CHAPTER 2

BLOCK COPOLYMERS AND THEIR POTENTIAL USE AS BIOMATERIALS

2.1 Introduction to Block Copolymers

A "block copolymer" is defined as a polymer comprising molecules in which there is a linear arrangement of blocks, a block being defined as a portion of a polymer molecule in which the monomeric units have at least one constitutional or configurational feature absent from the adjacent portions. In a block copolymer, the distinguishing feature is constitutional, i.e., each of the blocks comprise units derived from a characteristic species of monomer. A common shorthand notation system for representing block polymers is shown in Table 2.1, where a letter represents a block of the corresponding monomer units.

Table 2.1 : Block copolymer notations used in polymer science.

Copolymer Structure	Notation	Type of Block Copolymer
AAAAAAAAAABBBBBBBBBB	A-B	Diblock
AAAAABBBBBAAAAA	A-B-A	Triblock
AAAAAABBBBBBCCCCCC	A-B-C	Triblock
AAAAAABBBBBB(AAAABBBB)$_n$AAAABBBB	(A-B)$_n$	Multiblock
(AAAAAAAAABBBBBBBBB)$_n$-X	(A-B)$_n$-X	Star

It is important to note that the present IUPAC nomenclature recommendations for block copolymers do not specifically designate the length of a block, i.e. the minimum number of repeating units required. However, it is stated in these recommendations that, although short sequence-lengths are not strictly embraced within the definitions of "block", the same device may be usefully employed by using the general prefix "oligo" or the appropriate specific prefix (e.g. tri) [10].

2.2 Synthesis of Block Copolymers [10, 11, 12, 13]

A variety of approaches are applicable, in principle, for the synthesis of block copolymers using the methodologies of both chain-growth (addition) and step-growth (condensation) polymerisation.

However, only a few approaches lead to the formation of block copolymers with controlled and well-defined structures. "Living" chain-growth polymerisations provide the most general of these methods. Since "living" polymerisations proceed without the incursion of chain-termination or chain-transfer reactions, block copolymers can be prepared by simply adding different monomers sequentially, as shown in Scheme 2.1 where (*) represents an active center for chain growth, I is the initiating species, A and B are compositionally different monomers, and T is the terminating agent. "Living" polymerisation systems which can be used for the synthesis of block copolymers include anionic, cationic, group-transfer and Ziegler-Natta initiators and catalysts.

Initiation

$$I \longrightarrow I^{*}$$

$$I^{*} + A \longrightarrow I\text{-}A^{*}$$

Propagation, A

$$I\text{-}A^{*} + nA \longrightarrow I\text{-}(A)_{n}\text{-}A^{*}$$

Propagation, B

$$I\text{-}(A)_{n}\text{-}A^{*} + mB \longrightarrow I\text{-}(A)_{n+1}\text{---}(B)_{m-1}\text{---}B^{*}$$

Deliberate Termination

$$I\text{-}(A)_{n+1}\text{---}(B)_{m-1}\text{---}B^{*} + T \longrightarrow I\text{-}(A)_{n+1}\text{---}(B)_{m}\text{---}T$$

