

DEGRADATION MODELS FOR POLYESTERS AND THEIR COMPOSITES

Thesis submitted for the degree of

Doctor of Philosophy

at the University of Leicester

by

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May 2011

ABSTRACT

Intensive studies are being carried out to use devices made of bioresorbable polymers inside the human body to provide various temporary functions. Typical examples include scaffolds for tissue engineering, fixation screws for broken bones and drug-loaded matrices for controlled-release. The development is entirely based on trial and error. The degradation rate strongly depends on the shape and size of the devices, making it difficult to transfer experience from one device to another. The degradation time ranges from weeks to years; animal and ultimately human trials have to be carried out, making the trial and error approach time-consuming and expensive. The entire field would benefit enormously from mathematical models capable of predicting the degradation and property change of the devices. This PhD project will develop such models as following:

- a)** A multi-scale model for degradation of bioresorbable polyesters was developed. Events that occur at the molecular scale are modelled at the molecular scale using the kinetic Monte Carlo schemes while events that occur at the device scale are modelled using macroscopic diffusion model.
- b)** A phenomenological model for simultaneous crystallisation and biodegradation of biodegradable polymers was developed. This model completed the degradation theory developed by Wang *et al.* at University of Leicester.
- c)** The model in (b) was improved and applied to the analysis of accelerated degradation data. Temperature effects were taking into account by using Arrhenius relations.
- d)** A model for the biodegradation of composite materials made of polyesters and calcium phosphates was developed. A calcium phosphate effectiveness map is established to show the conditions under which incorporating calcium phosphates into polyesters is effective, saturated or ineffective.
- f)** A phase field model was developed for drug release from a swelling Hydroxypropyl methylcellulose matrix. This model can be readily extended to full three dimensional problems.

ACKNOWLEDGEMENTS

The author would like to deeply thank her supervisor Professor Jingzhe Pan in University of Leicester. Professor Jingzhe Pan has given the author extensive help and guidance. Furthermore his encouragements are so important which are beneficial for the author, not only throughout the whole PhD research but also in daily life. The author would also like to acknowledge her co-supervisors, Dr Wenguang Jiang and Dr Simon Gill, for their invaluable advices. Supports from staff and facilities in the Mechanics of Materials (MOM) group in University of Leicester and the Mathematical Modelling Centre, as well as continuous supports from the colleagues are highly appreciated.

Some of the experimental data were provided by Professor Ruth Cameron of Cambridge University and Dr Fraser Buchanan of Queen's University Belfast which are gratefully acknowledged. Significant contribution was made by Dr Wenjuan Niu of Chongqing University to the work presented in chapter six.

The author gratefully acknowledges funding in the form of PhD studentship from EPSRC research grants S57996, F037430 and the University of Leicester. The author also acknowledges the financial support from the Great Britain-China Educational Trust and Henry Lester Limited Trust.

Finally, the author would like to thank all her friends and her family for their continued supports.

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LIST OF SYMBOLS

- A_{cp} : surface area of a calcium phosphate particle
- A_d : dissolution rate constant of calcium phosphate
- $\bar{A}$: non-dimensionalised form of A
- $C_{Ca^{2+}}$: mole concentration of calcium ions
- C_{COOH} : molar concentration of –COOH end groups
- $C_{cp,solid}$: molar concentration of calcium phosphate in solid state
- C_e : mole concentration of ester bonds of amorphous polymer chains
- C_{e0} : initial value of C_e
- C_{end} : mole concentration of polymer chain ends.
- C_{end0} : initial value of C_{end}
- C_{H^+} : mole concentration of H^+
- C_i : mole concentration of i-th type of ester bonds on the polymer chains.
- C_{ol} : mole concentration of ester bonds of oligomers
- C_w : mole concentration of water molecules in the polymer
- D : effective diffusion coefficient of oligomers in degraded polymer.
- D_0 : diffusion coefficient of oligomers in non-degraded amorphous polymer.
- $D_1 D_{pore}$: diffusion coefficient of oligomers in liquid-filled pores.
- D_a : diffusion coefficient of oligomers in amorphous polymer
- D_{a0} : pre-exponential constant for D_a
- D_{GD} : drug diffusion coefficient
- $D_{\eta_w}, D_{\eta_d}, D_{\eta_t}$: Diffusion coefficients of for the phase field variables
- D_w : water diffusion coefficient
- E_{k1} : activation energy for non-catalytic hydrolysis reaction

