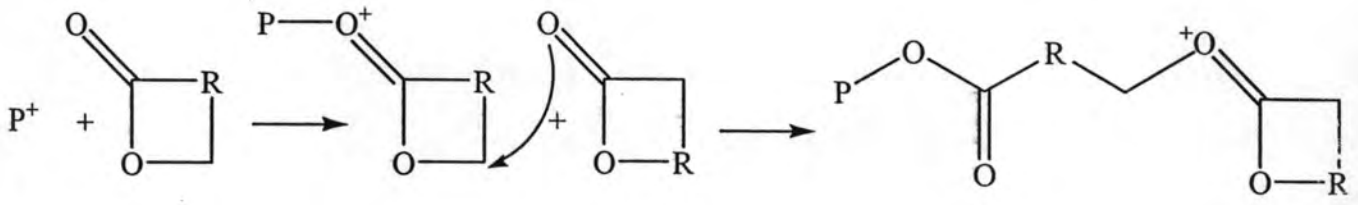
monomer polymer

Scheme 2.7 Ring opening polymerization of a cyclic ester. R=$(CH_2)_{0-3}$.

ROP can be performed either as a bulk polymerization, or in solution, emulsion, or dispersion. A catalyst or initiator is necessary to start the polymerization. Under rather mild conditions, high molecular weight aliphatic polyesters of low polydispersity can be prepared in short periods of time. ROP reaction was achieved either by cationic, anionic, or coordination insertion mechanisms.

2.4.1 Cationic ring opening polymerization (CROP)

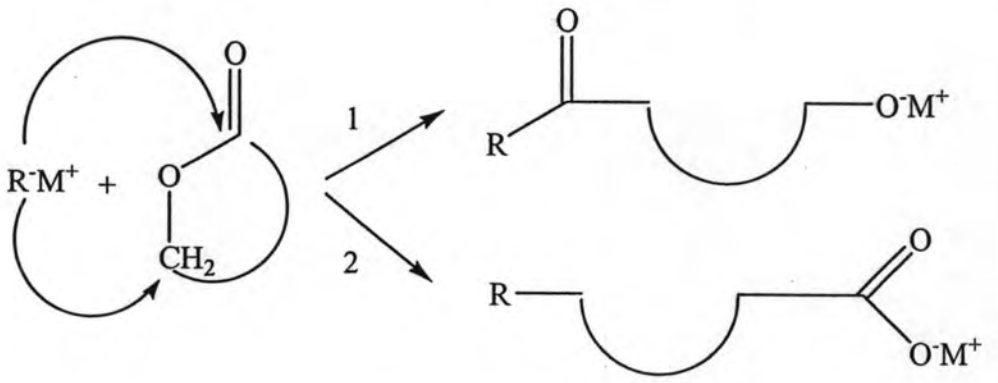
Among the cyclic ester, 4, 6, and 7 membered rings form polyesters when reacted with cationic catalysts. The cationic ROP involves the formation of a positively charged species which is subsequently attacked by a monomer. The attack results in a ring opening of the positively charged species through an S_N2 type process. The cationic polymerization is difficult to control and often only low molecular weight polymers are formed.



Scheme 2.8 The reaction pathway for the ROP of a cyclic ester by cationic initiation.

2.4.2 Anionic ring opening polymerization (AROP)

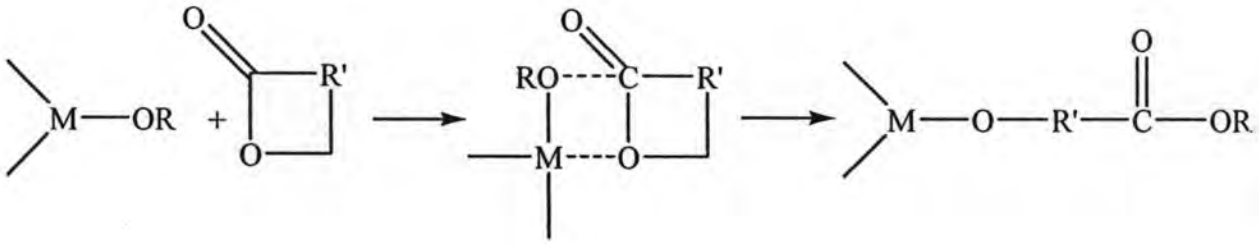
AROP of cyclic ester monomers takes place by the nucleophilic attack of a negatively charged initiator on the carbonyl carbon or on the carbon atom adjacent to the acyl oxegen. The propagating species is negatively charged and is counter balanced with a positive ion. One of the best controlled methods leading to high molecular weight polymers is anionic polymerization carried out in a polar solvent.



