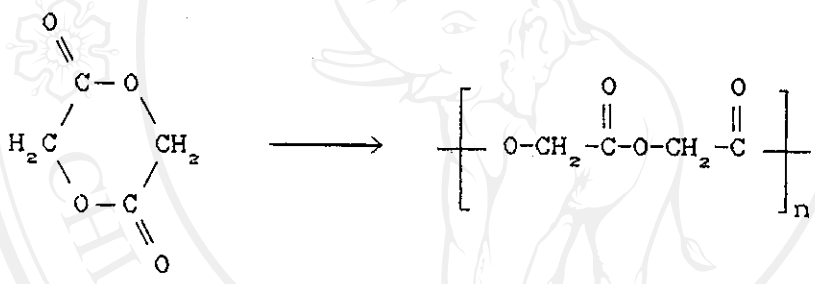
CHAPTER 4

DISCUSSION AND CONCLUSIONS

Poly(glycolic acid) (PGA), (III), is the simplest aliphatic polyester in structure whose repeat unit still forms the basic building block for all synthetic absorbable sutures currently in commercial use.

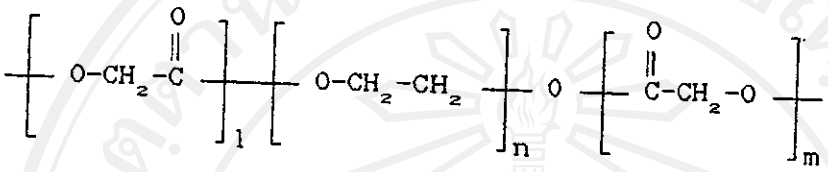


glycolide **PGA**

(III)

However, when melt spun in the form of monofilament sutures, PGA is too rigid, except in the very smallest sizes used in microsurgery. Consequently, PGA sutures for use in general surgery are produced in the form of braided multifilaments for increased flexibility ('Dexon'). It is the need for more flexible absorbable monofilaments which has provided the initial motivation for this project. One possible approach to solving this problem of suture stiffness is to introduce "soft" segments into the middle of an otherwise "hard" polymer chain. The intended product is an ABA-type triblock or possibly an AB-type

diblock copolymer comprised of interconnecting "hard" and "soft" chain segments. The structure of the series of block copoly(ester-ether)s studied in this project, comprising "hard" poly(glycolic acid) blocks attached to "soft" low molecular weight poly(ethylene glycol) segments, can be represented as:



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

In this project, PEG was selected as the "soft" block component for the following reasons [14]:

(1) PEG is biocompatible and non-toxic in tissue. At present, PEG is already utilized as a surface-lubricant for various absorbable braided surgical sutures in order to reduce tissue drag.

(2) PEG is widely used as a "flexibilizer" in the synthesis of block copolymers because of its high elastomeric properties. In addition, it has a considerable affinity for water so that its copolymers may exhibit enhanced hydrophilicity; at least, its introduction would not make the copolymer hydrophobic.

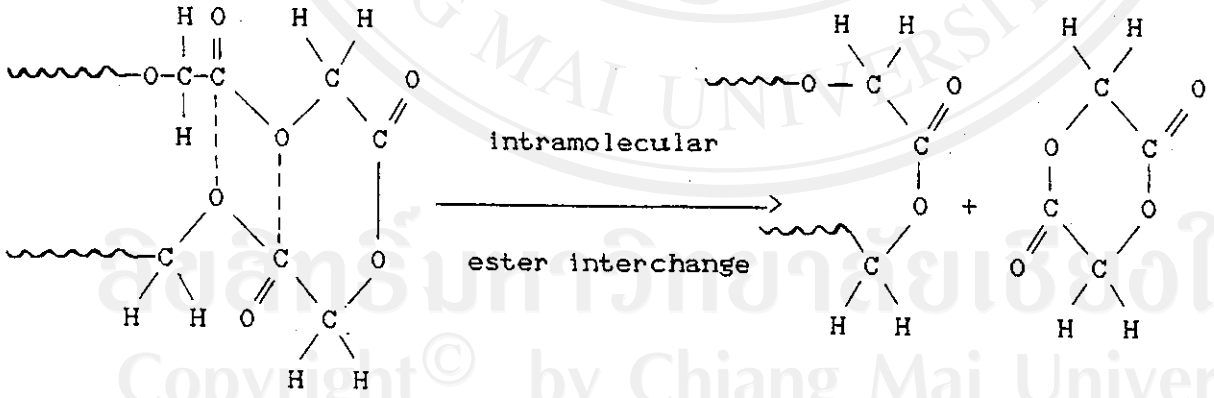
(3) The primary hydroxy groups on the PEG terminals are considered to have a reactivity similar to that of the hydroxy end-groups of PGA and are able to react with glycolide by a "scrambling" reaction to

allow the intended block copolymerisation.

4.1 Mechanism of the Polymerisation of Glycolide and Copolymerisation of Glycolide with PEG

4.1.1 Mechanism of Polymerisation of Glycolide

The first step in the synthesis of PGA was to make the intermediate glycolide monomer from glycolic acid. It is generally understood that the glycolide is not formed directly from the bimolecular cyclization of glycolic acid; instead, it is formed indirectly from the thermal decomposition of low molecular weight PGA aligomers. This thermal decomposition occurs via an intramolecular ester interchange mechanism, as also proposed for other members of the poly(∝-ester) series [34,35,36].



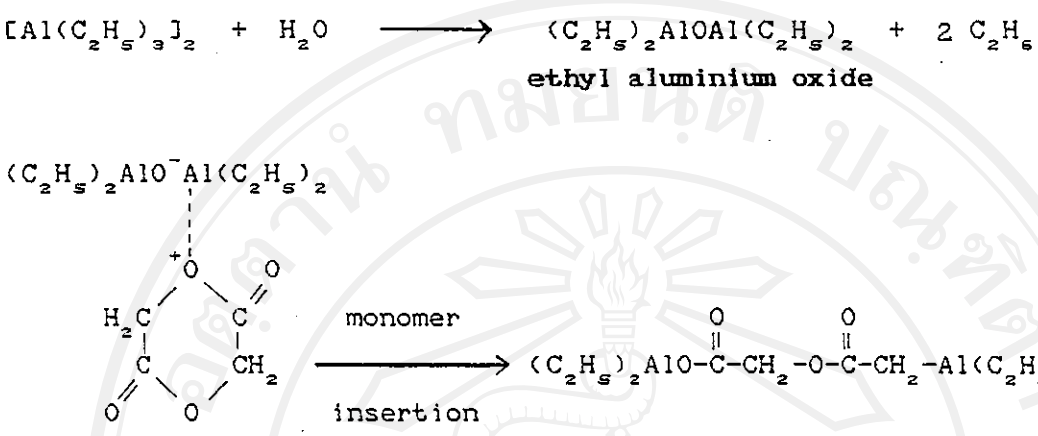
poly(glycolic acid) **glycolide**

The second step of the synthesis was then to try to obtain high molecular weight PGA from the ring-opening polymerisation of

