CHAPTER 1

INTRODUCTION

1.1 BIODEGRADABLE POLYMERS IN MEDICINE

1.1.1 Definitions [1-4]

In recent years, much attention has been focussed on biodegradable and biocompatible polymers, particularly from an ecological viewpoint. They are increasingly utilized for many applications in the areas of agriculture, forestry, wildlife conservation, waste management and, especially, for medical and surgical applications, such as surgical implant materials, drug delivery matrices, degradable sutures and therapeutic systems.

The term "**biodegradable**" refers to degradation induced by the vital activity of an organism, not simply the degradation of a material in a physiological environment. However, the term "**biodegradable polymer**" is now widely used to convey the meaning of a polymer that degrades in the human body.

The generally accepted definition of "**polymer biodegradation**" is: hydrolytic, enzymatic or bacteriological degradation processes occurring in a polymer which do not necessarily proceed to a stage where the physical form of the polymer is altered. Consequently, the design of biodegradable polymers with tailored properties has become one of the most challenging problems for polymer scientists. A basic prerequisite for medical applications is the absolute biocompatiblity of the polymers and their degradation products.

1.1.2 The Requirements of a Biodegradable Polymer [3-6]

The uses for synthetic polymers in medicine can be grouped roughly into four categories: (1) the use of polymers for the fabrication of implants and artificial organs, (2) the use of polymer membranes for haemodialysis or oxygenation, (3) the development of polymeric substitutes for plasma or blood, and (4) the use of implanted or soluble polymers as substrates for the slow release of drugs or birth control agents.

Polymeric systems constitute the most important group of biodegradable materials because of the non-toxicity of their degradation products for living organisms. Their degradation rate and therefore their physico-mechanical properties in a physiological medium are strongly dependent on factors related to their chemical structure, molecular weight, molecular weight distribution and crystallinity. Crystalline domains are more resistant than amorphous domains to biodegradation under physiological conditions, and the hydrophobic or hydrophilic character of the polymeric chains noticeably affects the biodegradation process.

The initial requirements in the selection or design of any biodegradable polymer are that it should have the following properties:

1). Correct Balance of Mechanical Properties

The mechanical properties of a polymer are largely controlled by its chemical structure, morphology and glass transition temperature (T_g). The material should be selected or designed such that T_g is outside the operating range of body temperatures in order that a discontinuity in properties does not occur in use. T_g not only effects the modulus but also diffusion coefficients and hydrolytic stability.

2). Property – Loss Profile Appropriate to Application

The degradable polymer will exhibit changes in its mechanical properties during its lifetime as it degrades and the property–loss profiles must be such that the material remains useful over the desired period. The onset of loss of mechanical properties may be synchronous with, occur prior to or later than the loss of molecular weight, depending on the mechanism of degradation.

3). Degradation Products should be Non-toxic and Biocompatible

The degradation products are necessarily released into the adjacent tissues and therefore must be non-toxic and biocompatible. They should preferably be water soluble, small molecules and, where possible, naturally occurring metabolites. In such cases, there is the chance that the degradation products will dissolve in the extracellular fluid as they are formed and be excreted via the kidneys and the lungs.

4). Minimal Tissue Reaction

The material must give minimal tissue reaction so as not to hinder the healing process or cause unnecessary additional pain to the patient.

5). Total Mass Loss within an Acceptable Period of Time

Total mass loss should occur within an acceptable period of time so as to avoid possible side effects such as stone formation.

1.2 MECHANISM OF BIODEGRADATION [2-3]

There are four major mechanisms that can be utilized in the design of biodegradable polymers:

1.2.1 Solubilization

Solubilization is strictly applicable to polymers that are water-soluble. The degradation process involves diffusion of water into the polymer matrix followed by continuous solvation and swelling until either fragmentation or dissolution occurs. Since large molecular weight are involved, the degree of agitation (fluid flow) at the interface is a prime factor in the dissolution process. Mechanical movements and flexing of the device within the tissue, if excessive, will lead to fragmentation as the material swells and softens.