Scheme 2.9 The reaction pathway for the ROP of a cyclic ester by anionic initiation. ROP of monomer by 1) acyl oxygen bond cleavage and 2) alkyl oxygen bond cleavage.

2.4.3 Coordination insertion ring opening polymerization

The AROP is often referred to coordination insertion ROP, since the proparation is thought to proceed by coordination of the monomer to the active species, followed by insertion of the monomer into the metal oxygen bond by rearrangement of the electrons. The growing chain remains attached to the metal through an alkoxide bond during the propagation. The reaction is terminated by hydrolysis forming a hydroxyl end group. With functional alkoxy substituted initiators, macromers with end groups active in post polymerization reactions are producted.



Scheme 2.10 The proposed reaction pathway for the ROP of a cyclic ester by the coordination insertion mechanism.

2.5 Literature review

2.5.1 Literature review on synthesis of poly(lactide-co-glycolide)

Avgoustakis, *et al.* (1991) studied the synthesis and evaluation of matrix tablets using poly(lactide-co-glycolide) as the matrix forming material. The synthesis of poly(lactide-co-glycolide) was conducted using two different proportions of monomer mixture, at 90:10 and 70:30 lactide:glycolide (w/w). The factor variables studied were the catalyst type and concentration, the co-catalyst (lauryl alcohol) concentration, time, and temperature of polymerization. Lewis acids [Dong, *et al.*, 2001] and organometallic compounds [Fan, *et al.*, 2005] are two types of catalyst that have been reported to be particularly effective in the ring opening polymerization of lactide and glycolide. Two types of catalyst were compared as antimony trifluoride and stannous octoate. Under both polymerization conditions, the results obtained when using these catalysts are revealed that stannous octoate was far more effective.

The effect of catalyst concentration on the polymer molecular weight under polymerization at 130°C for 4 hours and 190°C for 4 hours was investigated. At both temperatures there was an initial sharp increase in the molecular weight at low catalyst levels, but this passed through a maximum before falling at higher levels of catalyst. It appears that higher molecular weight polymers were obtained at 130°C. The results show that effective catalyst concentrations depend on the temperature. Temperatures in the excess of 190°C have been observed polymer decomposition. The percentage yield is less affected by the temperature than by the catalyst level. Glass transition temperature as low as 37°C was measured which could have a significant effect on drug release [Avgoustakis, *et al.*, 1991].

Li, *et al.* (1997) studied the synthesis of brush like graft PLA and PLGA containing water soluble charged dextran sulphate sodium and diethylaminoethyl dextran chloride as backbones were synthesized in a bulk polymerization reaction using stannous as catalyst. Reaction temperatures and times ranged from 150-170°C for 4 hours. The solubility of dextran sulphate sodium in the melt of lactide and glycolide is only limited, therefore, higher reaction temperature are needed and residual amounts of unreacted dextran sulphate sodium are removed by exhaustive extraction with water to obtain pure polymers. Both conversion of lactide and glycolide were higher than 90%. The yields were in the range of 90% or higher.

Breitenbach, *et al.* (1998) studied the synthesis of the bulk polymerization of brush like grafted polyesters of lactide and their random copolymer with glycolide containing different characterization poly(vinyl alcohol) (PVA) as backbone using $Sn(Oct)_2$ as catalyst was established. To investigate the influence of the reaction condition a series of PLA-PLGA was prepared under variation of reaction time and temperature. Polymers were synthesized under rigorously anhydrous conditions. PVA was carefully dried, to avoid an initiation by water, which would lead to a mixture of linear and grafted products. The most suitable reaction condition was 130°C and 3 hours. At lower temperatures the solubility of PVA in the melt of the monomers was insufficient. At higher temperatures discoloration of the reaction products, accompanied by increased polydispersity and only partial solubility in DCM were observed.