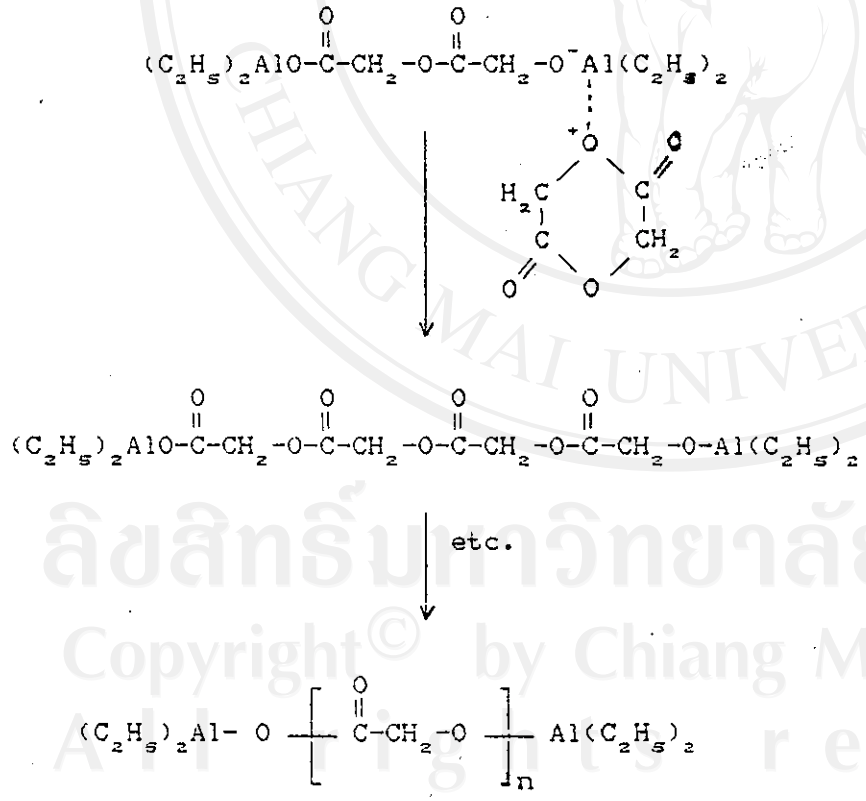
glycolide. This involved the use of aluminium triethyl and stannous oxalate as catalysts. Aluminium triethyl is a catalyst which usually combines with trace amounts of water present in the system (as cocatalyst) to form an ethyl aluminium oxide as the active initiating species. In the case of glycolide, the mechanism is believed to be cationic in nature, as described in Scheme 4.1. In contrast, stannous oxalate is generally considered to be anionic in its initiating action, as shown in Scheme 4.2.

(a) Using Aluminium Triethyl as Initiator

(i) Initiation



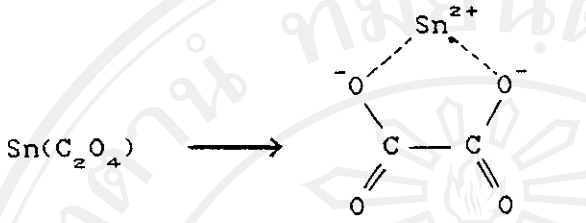
(ii) Propagation

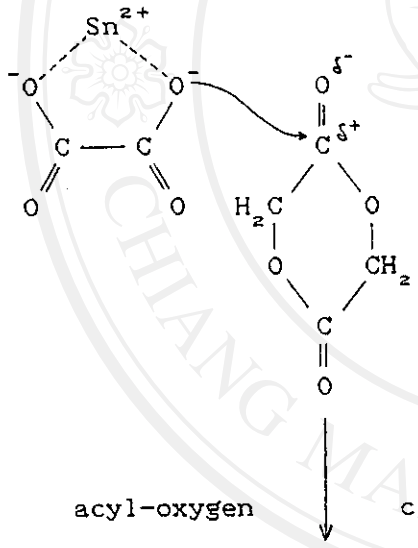


Scheme 4.1 : Postulated mechanism for the aluminium triethyl initiated ring-opening polymerisation of glycolide.