E_{k2}	: activation energy for autocatalytic hydrolysis reaction
E_D	: activation energy for oligomer diffusion in amorphous polymer
E_G	: activation energy for crystal growth
E_ξ	: activation energy for crystal nucleation
G	: linear growth rate of a single crystal
G_0	: pre-exponential constant for G
J	: dissolution flux of calcium phosphate
K_a	: acid disassociation constant for R-COOH end groups
K_1, K_2, K_3	: equilibrium constants for buffering reactions
K_s	: solubility of calcium phosphate
L	: Thickness of the tablet
M_0	: molecular weight of a repeating unit of the polymer
M_D	: molar mass of drugs
M_n	: number averaged molecular weight of polymer
M_{unit}	: molecular weight of a repeating unit of polymer chains
M_w	: molar mass of water
N_0	: initial mole concentration of nuclei of crystallisation
N_{chain}	: mole concentration of polymer chains
N_{e0}	: total mole number of ester bonds
p	: porosity of degrading polymer due to leaving oligomers.
P_i	: number of trials
R	: radius of a representative unit
R_i	: mole concentration of total chain scissions of the i -th type of ester bonds.
R_s	: mole concentration of polymer chain cleavages
R_{ol}	: mole concentration of ester bonds of all the oligomers ever produced (= C_{ol} if

	oligomer diffusion can be ignored)
$\Delta R^{\max}$	: maximum number of chain cleavages.
ΔR_i	: number of successful <i>i</i> -th type chain cleavage.
S_{cp}	: relative rate of calcium phosphate dissolution to auto-catalytic hydrolysis
T	: absolute temperature
T_s	: reference temperature in Vogel-Tammann-Fulcher (VTF) relation
V_0	: volume of representative unit of KMC simulation.
$V_{crystal}$	: volume of crystalline core
V_{gel}	: volume of gel phase
V_{HPMC}	: volume fraction of HPMC in the tablet
$V_{polyester}$	: volume of polyester in the representative unit
V_{sin}	: volume of a single crystal
V_{total}	: total volume of tablet
X_c	: volume degree of crystallinity
X_{ext}	: extended volume degree of crystallinity
c_w	: water concentration
c_w^*	: threshold of water concentration for swelling
c_d	: mole concentration of drug
$c_{d,eq}$	: equilibrium drug concentration
$c_{w,eq}$	: equilibrium water concentration
$j_{w,r}$	: water flux in <i>r</i> direction
$j_{d,r}$	: drug flux in <i>r</i> direction
k	: hydrolysis reaction rate constant
k_0	: pre-exponential constant of <i>k</i>
k_1	: reaction rate constant of non-catalytic hydrolysis

k_{10}	: pre-exponential constant for k_1
k_2	: reaction rate constant of autocatalytic hydrolysis
k_{20}	: pre-exponential constant for k_2
k_c	: Avrami constant for crystallisation
k_{end}	: rate constant for uncatalytic hydrolysis reaction for end scission.
k_{end}^a	: rate constant for autocatalytic hydrolysis reaction for end scission.
k_i	: rate constant of uncatalytic hydrolysis reaction for i -th type ester bonds.
k_i^a	: rate constant for autocatalytic hydrolysis reaction for i -th type ester bonds.
k_{random}	: rate constant for uncatalytic hydrolysis reaction for random scission.
k_{random}^a	: rate constant for autocatalytic hydrolysis reaction for random scission.
n_A	: Avogadro' number (= 6.02×10^{23})
p	: porosity of degrading polymer due to leaving monomers
r_e	: radius of erosion front
r_{max}	: maximum size of a single crystal
r_s	: radius of swelling front
r_d	: Radius of drug diffusion front
t	: degradation time.
t_0	:characteristic time of auto-catalysed hydrolysis reaction
v_e	: Migration rate of erosion front
v_s	: Migration rate of swelling front
v_d	: Migration rate of drug diffusion front
w_{cp0}	: initial weight fraction of calcium phosphate
x_i	: ($i=1,2,3$) Cartesian coordinates
ρ_D	: drug density
ρ_w	: water density