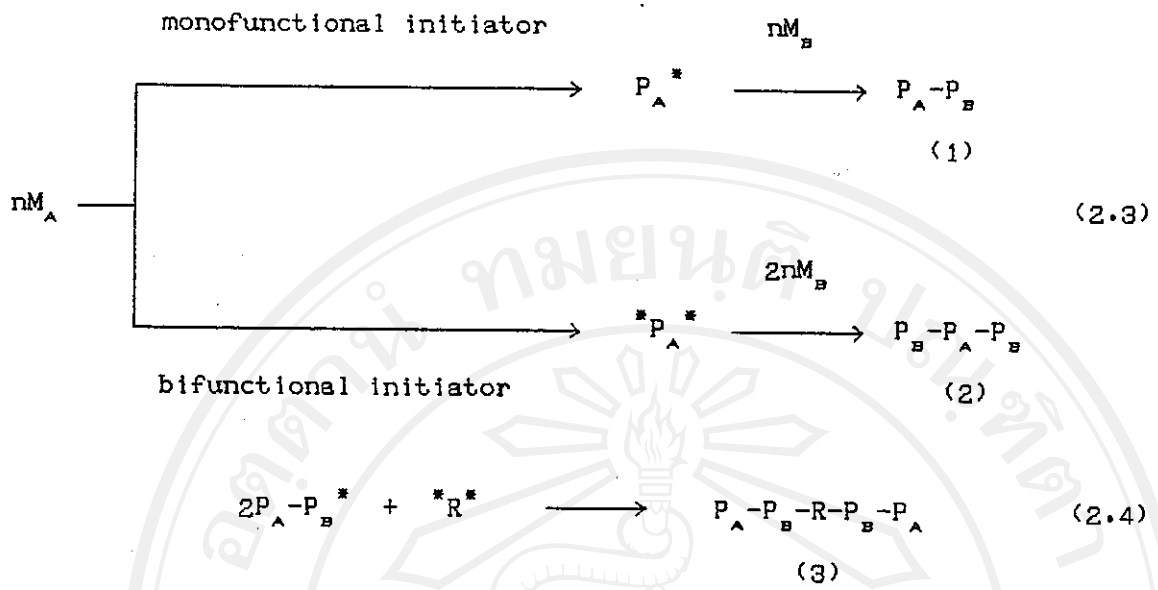
Scheme 2.1 : Synthesis of block copolymers by adding different monomers in a "Living" polymerisation system.

Another chain-growth method for block copolymer synthesis involves the generation of active sites for chain growth at the chain ends of a polymer, as shown in equations 2.1 and 2.2, where Z is a functional end-group which can generate an active chain-end site (*). The polymerisation of monomer B could proceed by anionic, cationic, radical, or Ziegler-Natta-type active centers.

$$/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash-Z \longrightarrow /\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash^* \qquad (2.1)$$

$$/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash^* + nB \longrightarrow /\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash/\backslash-(B)^*_n \qquad (2.2)$$

This class of reaction is represented most prominently by the "living" anionic polymerisations in which a first monomer M_A is converted to its corresponding polymer P_A having propagatively reactive groups at one or both ends of its chain according to whether a mono- or a bi-functional initiator is employed. The "living" polymer then serves as the initiator for the polymerisation of a second monomer M_B, yielding a diblock copolymer (1) or a triblock copolymer (2) depending on the functionality of P_A (equation 2.1). This concept is open to considerable elaboration. Thus, the diblock polymer (1), while still reactive, may be coupled with a suitable bifunctional reagent to form a triblock copolymer (3) having P_A units at the outsides of the molecule rather than in the centre as in (2) (equation 2.2). The reactive forms of (1) and (2) may also be used to initiate the polymerisation of a further monomer M_C to give products P_A-P_B-P_C (4) and P_C-P_B-P_A-P_B-P_C (5) with three species of blocks per molecule.



$$2P_A\text{-}P_B^{*} \; + \; {}^{*}R^{*} \longrightarrow P_A\text{-}P_B\text{-}R\text{-}P_B\text{-}P_A \qquad (2.4)$$

(3)

Success in such a continued sequential reaction depends critically upon the real natures of the substances involved, on the reactivity of the end-groups existing at each stage or formed by intermediate refunctionalization, on the efficiency of the reactions employed, and upon the avoidance of interfering side reactions whether extrinsic (e.g. due to terminating impurities) or intrinsic (e.g. due to the occurrence of transfer reactions). In favourable cases, the consecutive stages can be achieved with high precision leading to polymers of accurately known structures composed of blocks of predetermined sizes and with narrow MW distributions ($\overline{M}_w/\overline{M}_n$ close to unity).