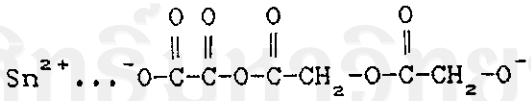
(b) Using Stannous Oxalate as Initiator

(i) Initiation





acyl-oxygen cleavage



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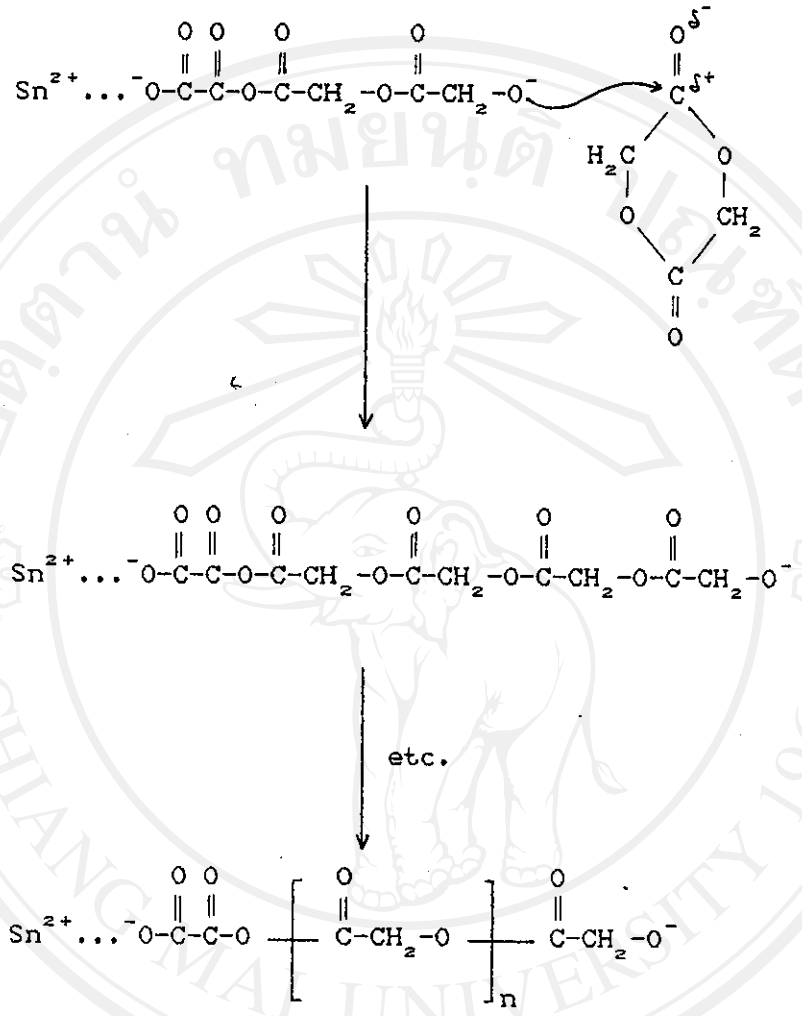
(ii) Propagation



(iii) Termination

Scheme 4.2 : Postulated mechanism for the stannous oxalate initated ring-opening polymerisation of glycolide.

4.1.2 Mechanism of Copolymerisation of Glycolide with PEG

The copolymerisation was carried out by adding PEG to the bulk polymerisation system of glycolide pre-mixed with either the aluminium triethyl or stannous oxalate initiator. Conceivable reaction mechanisms for the respective block copolymerisations are shown in Schemes 4.3 and 4.4.

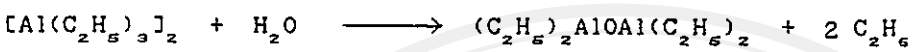
(a) Using Aluminium Triethyl as Initiator

On the basis of the previous mechanism for glycolide homopolymerisation described in Scheme 4.1, the use of aluminium triethyl as initiator would appear to favour the formation of an ABA-type triblock copolymer with the "soft" PEG block as the middle component. Because of their primary OH end-groups, the PEG molecules can be expected to react with the dimeric $[Al(C_2H_5)_3]_2$ in much the same way as H_2O molecules present in the system. Glycolide insertion then follows on either side of the PEG block to produce the intended triblock structure, as proposed in Scheme 4.3. However, it must also be expected that some accompanying glycolide homopolymerisation will occur, as in Scheme 4.1. If so, the final product would, in actual fact, be a compatible blend of triblock copolymer and PGA.

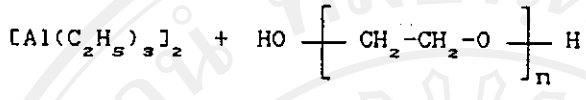
Some support for these proposals is provided by an earlier literature report [14] in which L(-)-lactide was copolymerised with poly(propylene glycol) using trimethylaluminium-water as initiator. The authors claimed that the major product, as determined by a combination of spectroscopy, thermal analysis and gel permeation

chromatography, was the ABA triblock copolymer similar to that proposed here. However, the mechanism of its formation was explained in much less detail than attempted here in Scheme 4.3.