Dobrzynski, *et al.* (2002) studied the synthesis of biodegradable PLGA copolymers with the use of low toxic iron compounds as initiators. Copolymerization of lactide and glycolide has been performed in bulk at moderate temperatures in the range of 100-150°C by a conventional method using a vacuum line for degassing. The copolymerization was carried out with the use of initiator required higher temperature (150°C) because of the low solubility of this compound at 100°C. Iron (III) acetylacetonate and iron (III) ethanolate initiators enabled one to obtain copolymer with yields up to 100% and possessing good mechanical properties. The chain propagation process and the influence of the transesterification was examind. On the basis of NMR examination and DSC thermograms, it was shown that samples obtained at the temperature of 100°C with the use of the initiators have quasi-segmental chain microstructure.

2.5.2 Literature review on the nicotine controlled release

Chung (1999) prepared controlled release nicotine by using proliposomes delivery system. Release of nicotine from the powder was rapid but that from the proliposomes was significantly retarded, indicating proliposomes can be a sustained release dosage form of nicotine.

Rafferty and Koenig (2002) prepared controlled release nicotine by studying diffusion of nicotine in ethanol/water mixtures into an ethylene-vinyl acetate copolymer membrane membrane. First, copolymer with lower vinyl acetate contents is more hydrophobic, and hence aqueous drug solutions diffuse more slowly through them compared to copolymer with higher vinyl acetate contents. Second, nicotine diffuses into ethylene-vinyl acetate copolymer ahead of the solvent for 0-60 wt% ethanol/water mixtures, but the segregation behavior changes as the ethanol in the solvent increases to 80 wt% ethanol/water mixtures, D_2O leads the diffusion front, and for the 100% ethanol solvent, ethanol diffuses into the ethylene-vinyl acetate copolymer first. Therefore, the concentration profiles suggest that the segregation of the components at the diffusion front depends on the solvent composition.

Olivier, Rabouan, and Couet (2003) studied and compared in vitro the performances in delivering nicotine of Nicorette (8.3 mg/10 cm^2 nicotine content) and Nicopatch (17.5 mg/10 cm^2) transdermal delivery system. Nicotine release followed the polymer matrix diffusion-controlled process. In term of release efficiency both transdermal delivery system were similar. They released around 50% of their nicotine content at 24 hours.

Bobiak, and Koenig (2005) improved analysis method for analyzing polymer-liquid interface used to compare the rates of diffusion of nicotine into poly(ethylene-co-vinyl acetate) film from aqueous solutions containing anionic and nonionic surfactants. The ability of different surfactants either to wet the hydrophobic polymer film or to form complexes with nicotine molecules either enhanced or inhibited the uptake of nicotine, respectively, relative to a solution without surfactant. Nonionic surfactant caused faster nicotine uptake than a nicotine-water mixture, whereas the same level of anionic surfactant reduced the uptake. These observation can be attributed to complex formation and different wetting abilities of each surfactant on the polymer interface.

Davaran, Rachidi, Khandaghi, and Hashemi (2005) prepared the patch containing a cross-linked polyvinyl alcohol used in the rate controlling membrane. The inclusion complex formed between the nicotine and β-cyclodextrine was used in drug depot. The carbopol polymer and propylene glycol on transdermal permeation of nicotine through the rat skin was investigated. The maximum flux of 42 $\mu g\ cm^{-2}h^{-1}$ after 48 hours when the propylene glycol concentration was 15% and the nicotine-β-cyclodextrine mole ratio 3:1. The initial amount of nicotine and propylene glycol can influence the flux value of nicotine and the concentration needed for suitable flux depends upon the type of polymer used as dug reservoir gel.