2.3 Block Copolymers as Biodegradable Materials

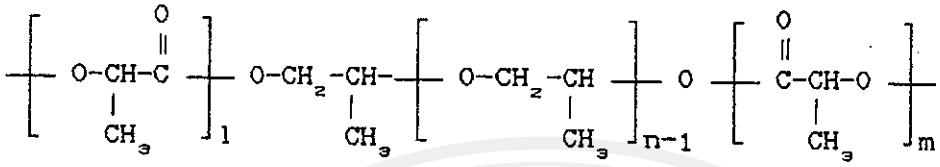
2.3.1 Previous Work and its Relevance to This Study

With regard to the aims of this study, it is clear that there are various approaches to the design of biodegradable polymers for use

in medical applications. However, where the application is as an absorbable surgical suture, then the range of polymer options is mainly restricted to aliphatic polyesters and copoly(ester-ether)s. This is because these polymers have been shown to possess the best balance of properties required in suture applications. The type of polymer structure of particular interest in this research project is that of a block copoly(ester-ether).

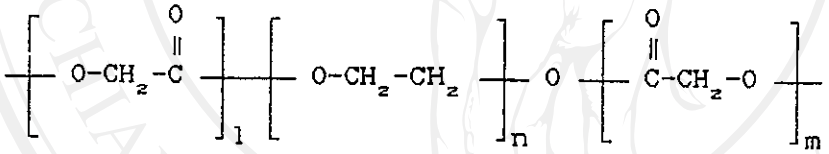
Block copolymers have yet to achieve commercial importance as absorbable suture materials. However, interest in them remains because of the attractiveness of the idea of introducing a "soft" segment block into the middle of an otherwise "hard" crystallizable polymer chain. The intended product is an ABA-type triblock copolymer comprised of interconnecting "hard-soft-hard" chain segments. This type of variation in segmental morphology is seen as a way of extending the range of applications of biodegradable polymers by tailoring polymer properties to suit specific needs.

The most recent example of this type of material found in the literature is that of a series of block copoly(ester-ether)s comprising poly(L-lactide) and polyoxypropylene segments [14]. The authors claimed that the copolymers obtained (I) were of sufficiently high molecular weight to be melt-spinnable and drawable by conventional methods. The properties of the fibres were studied, including their biodegradabilities 'in vitro' and 'in vivo'.



(I) ABA poly(L-lactic acid-b-oxypropylene)

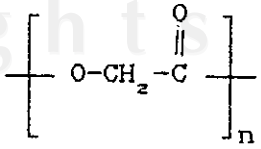
A logical starting point for this type of copolymer would seem to be the simplest in chemical structure, i.e. that comprising poly (glycolic acid) segments attached to low molecular weight polyoxyethylene. The latter, more commonly referred to as poly (ethylene glycol), is the "comonomer" with glycolide and forms the "soft" middle segments, as represented in (II) [15].



(II) ABA poly(glycolic acid-b-oxyethylene)

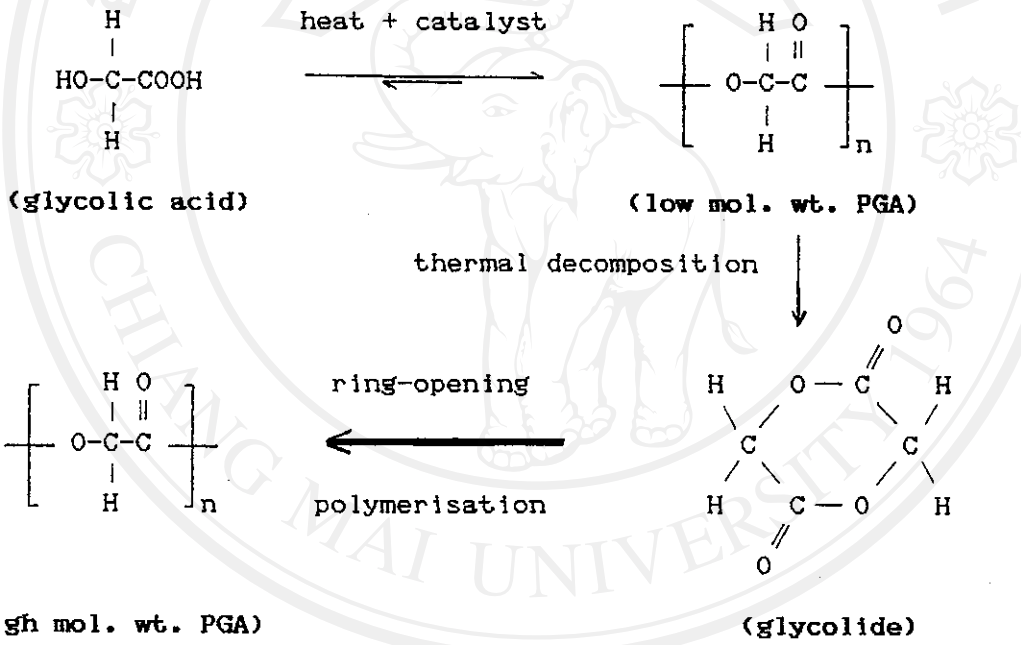
2.3.2 Poly(glycolic acid)