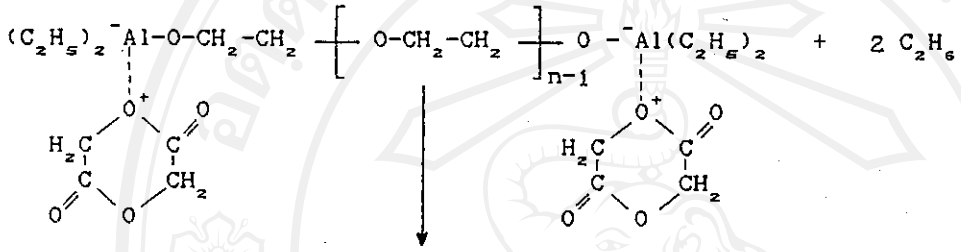
(i) Initiation

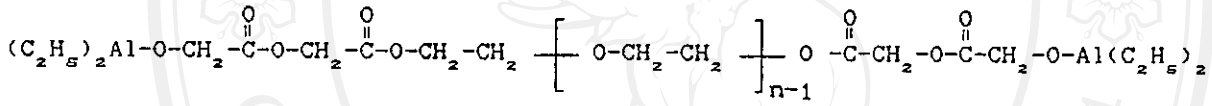


Similarly, by reaction with the primary OH end-groups in PEG

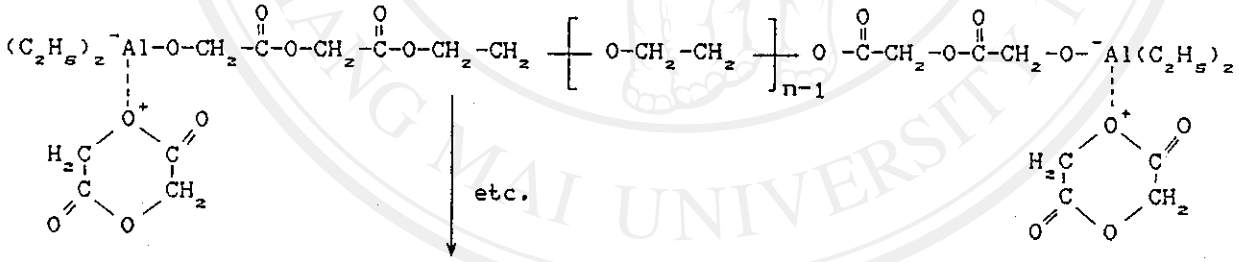


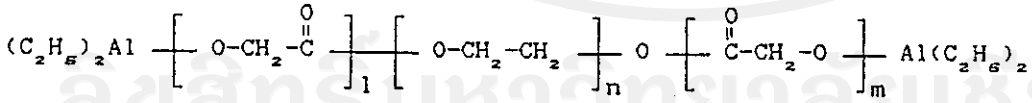
PEG





(ii) Propagation



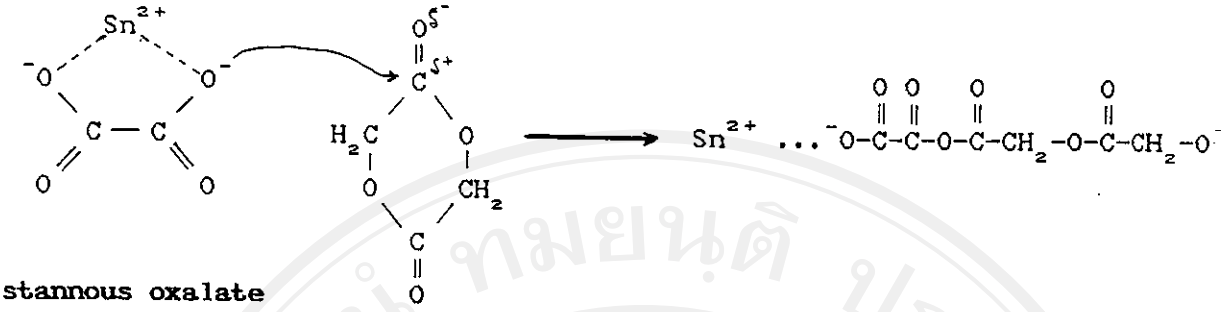


Scheme 4.3 : Proposed mechanism of triblock copolymerisation of glycolide and PEG to give ABA poly(glycolic acid-b-oxyethylene) using aluminium triethyl as initiator.

(b) Using Stannous Oxalate as Initiator

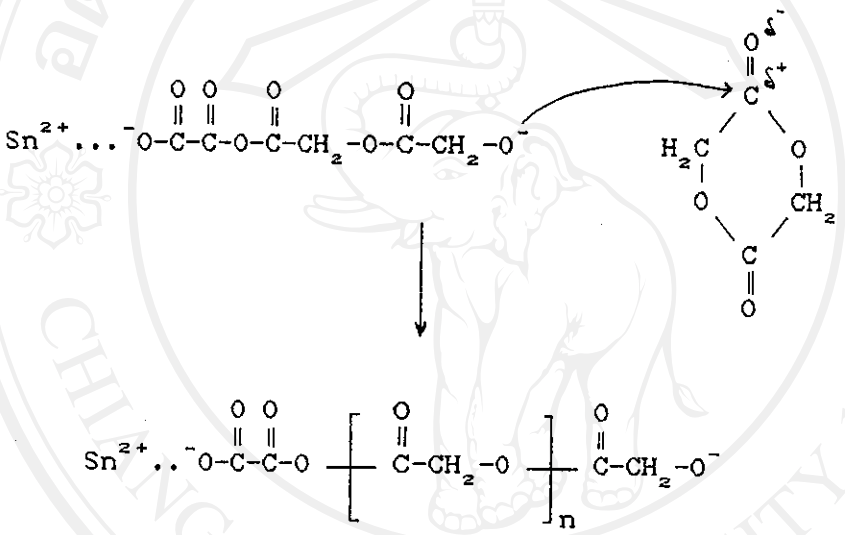
The mechanism of the stannous oxalate-initiated block copolymerisation of glycolide and PEG is less obvious than that for aluminium triethyl. Firstly, stannous oxalate is a more conventional type ionic initiator than aluminium triethyl with the initiating species likely to be the oxalate anion. Propagation then proceeds in the normal way by monomer addition at the growing chain end, as shown in Scheme 4.4. Since the mechanism of initiation is not an "insertion-type" mechanism, as in the case of aluminium triethyl, the most likely way in which the PEG can be incorporated into the copolymer structure would appear to be by chain transfer with the growing PGA chain-end followed by re-initiation of a new chain by the PEG anion. Logically, this should eventually lead to an ABA-triblock copolymer with the PEG as the "soft" middle segment. However, it seems probable that the final product will also contain some AB-diblock and possibly even some $(AB)_n$-multiblock copolymer as well as, inevitably, some homopolymeric PGA terminated by reaction with H_2O in the system. A possible mechanism is proposed in Scheme 4.4.