ρ_{HPMC}	: HPMC density
ρ_{cp}	: density of calcium phosphate
ρ_{poly}	: density of polyesters
α, β	: parameters in the relation between chain scission and oligomer production
ξ	: probability of formation of growth nuclei per nucleus per unit time
ξ_0	: pre-exponential constant for ξ
ξ_1, ξ_2	: uniform random numbers.
ε	: small empirical number controlling the timestep length.
$\dot{\varepsilon}_v$	: strain rate of the gel phase
ε_0	: initial porosity of complete matrix system
δ	: thickness of surface layer in which hydrolysis is uncatalytic.
λ, η	: impingement parameters for crystallisation, $\eta = 1/(\lambda - 1)$
η_w, η_d, η_t	: phase field variables
τ	: life time of a single crystal
ω	: molar concentration of ester bonds of crystalline phase
σ	: relative undersaturation of calcium phosphate in the polymer matrix
$div(X)_{x_i}$	: divergence of the Vector X in Cartesian coordinates x_i
$grad(X)_{x_i}$	: gradient of scale variable X in Cartesian coordinates x_i

LIST OF ACRONYMS

BMPs: bone morphogenetic proteins
CGMC: coarse grain Monte Carlo
DSC: differential scanning calorimetry
GF: growth factor
HA: hydroxyapatite
HAP: hydroxyapatite
HPMC: hydroxypropyl methylcellulose
KMC: kinetic Monte Carlo
MD: molecular dynamics
NHS: National Health Service
PBS: phosphate buffered saline
PCL: polycaprolactone
PDI: polydispersity index
PDLA: poly (D-lactide)
PDLLA: poly (DL-lactide)
PE: polyethylene
PGA: polyglycolide
PLA: poly-lactide
PLGA: PGA-co-PLA
PLLA: poly (L-lactide)
PVA: poly(vinyl alcohol)
TCP: tricalcium phosphate
TGF- β : transforming growth factor- β
SAXD: small angle X-ray diffraction
VTF: Vogel-Tammann-Fulcher
WAXD: wide angle X-ray diffraction
bFGF: fibroblast growth factor

LIST OF PUBLICATIONS AND CONFERENCE PRESENTATIONS

Journal Publications

1. Han X, Pan J, 2011. *Polymer chain scission, oligomer production and diffusion- a two scale model for degradation of bioresorbable polymers*. Acta Biomaterialia. Volume 7, Pages 538-547.
2. Han X, Pan J, Buchannan F, Weir N, Farrar D, 2010. *Analysis of degradation data of poly (l-lactide co-l,d-lactide) and poly(l-lactide) obtained at elevated and physiological temperatures using mathematical models*. Acta Biomaterialia. Volume 6, Pages 3882-3889.
3. Han X, Pan J, 2008. *A model for simultaneous crystallisation and biodegradation of biodegradable polymers*. Biomaterials. Volume 30, Pages 423-430.
4. Pan J, Han X, Niu W, Cameron R and Farrar D, 2011. *A Model for Biodegradation of Composite Materials Made of Polyesters and Calcium Phosphates*. Biomaterials. Volume 32, Pages 2248-2255.
5. Wang Y, Han X, Pan J, Csaba Sinka, 2010. *An Entropy Spring Model for the Young's Modulus Change of Biodegradable Polymers during Biodegradation*. Journal of the Mechanical Behaviour of Biomedical Materials. Volume 3, Pages 14-21.
6. Wang Y, Pan J, Han X, Csaba Sinka, L Ding, 2008. *A phenomenal model for degradation of biodegradable polymers*. Biomaterials. Volume 29, Pages 3393-3401.

Conference presentations

1. 2008, A Reaction-Diffusion model for biodegradation of biodegradable polymers. Oral presentation in Leicester-Oxford Workshop, Leicester, U.K.
2. 2008, Modelling Simultaneous Crystallization and Biodegradation of Biodegradable Polymers. Oral presentation in MOM Group Seminar, Leicester, U.K.
3. 2009, A multi-scale model for degradation of bioresorbable polymers. Oral presentation in the Workshop held in Queens University, Belfast, U.K.
4. 2009, Modelling Simultaneous Crystallization and Degradation of Bioabsorbable Polymers. Posters presentation on 2009 annual meeting of US Society for Biomaterials,

San Antonio, US.