The most widely studied biodegradable polymer has been poly (glycolic acid) (PGA). The molecular formula of PGA is as shown below:



poly(glycolic acid)

PGA is the simplest member of the poly(∝-ester) series. In its synthesis, glycolic acid (hydroxyacetic acid) is converted to PGA by initially reacting glycolic acid with itself to form the cyclic diester glycolide which, in the presence of heat and a catalyst, is converted to a high molecular weight, linear-chain polymer from which filaments can be extruded. The commercial PGA multifilament suture is manufactured by orienting these filaments by means of stretching and braiding (trade name : 'Dexon') [16].



Scheme 2.2 : Interconversions involved in the synthesis of poly(glycolic acid) (PGA).

The biodegradation of PGA occurs essentially by simple hydrolysis of the ester bonds. Simple hydrolysis is the depolymerisation process which can be seen as the reverse of polycondensation. It is

feasible in the aqueous extracellular fluid, although a number of conditions have to be met, such as:

(a) The polymer has to contain hydrolytically unstable bonds.

(b) For any significant degradation to occur, the polymer should be hydrophilic, otherwise the medium producing the hydrolysis will have very limited opportunity for gaining access to the hydrolysable bonds.

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

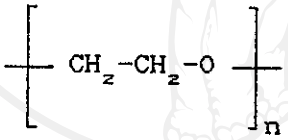
Heterochain polymers, particularly those containing oxygen and/or nitrogen atoms in the main chain, are generally susceptible to hydrolysis. Depending on the structure, this hydrolysis may be favoured by either acid or alkaline conditions and, naturally, is much faster at elevated temperature. It is in this context that enzymes, and especially hydrolytic enzymes, are most likely to have an effect. Other polymers, apart from polyesters, which have been shown to degrade by hydrolysis 'in vivo' are polyamides (nylons and poly(amino acid)s), some polyurethanes, and cyanoacrylates [17].

'In vitro' tests on PGA sutures ('Dexon') show that degradation occurs in two stages. The first stage consists of diffusion of water into the amorphous regions of the polymer leading to random hydrolytic chain scission of the ester groups. The second stage starts when most of the amorphous regions have been degraded, hydrolytic attack then focussing on the crystalline domains. An apparent increase in

crystallinity with (degradation) time is explained by the chain fragments of the hydrolysed amorphous regions having a lesser degree of entanglement and by their ability to re-align themselves into a more ordered crystalline state [1]. PGA sutures are synthetic, non-collageneous, absorbable sutures with surgical handling properties similar to those of silk. The material has been shown to be completely non-toxic upon implantation into animals [19] and to function satisfactorily when used in a wide variety of surgical operations.

2.3.3 Poly(ethylene glycol) [1, 2]

The molecular formula of poly(ethylene glycol) (PEG) is as shown below:



PEG is commercially available with molecular weights ranging from 200 to 10,000 and, under the name of poly(ehtylene oxide), from 300,000 to 4,000,000. This type of polymer has been used in biomedical applications as the base for tablets, suppositories, and creams. By adjusting the blend of high and low molecular weight components, it is possible to vary both the softening point and rate of solubility.

The biodegradation of poly(ethylene glycol) occurs by 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 weights 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 bed, if excessive, will lead to fragmentation as the material swells and softens.