(i) **Initiation**

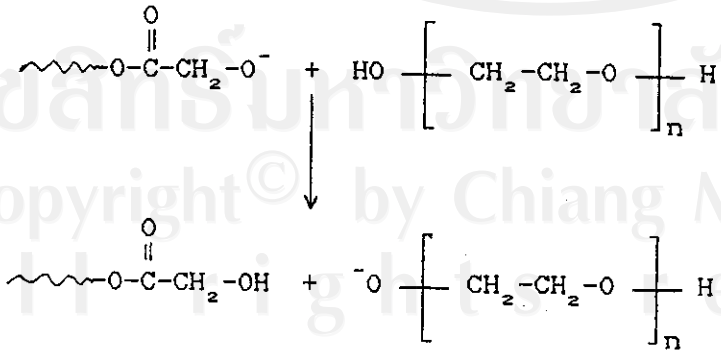


stannous oxalate

(ii) **Propagation**



(iii) **Termination (by chain transfer to PEG)**



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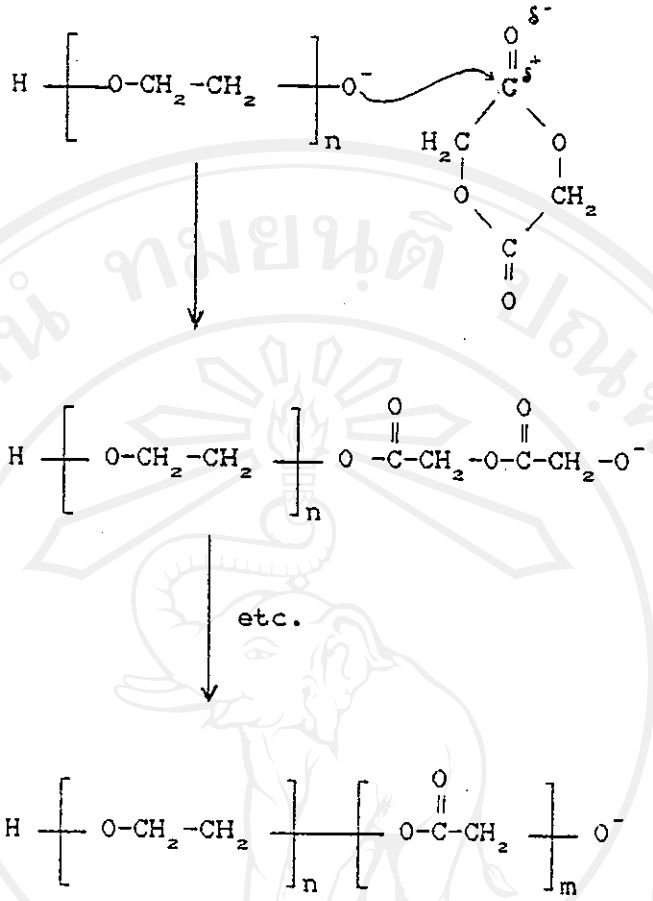
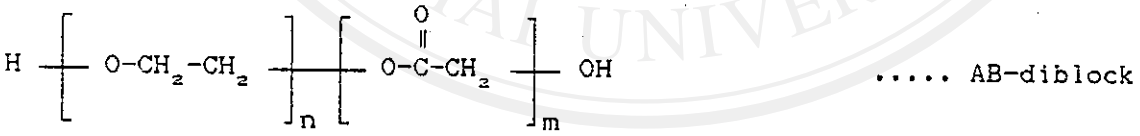
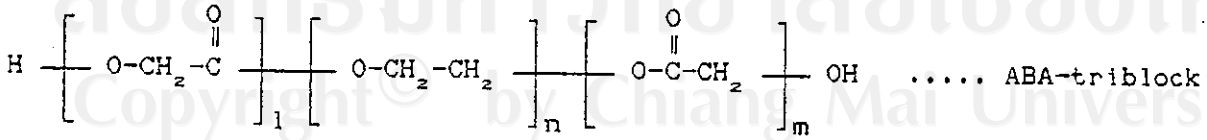
(iv) Re-initiation by PEG anion



(v) Repeat (iii) and (iv)

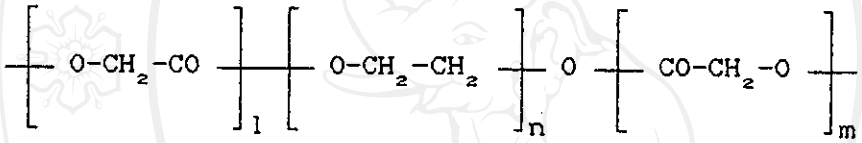




Scheme 4.4 : Proposed mechanism of block copolymerisation of glycolide and PEG to give a probable mixture of products using stannous oxalate as initiator.

4.2 Copolymer Characterisation - Analysis and Conclusions

As stated at the outset of this thesis (see page 7-8), the main object of this research project has been to design and synthesize a block copolymer consisting of interconnecting "hard" (i.e., rigid) and "soft" (i.e., flexible) segments. The particular copolymer chosen for study has been poly(glycolic acid-b-oxyethylene), as represented by the structural formula:



glycolic acid **oxyethylene** **glycolic acid**

"hard" **"soft"** **"hard"**

From the combination of analytical techniques used here, the results obtained allow the following conclusions to be drawn regarding the microstructure of the copolymers prepared.

4.2.1 Copolymer Composition

The most direct and therefore the most convincing evidence is provided by the high-resolution ^{1}H-NMR spectra in section 3.4 Quantitative analysis of the spectra (see Table 3.17 on page 67) of P(GA-b-PEG 200) showed that the final copolymer compositions after purification (by alcohol extraction) corresponded very closely with

the initial comonomer feeds. This overrides earlier suggestions from weight loss measurments on solvent extraction of reduced PEG 200 contents in the copolymers. Instead, it must be concluded from the NMR data that, under the conditions of synthesis employed in this project, the PEG 200 has been successfully polymerised in proportionate amounts with the more reactive glycolide. However, what the NMR spectra cannot show is the amount of PGA hompolymer which the final product may contain. If, as seems likely, some homopolymerisation of glycolide did occur, then the PGA fraction will almost certainly form a compatible blend with the copolymer. A technique which might be able to separate these different constituents would be high-temperature gel permeation chromatography (GPC) which, unfortunately, was not available in this project.

4.2.2 Copolymer Microstructure

From the previous section 4.1 on copolymer synthesis, if the mechanisms proposed in Schemes 4.3-4.4 are correct, then the most logical end-products would appear to be ABA-type triblock copolymers with PEG as the "soft" centre blocks. In fact, the experiments were designed with this result in mind. However, although this may be the case, the results presented here cannot confirm this or, indeed, any of the other microstructural features which are known to affect the properties of segmented copolymers [37]. These features include:

(1) the number of blocks per chain, i.e.

2 for AB-type diblock copolymers

3 for ABA-type triblock copolymers

2n for $(AB)_n$—type multiblock copolymers

(2) the sequence of the blocks, i.e. ABA or BAB in the case of a triblock copolymer

(3) the average lengths of the blocks

(4) polydispersity, i.e. chemical inhomogeneity, in any or all of the above

Clearly, a complete description of copolymer microstructure is a major study in itself, requiring a powerful combination of advanced analytical techniques. This is beyond the scope of this project but is obviously an area of fundamental importance which a future project will need to consider.

4.2.3 Copolymer Molecular Weight

In this project, dilute-solution viscometry was used to provide some indication of the level of molecular weight of the PGA and P(GA-b-PEG) copolymers. Because this method is not an absolute method, values of the polymer-solvent interaction constants, k and a, in the Mark-Houwink-Sakurada Equation, $[\eta] = k\bar{M}_v^a$, need to be known if the "viscosity-average molecular weight", $\bar{M}_v$, is to be calculated from the measured intrinsic viscosity $[\eta]$. Since these constants are not available for any of the materials synthesized here, only their $[\eta]$ values can be determined. However, some indication of their molecular weights levels can be gauged from the fact that commercial PGA sutures

('Dexon'), which are generally described as having "number-average molecular weights ", $\bar{M}_n$, in the region of $\bar{M}_n \simeq 20{,}000\text{-}50{,}000$, has been characterised in an earlier project [26] as having an intrinsic viscosity of:

$$[\eta] = 0.80\ dl.g^{-1},\ \text{at}\ c = 0.239\ g.dl^{-1}\ \text{in DMSO at}\ 120\ ^{\circ}C$$

This value was obtained in a similar way (Solomon-Ciuta One-Point Method) to those reported in this thesis. Thus, the values of:

$$[\eta] < 0.1\ dl.g^{-1},\ \text{at}\ c = 0.500\ g.dl^{-1}\ \text{in DMSO at}\ 90\ ^{\circ}C$$

generally found for the PGA and P(GA-b-PEG) products obtained in this work must be taken as being indicative of low molecular weights, probably $\bar{M}_n < 5000$, $n < 100$.