1.2.2 Ionization followed by Solubilization

Utilization of the ionizing mechanism for bringing about solubility allows materials to be designed that are relatively hydrophobic prior to ionization. However, when these polymers are placed in an environment which causes them to become ionized, their surfaces absorb water, swell, and finally dissolve and surface erode.

1.2.3 Enzyme–Catalyzed Biodegradation

Enzyme catalyzed biodegradation is perhaps the classical mechanism by which implants are removed from the body. This mechanism has more effect in naturally occurring polymers than in synthetic polymers, for example in the case of absorbable suture materials.

1.2.4 Simple Hydrolysis

Simple hydrolysis is the depolymerisation process which can be seen as the reverse of polycondensation. Its occurrence is feasible in the aqueous extracellular fluid, although a number of conditions have to be met:

(a) The polymer has to contain hydrolytically unstable bonds, e.g., esters bonds.

(b) The polymer should be hydrophilic to at least a certain extent, otherwise the medium producing the hydrolysis will have very limited opportunity for gaining access to the hydrolysable bonds.

(c) The hydrolysis has to be able to take place at the physiological pH (around 7.40) and temperature (37°C).

1.3 THE NEED FOR BIODEGRADABLE MATERIALS IN MEDICINE [3]

Biodegradable polymers have three major applications in medicine:

1.3.1 The Temporary Scaffold

The temporary scaffold has received the most attention and includes the absorbable (or soluble) suture. In this application, the natural tissue bed experiences a temporary weakness due to surgical trauma, and requires artificial support. The healing wound has little strength during the first 6 days other than that of the coagulated protein-forming scab. The suture is used to hold both sides of the wound in close apposition until sufficient collagen synthesis has taken place to hold the wound together unassisted; movement of the healing surfaces results in thicker scarring. Seventy to eighty percent of total collagen synthesis usually occurs within the first 3 weeks, the final 20 to 30% requiring periods of 3 to 6 months. Although the suture is a clearly defined application, the availability of biodegradable polymers with the ideal combination of application, the properties would broaden the scope of opportunities. Blood vessel, ureter, bladder, bile duct, and heart valve design could have added dimension were it possible to use composite structure of biodegradable and non biodegradable polymers

1.3.2 The Temporary barrier

Although less widely applicable than the scaffold, is of similar importance in the fields of tendon, spinal, and open heart surgery. Surgical adhesions caused by blood, clotting and later fibrosis between the sliding surfaces of the tendon, or between the cardiac wall and the pericardial sac, cause pain, debilitation, and major problems during subsequent surgery. A temporary barrier which would stop adhesions forming and remain "in situ" until all the fibrin had been phagocytosed (at about 2 weeks), degraded, absorbed, and excreted, would be a further invaluable aid to the surgeon.

1.3.3 A Drug Delivery Matrix

A drug delivery matrix is no less a challenge to the innovative polymer chemist in that the optimal drug delivery profile is as variable as the drugs available for different treatments. The problem reduces theoretically to one of being able to load a biodegradable polymer matrix with as high a concentration of drug as possible, that is, 50 weight %, and to have the matrix degrade at a predictable rate so that the release of the drug into the tissues of the target organ is controlled. The matrix is simply a vehicle which should disappear as rapidly as possible after the pharmacologically active agent has been delivered. In practice however, 20 to 25 weight % is the upper limit for drug loading and the delivery mechanism is usually a combination of matrix degradation and diffusion. The role of diffusion becomes more important as the hydrophilicity of the drug molecule increases and its molecular weight decreases. Most biodegradable polymers by their very nature are hydrophilic and, once water has penetrated the matrix, the more hydrophilic the drug, the more easily is it removed. The role of the biodegradable polymer thus becomes one of water-proofing the drug, and one special configuration of the biodegradable matrix is microencapsulation.

1.4 BIODEGRADABLE POLYESTER [4,7]

In the biomedical field, polyesters and copolyesters of several α-, β-, and ω-hydroxyacids have been found as a versatile family of materials with interesting applications in surgery and pharmacology due to their biocompatibility and biodegradability into non-toxic by-products under the conditions of the living organism's physiological medium. The major method used to synthesize these polymers has been via the ring-opening polymerization (ROP) of cyclic esters.

Table 1.1 Some commercial biodegradable polyester medical products [8].