5. 2009, Modelling Degradation of Scaffolds for Tissue Engineering Made of Bioresorbable Polymers. Oral presentation on 22nd European Conference on Biomaterials, Lausanne, Switzerland.
6. 2009, A Monte Carlo Study of Degradation of Bioresorbable Polymers. Poster presentation on 2nd China-Europe Symposium on Biomaterials in Regenerative Medicine, Barcelona, Spain.
7. 2010, Modelling Biodegradation of Biodegradable Polymers. Oral presentation in MOM Group Seminar, Leicester, U.K.
8. 2010, An entropy spring model for the Young's modulus change of biodegradable polymers during biodegradation. Oral presentation on The 20th International Workshop on Computational Mechanics of Materials. Loughborough, U.K.

CHAPTER ONE - BIODEGRADABLE POLYMERS AND THEIR APPLICATIONS

This thesis is to study degradation behaviours of bioresorbable polymers. A complete theory is established by the aid of mathematical methods. This chapter will provide the background of biodegradable polyesters which includes the introduction, applications and degradation mechanisms.

1.1. MOST COMMONLY USED BIODEGRADABLE POLYMERS

Polyesters, especially polyglycolide (PGA), poly (L-lactide) (PLA) and their copolymers (PGA-co-PLA) (PLGA), are most commonly used biodegradable polymers because of their well established biodegradability, biocompatibility, thermo-elasticity and good mechanical properties. Furthermore they are nontoxic to environment and human body. All the polymers mentioned in this thesis are linear polyesters. PLA, also known as polylactide is a biodegradable, thermoplastic and aliphatic polyester derived from renewable resources. Lactide is a cyclic dimer of lactic acid that exists in two stereoisomeric forms, D and L: L-lactide is a naturally occurring isomer while D-lactide is its mirror image. The homopolymer of L-lactide (PLLA) or D-lactide (PDLA) is a semi-crystalline polymer (up to 40% initial crystallinity) with a melting point of 170°C-195°C, and a glass-transition temperature from 50°C-60°C (Karst and Yang, 2006). Poly DL-lactide (PDLLA) is usually an amorphous polymer exhibiting a random distribution of both isomeric forms of lactic acid and accordingly is unable to arrange into an organized crystalline structure and is soluble in most common organic solvents. This material has lower tensile strength and higher elongation at break, and degrades faster, making it attractive for drug delivery systems. The degradation time of PLLA is much slower than that of PDLLA, requiring more than two years to be completely absorbed. Copolymers of L-lactide and D-lactide have been prepared to disrupt the crystalloid of L-lactide and accelerate the degradation process. Biodegradability of PLLA and PDLA blends is however different from PDLLA. The percentage of PLLA and PDLA in polymer blends affects the crystal structure, melting point and glass-transition of PLA (Karst and Yang, 2006). A 50/50 PLLA/PDLA blend can

have a different crystal structure from that of pure PLLA or PDLA (Karst and Yang, 2006). The 50/50 blend can form a stereocomplex, which is a complex between PLLA and PDLA (Karst and Yang, 2006). The stereocomplex structure of the 50/50 PLLA/PDLA blend has a glass-transition temperature of 65°C - 72°C and a melting point of 220°C - 230°C (Karst and Yang, 2006), which are both higher than those of pure PLLA and PDLA. Additionally PLLA and PDLA blends have relatively high Young's modulus and tensile strength compared to pure PLLA and PDLA due to stereocomplex crystallites. PGA is the simplest linear, aliphatic polyester and highly crystalline. It is the most hydrophilic one among the three and fully biodegrades within 4-6 months (Miller et al., 1977). It can be prepared starting from glycolic acid by means of polycondensation or ring-opening polymerization. PGA is semi-crystalline ($45 \pm 55\%$), with a high melting point of 224°C-226°C and a glass-transition temperature of 36°C-40°C (Miller et al., 1977).

1.2. APPLICATIONS OF BIODEGRADABLE POLYMERS

Sutures made of bioresorbable polymers have been successfully used in surgeries since the 1970s. Screws and plates made of similar polymers are being increasingly used to fix broken bones. Bioresorbable wafers loaded with anticancer drugs are placed into resection cavities after cancer surgery to slowly release the drugs, helping to prevent the cancer from returning. The details of biodegradable polymer applications are described in this section.