There are various possible reasons for these low molecular weights such as an excessively high initiator concentration, chain transfer reactions, premature solidification, and thermal degradation. Of these possiblities, chain transfer reactions were minimized as far as possible by the strict exclusion of moisture, while prolonged melt polymerisation without thermal degradation was achieved by the appropriate choice and careful control of temperature. This leaves the initiator concentration which, at the level of 1% by mole based on monomer(s), may possibly have been excessive; perhaps 0.1% might have been sufficient. A future research project might focus its attention on determining the optimum initiator concentration in order to combine high molecular weights with acceptably high reaction rates.

4.2.4 Copolymer Morphology

In this work, information relating to the morphology of the materials studied has been provided by studying their melting behaviour via differential scanning calorimetry (DSC). The main conclusions arising from the DSC results are:

(1) The PGA homopolymers synthesized here had % crystallinities in the range 46-48 %. This agrees with a value of 48 % obtained in a earlier project for a commercial 'DEXON' sample under the same conditions [26].

(2) Although their actual % crystallinities cannot be calculated, their heats of fusion suggest that as the PEG content in the P(GA-b-PEG) copolymer increases, its % crystallinity decreases. This can be interpreted to mean that as the concentration of PEG segments in the copolymer matrix increases, the degree of structural irregularity increases, and so the close packing together of the PGA segments is partially disrupted. Hence, the % crystallinity decreases.

(3) As the PEG content in the copolymers increases, the melting range is both lowered and broadened, as evidenced by the position and shape of the DSC melting peak. This indicates that the PGA crystalline regions are smaller, less cohesive, and have a wider size distribution. The question arises: do the PEG segments segregate as microdomains or remain separate within the PGA matrix ? Segmental segregation depends upon the length of the

"soft" segments and their concentration. Longer segments generally lead to more segregation than shorter ones. Since the "soft" PEG 200 and 1500 segments here are only short and present in relatively small amounts (< 10 % by mole), it does not seem very likely that they will segregate into discrete microdomains. Instead, they are probably "frozen in" at random throughout the mainly PGA semi-crystalline matrix. While it would be expected that most of the PEG blocks would be contained in the amorphous regions, it is conceivable that some of them may be entrapped in regions of crystallinity. This would account for the observed changes in the melting endotherms. The increased molecular motion in the amorphous regions together with the increased disorder in the crystalline regions would explain how the flexible PEG blocks lower and broaden the melting range. A simplistic attempt to represent these effects is made in Figs. 4.1 and 4.2 in which the fringed-micelle models of the semicrystalline PGA and P(GA-b-PEG) matrix morphologies are visualized and compared.

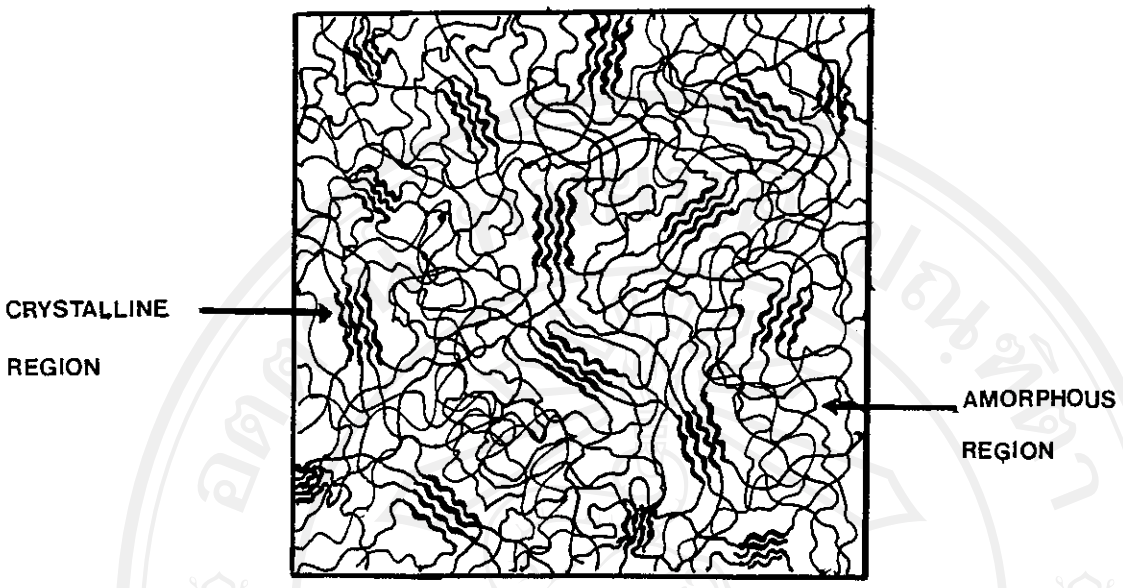


Fig. 4.1 : Visualized fringed-micelle model of semi-crystalline PGA.