Application	Trade Name	Composition*	Manufacturer
Sutures	Dexon	PGA	Davis and Geck
	Maxon	PGA-TMC	Davis and Geck
	Vicryl	PGA-LPLA	Ethicon
	Monocryl	PGA-PCL	Ethicon
	PDS	PDO	Ethicon
	Polysorb	PGA-LPLA	U.S. Surgical
	Biosyn	PDO-PGA-TMC	U.S. Surgical
	PGA Suture	PGA	Lukens

Table 1.1 (Continued)

Interference screws	Sysorb	DLPLA	Synos
	Endofix	PGA-TMC or LPLA	Acufex
	Arthrex	LPLA	Arthrex
	Bioscrew	LPLA	Linvatec
	Phusiline	LPLA-DLPLA	Phusis
	Biologically Quiet	PGA-DLPLA	Instrument Maker
Suture anchor	Bio-Statak	LPLA	Zimmer
	Suretac	PGA-TMC	Acufex
Anastomosis clip	Lactasorb	LPLA	Davis and Geck
Anastomosis ring	Valtrac	PGA	Davis and Geck
Dental	Drilac	DLPLA	THM Biomedical
Angioplastic plug	Angioseal	PGA-DLPLA	AHP
Screw	SmartScrew	LPLA	Bionx
Pins and rods	Biofix	LPLA or PGA	Bionx
	Resor-Pin	LPLA-DLPLA	Gelstich
Tack	SmartTack	LPLA	Bionx
Plates,mesh, screws	LactoSorb	PGA-LPLA	Lorenz
	Antrisorb	DLPLA	Atrix
Guided tissue	Resolut	PGA-DLPLA	W.L. Gore

*** Key to material composition:**

DLPLA - poly(DL-lactide)

LPLA - poly(L-lactide)

PGA - polyglycolide

PDO - poly(dioxanone)

PGA-TMC - poly(glycolide-co-trimethylene carbonate)

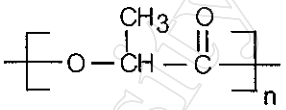
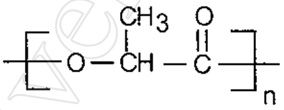
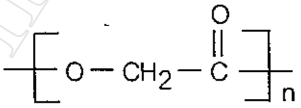
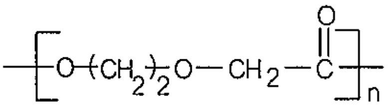
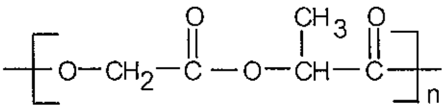
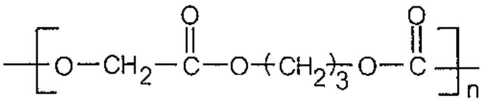
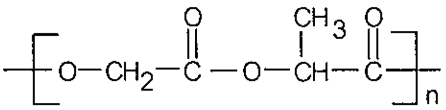
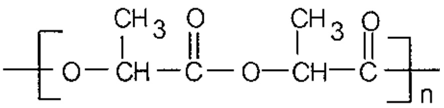
PGA-LPLA - poly(glycolide-co-L-lactide)

PGA-DLPLA - poly(glycolide-co-L-lactide)

LPLA-DLPLA - poly(L-lactide-co-DL-lactide)

PDO-PGA-TMC - poly(dioxanone-co-glycolide-co-trimethylene carbonate)

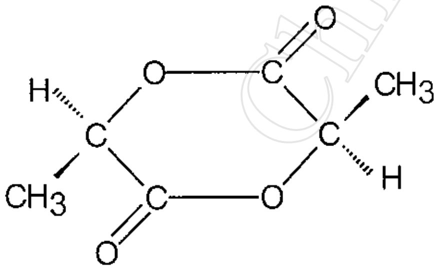
Table 1.2 Abbreviations, names and chemical structures of some synthetic biodegradable polyesters [8].