Bone fixation

It is estimated that there are over 1.1 million bone fractures each year in the UK. About 10% of these need internal fixation devices to help the fracture bond healing. Once the fractured bone healed, these devices are no longer needed. Removal of metallic implants is often carried out at the request of the patient or to meet a clinical need such as pain, implant failure or infection. However, hardware removal can also result in complications such as infection and nerve damage. There are about 30,000 operations each year to remove metal implants and the cost to the NHS is around £60m. Orthopaedic surgery normally includes fractures of the long bones (such as in arms and legs), the smaller bones (such as in feet and hands) and fractures of the joints (such as ankles, wrists and shoulders). Treatments of these

injuries are dominated by fixation devices, which may be either internal or external (National Institute for Health and Clinical Excellence, 2008). Biodegradable polymers are now widely used to produce internal fixation devices. The advantage of using biodegradable fixation devices instead of metallic screws, pins and plate in bone orthopaedic surgery is obvious - the device simply disappears after the bone heals. Additionally load can slowly shift from the degrading polymer device to the healing bone which ensures a complete healing of the bone. Patients are therefore benefited from avoiding a second removal procedure. Dedicated commercial companies have been set up to manufacture such devices. In orthopaedic surgery the major mechanism people concern about is device degradation rate compared with bone healing rate. It is well known that the bone density is adaptive to the loadings during the remodelling process. Once degradable devices are implanted their mechanical properties are reduced due to degradation. Thus the degradation rate and bone healing rate should follow a certain relationship. Unlike the metallic implants they are gradually resorbed by the body and replaced by newly generated bone. Typical polymers are linear aliphatic polyesters, PGA, PLA and their copolymers, whose backbones are highly hydrolysable and the degradation products are eventually metabolized into carbon dioxide and water. The advantages of using bioresorbable polymers or their calcium phosphate composites as fixation devices include (a) second surgical procedure to remove implant is not required; (b) complications associated with metal implants (e.g. stress shielding, corrosion, release of metal ions) are avoided; and (c) they can be used to deliver bioactive agents.

PGA, PLA and their copolymers have different degradation rates and mechanical properties. The degradation time can be tailored from weeks to years to suit different applications by changing the average molecular weight and the initial degree of crystallinity, and by copolymerising or blending in different proportions. They are therefore commonly used to make resorbable fixation screws and plates for orthopaedic surgery, scaffolds for tissue engineering and carriers for controlled drug delivery systems. The treatment, medication, assessment can all be influenced by using bioresorbable fixations as substitutes. Both healing time and risk of inflammatory reactions will be reduced. The second surgical procedure of implant retrieval will no longer be necessary. Average length of stay in

orthopaedics would have reduced as a result of using the new resorbable devices followed by the use of step-down intermediate care services to support patients in their pathways.

Tissue engineering

The number of people suffering from joint diseases, back pains and osteoporotic fractures has been increasing significantly as the aged population has been doubled in the last decade in most countries. Current clinical therapies, including autologous, allografts and manmade material bone grafting, need additional surgical costs for the harvesting procedure, infection and pain at the harvesting site. For example, harvesting an ileac crest graft can cost from £1,000 to £6,000 per procedure for the harvesting operation and the additional hospital stay (Laurencin, 2009). Bone tissue engineering is an emerging interdisciplinary field which is used to address these problems. Bone tissue engineering utilises scaffold which is biocompatible, biodegradable and allows cells to attach, proliferate, and migrate throughout its structure. Then the damaged tissue can be replaced slowly over time and the newly generated tissue can completely replace the synthetic scaffold initially implanted. Therefore tissue engineering can fully regenerate the tissues rather than simply replace it. This form of therapy differs from standard drug therapy or permanent implants in that the engineered bone becomes integrated within the patient, affording a potentially permanent and specific cure of the disease state.

In bone tissue engineering, neotissues are constructed by seeding the functional cells and the signal molecules to a highly porous scaffold in a shape of desired bone followed by *in vitro* culture and *in vivo* implement to the desired sites to guide the growth of a new bone tissue. Firstly, the cells used to seed to the porous scaffold in bone tissue engineering can be either undifferentiated, such as bone marrow cells and mesenchymal stem cells or differentiated cells, pre-differentiated osteoblasts for instance which can be obtained by three approaches: autologous (donated by the patient), allogenic (donated by another person), xenograph (from an animal). Secondly, the signal molecules, growth factor for example, used in bone tissue engineering include: bone morphogenetic proteins (BMPs), transforming growth factor- β (TGF- β) and basic fibroblast growth factor (bFGF), etc. The growth factors are proteins secreted by cells that act on the appropriate targets cells to carry