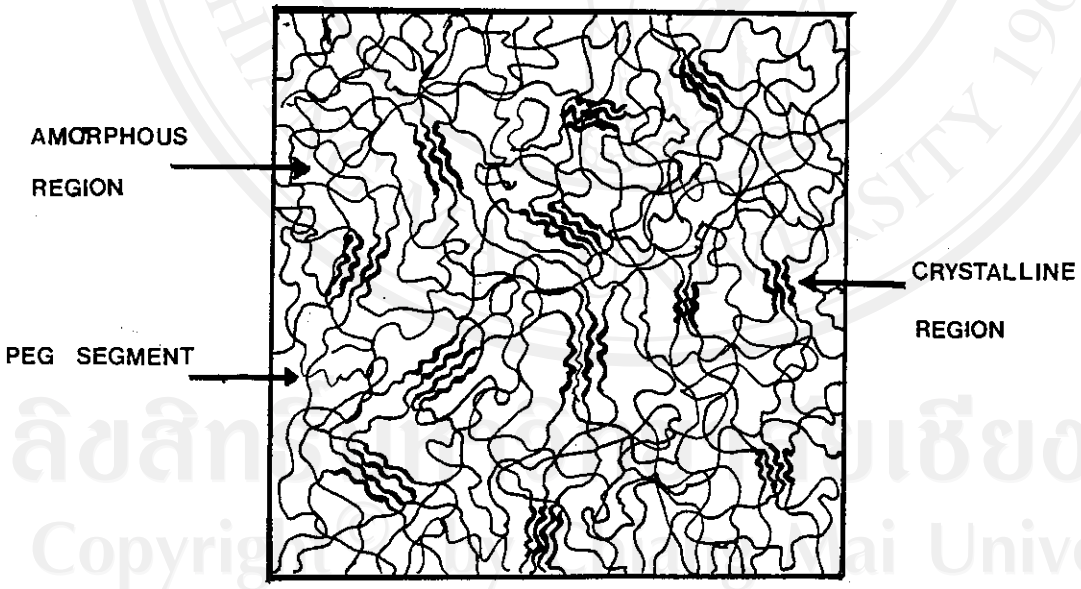


Fig. 4.2 : Visualized fringed-micelle model of semi-crystalline P(GA-b-PEG 200), showing the matrix distribution of the PEG segments.

4.2.5 Copolymer Thermal Stability

One of the problems encountered with the introduction of flexible segments into an otherwise more rigid polymer chain is the effect that it can have on the thermal stability of the copolymer. This is relevant to the case in point here since PEG has a significantly lower thermal stability than PGA. A problem arises if the PEG segments degrade at the temperature required to melt the PGA ($T_m \simeq 220\,^{\circ}C$). Since the ultimate objective of this work is to produce a material which can be made into a fibre by melt spinning, this is an important consideration.

From the thermogravimetric (TG) reuslts described earlier in section 3.6, the indications are that the P(GA-co-PEG) copolymers prepared here may undergo some thermal degradation during melt processing. Evidence for this come from the fact that, even though the short PEG blocks would undoubtedly be stabilised to some extent by the much longer PGA blocks on either side, the copolymer thermal degradation profiles exhibit initial weight losses below $200\,^{\circ}C$, i.e., slightly below their melting ranges. These weight losses may come either from the PEG segments or from low molecular weight PGA fractions still present. A better understanding of this problem should form the subject of a future project in which the aim should be to create a "processing window" wide enough for melt processing to be carried out without accompanying thermal breakdown.

4.3 'In Vitro' Biodegradability of PGA and P(GA-b-PEG)

Biodegradability is a polymer property dependent not only on chemical structure but also on various physical characteristics such as geometric configuration, surface-to-bulk ratio, macroporosity, molecular weight and its distribution, and matrix morphology. From the conclusions on page 134-137, it can be expected that, relative to PGA, the "soft segment" PEG blocks will increase the initial hydrophilicity of the copolymers and therefore the rates at which water molecules can adsorb at the surface and diffuse into the interior matrix. In addition, increasing the PEG content will enhance the contribution of the solubilization mechanism to the overall absorption process.

The combination of biodegradation mechanisms in P(GA-b-PEG) of simple hydrolysis (for PGA) and solubilization (for PEG), as shown in Fig. 4.3, provides a potential means of controlling the rate of absorption in an aqueous environment, either 'in vivo', such as in the extracellular field in the human body, or 'in vitro', as in this study.

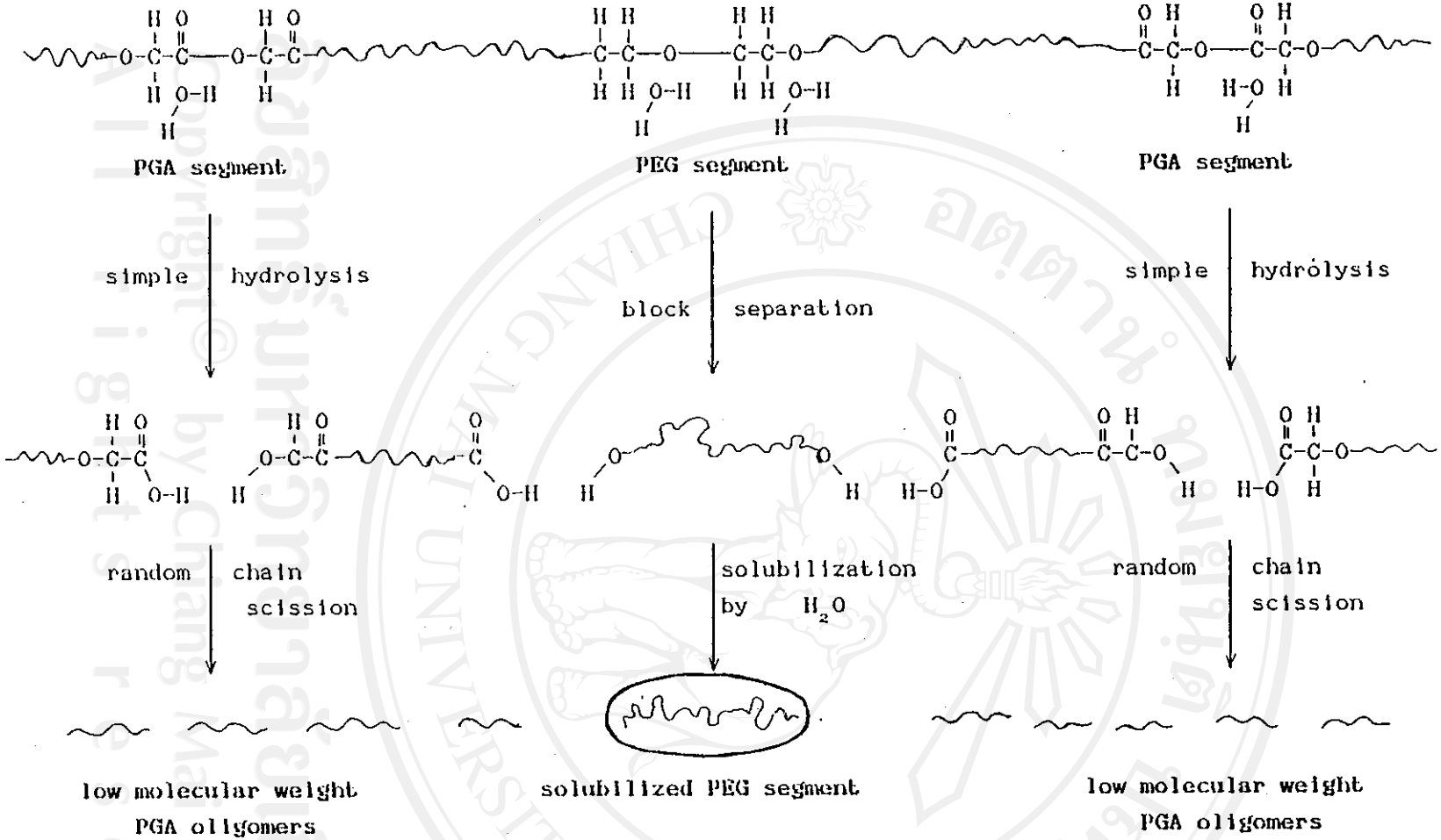


Fig. 4.3 : Simple hydrolysis and solubilization of the PGA and PEG blocks respectively in a P(GA-b-PEG) copolymer.