ABBREVIATION	POLYMER NAME	CHEMICAL STRUCTURE
PDLLA	Poly(DL-lactide)	 $\left[-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PLLA	Poly(L-lactide)	 $\left[-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PGA	Polyglycolide	 $\left[-O-CH_2-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PDO	Polydioxanone	 $\left[-O-(CH_2)_2-O-CH_2-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PGA-PLLA	Poly(glycolide-co-L-lactide)	 $\left[-O-CH_2-\overset{O}{\overset{\Vert}{C}}-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PGA-TMC	Poly(glycolide-co-trimethylene carbonate)	 $\left[-O-CH_2-\overset{O}{\overset{\Vert}{C}}-O-(CH_2)_3-O-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PGA-PDLLA	Poly(glycolide-co-DL-lactide)	 $\left[-O-CH_2-\overset{O}{\overset{\Vert}{C}}-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}- \right]_n$
PLLA-PDLLA	Poly(L-lactide-co-DL-lactide)	 $\left[-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}-O-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\Vert}{C}}- \right]_n$

Aliphatic poly-∝-esters, typified by polyglycolide and polylactide, constitute a class of polymers represented by the general formula $-[\mathrm{O-CHR-CO}]-_n$ where R = H or alkyl. Both polyglycolide and polylactide undergo hydrolysis through a simple non-enzymatic mechanism in which the catalytically active species which promotes the hydrolysis is known to be hydroxyl ions [9]. The simple hydrolysis mechanism occurs by random hydrolytic scission of the main chain ester bonds. The rate of hydrolysis is modulated both by crystallinity and by the hydrophobicity of the monomer components of the polymer chains.

1.5 AIM OF THIS STUDY

The main aim of this research project is to study the reaction profile of the ring-opening bulk polymerization in bulk L-lactide using either stannous octoate or stannous oxalate as catalyst and diethylene glycol as initiator. The polymerization mechanism is generally believed to be of the coordination-insertion type. The relative efficiencies of the 2 stannous catalysts are to be compared under identical conditions.



$\mathrm{HO-CH_2-CH_2-O-CH_2-CH_2-OH}$

L-lactide

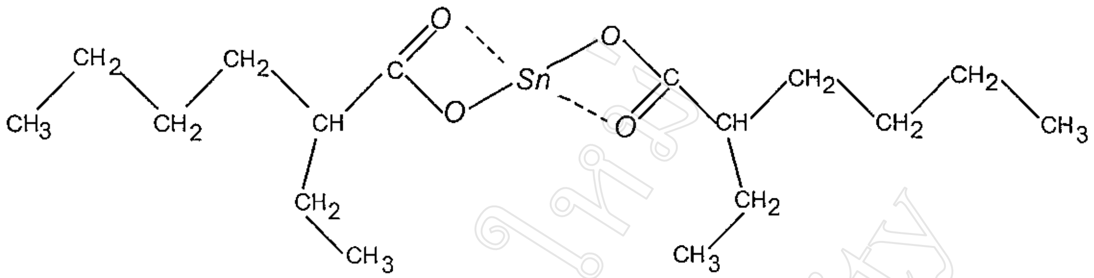
3,6-dimethyl-1,4-dioxane-2,5-dione

(monomer)

diethylene glycol

bis (2-hydroxyethyl) ether

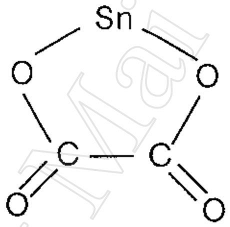
(initiator)



stannous octoate

tin(II) bis-2-ethyl hexanoate

(catalyst 1)



stannous oxalate

tin(II) oxalate

(catalyst 2)

The reaction profile is to be characterised in terms of the increases in ***%conversion*** and ***polymer molecular weight*** with time. The %conversion is to be estimated by various methods (gravimetry, FT-IR, ^{1}H-NMR) and the methods compared. The polymer molecular weight is to be determined by dilute-solution viscometry.

From the results obtained, it is hoped to gain an understanding of how the reaction proceeds, particularly with respect to the build-up of molecular. Apart from its catalytic role in polymerization, stannous octoate has also been reported in the literature as being a transesterification catalyst. Since transesterification is a degradation reaction which would decrease the polymer molecular weight, it will be interesting to see if and to what extent these 2 contrasting roles complete against each other under the reaction conditions which are to be studied here.