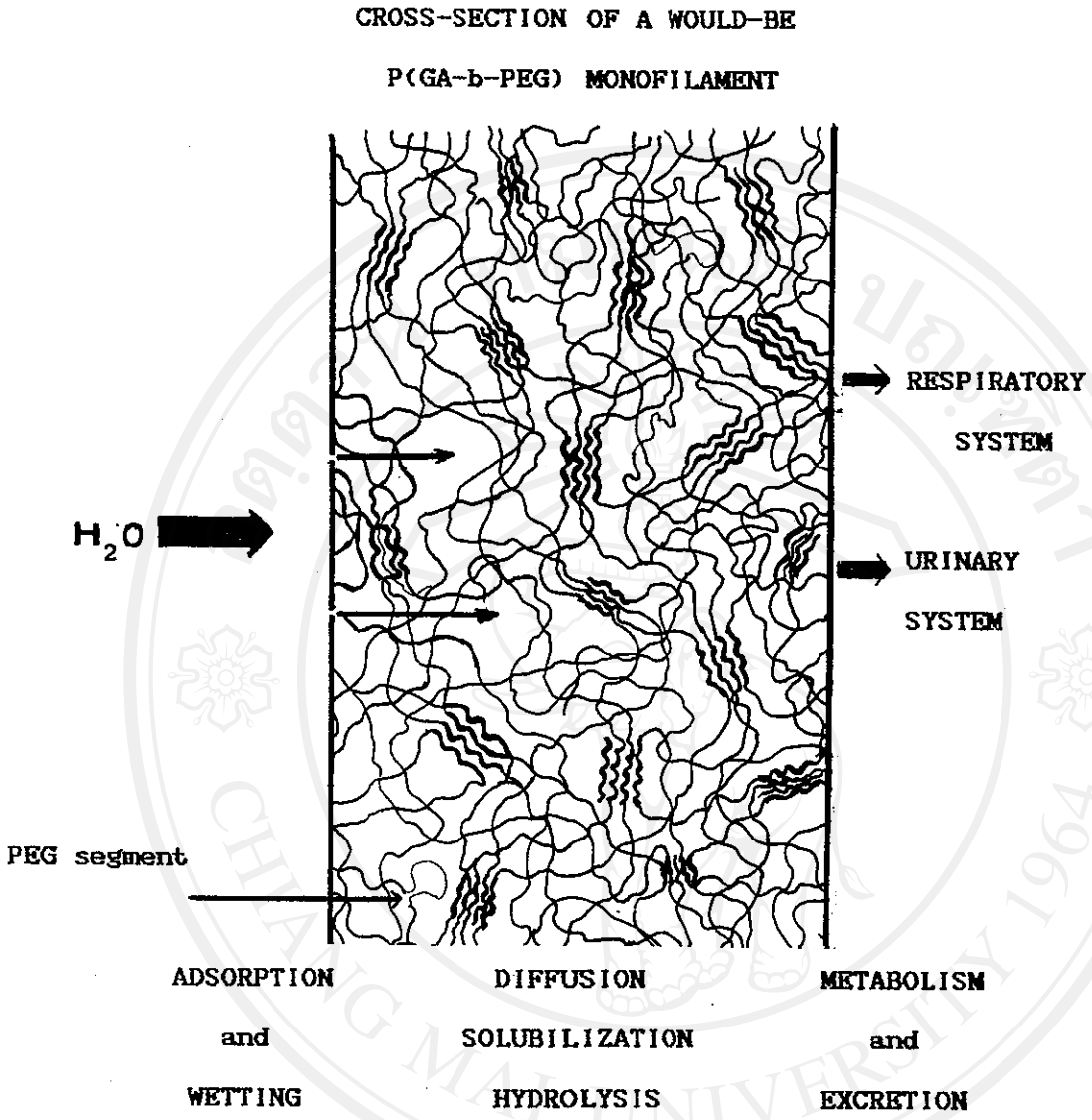


Fig. 4.4 : The various physico-chemical processes involved in P(GA-b-PEG) absorption.

As depicted in Fig. 4.4, the first step in any polymer absorption is adsorption of water and wetting at the outer surface. The rates of these physical processes depend primarily on the hydrophilicity of the polymer. PGA is the most hydrophilic of all known polyesters, although it is not actually water-soluble. On the other hand, PEG is a

water-soluble polyether which is even more hydrophilic so that adsorption and wetting of P(GA-b-PEG) can be expected to occur even more easily and quickly than PGA.

Thus, in P(GA-b-PEG), it can be expected that, as water diffuses into the copolymer's semi-crystalline matrix, hydrolysis and solubilization occur simultaneously, probably in the amorphous regions first where the chains are more loosely packed than in the highly ordered crystalline regions. As a consequence of the hydrolysis, and the resulting chain scission, the copolymer molecular weight decreases until the degradation products are small enough in size to diffuse out of the matrix. The weight then starts to decrease and the matrix becomes more porous, thus facilitating further diffusion in and out of water and products respectively. Eventually, as bulk erosion reaches an advanced stage, the copolymer in whatever physical form it is in (in this work, it was made into a compressed disc) breaks up into smaller fragments. 'In vitro', the degradation products dissolve in the immersion medium, but if the copolymer were to be used in the human body, i.e. 'in vivo', then the products would be removed by the body's natural processes of metabolism and excretion. In the case of P(GA-b-PEG), the primary hydrolysis product, glycolic acid, would be converted into a Kreb's Cycle intermediate (e.g., acetic acid) which would then break down to give carbon dioxide and water before being excreted through the respiratory system . The solubilized PEG segments would probably be transported to and excreted by the kidneys [38].