out a specific action which is a crucial factor in practicing of bone tissue engineering. It can be adhered into the scaffold or incorporated directly into the scaffold. Thirdly, highly porous scaffolds are usually fabricated for bone tissue engineering using synthetic polymers, ceramics, native polymers and composites. An appropriate scaffold design should follow: biocompatibility, osteoconductivity, osteoinductivity, osteogenicity, osteointegrity and properly mechanical properties (Yang *et al.*, 2004; Yang *et al.*, 2002; Baas *et al.*, 2010; El Haj *et al.*, 2005). No material can satisfy all the requirements. Therefore, for an ideal bone tissue scaffold, it is a reasonable strategy to combine two or more materials into a composite (Yang *et al.*, 2002). Next step after the preparation is seeding cells and molecules to the scaffold and bioreactor cultivation. As the scaffold provides a three-dimensional framework for tissue generation the bioreactors provide control over the conditions of cell seeding, tissue cultivation, affected construct structures and compositions. The choice of bioreactors to cultivate three-dimensional constructs depends upon the tissue to be engineered and its functional biomechanical environment (El Haj *et al.*, 2005). The common bioreactors used in bone tissue engineering include both static and dynamic bioreactors: static culture, spinner flask, rotating-wall vessels, perfusion system and perfused column, etc. Cultured constructs are then implemented into the defect to induce and direct the desired bone. This approach holds great promise as a bone repair model provided that the nature and structure of bone is considered in the scaffold design.

A major concern for implanted tissue constructs is that the implant will not develop adequate vascularisation for long-term survival (Rose and Oreffo, 2002). The vasculature transports oxygen, nutrients and soluble factors to the tissues. The efficacy of cells which are seeded to the scaffold will depend on local vasculature. Cells without a blood supply will die, and mass infection will occur. Angiogenesis therefore plays a critical role in bone fracture repair as bone is a highly vascularised tissue which depends on the connection between blood vessels and bone to maintain its integrity. However, in general, direct injection of growth factors which will enhance the differentiation of mesenchymal stem cells in solution into the regeneration site is ineffective, as the injected growth factor rapidly diffuses out from the site within one day. To address this problem, technique like drug delivery system is employed. This promising technique is the controlled release of

growth factor at the site of action over a long time period by incorporating the factor into an appropriate carrier (bioabsorbable scaffolds). This approach allows to protect the drug which contains growth factor from rapid clearance and to provide a sustained release (Langer, 1990). The continuous release occurs either by diffusion of the drug or by the degradation of the polymeric scaffold. There are many approaches to embed growth factors in a scaffold matrix. The simplest way consists of adding the signalling molecule directly to the polymer solution or powder (Lo *et al.*, 1996). Alternatively a water phase containing the proteins can be mixed with a polymer dissolved in an organic solvent to form a water-in-oil emulsion (Hile *et al.*, 2000; Whang *et al.*, 2000). These methods provide a chance to control either the release rate or the release profile. Additionally the selected scaffold processing methods should not induce the loss of the biological activity of the proteins by using appropriate temperature and pressure.

Some experimental observations showed that tissue regeneration occurred only in the surface layer and no neotissues regenerated in the central area. The reasons of such heterogeneous profile of cells or tissue can mainly be raised from nutrient transport, oxygen depletion and waste diffusion. Oxygen and other nutrients diffuse into the scaffold from external environment which will cause gradients between inside and on the surface. In the central area, little or even no oxygen or nutrients can be found which would lead to cell death (Lewis *et al.*, 2005). Additionally, the microstructure of scaffold and the growing tissues act as restrictions which will also affect nutrient transport and waste diffusion out of the scaffold. These restrictions therefore can be overcome by a better scaffold design (Rose and Oreffo, 2002) as well as by controlling the physical and biochemical environment in a bioreactor (El Haj *et al.*, 2005; Singh *et al.*, 2005; Vunjak-Novakovic *et al.*, 1999). For example, fully interconnected pores will enhance the transport mechanisms while by using the bioreactor nutrient can be supplied continuously avoiding the oxygen depletion (Bancroft *et al.*, 2002). In a word, novel tools should be developed in optimising scaffold design and controlling the biomimic environment.

Bioresorbable polymers, such as PGA, PLA and their copolymers PLGA, have been fabricated into porous three-dimensional scaffolds intensively to engineer osseous tissues

with varying successes (El Haj *et al.*, 2005; Whang *et al.*, 2000; Peter *et al.*, 2001; Pamula *et al.*, 2008). These polymers are demonstrated to be biocompatible and biodegradable. In addition, they also have great three-dimensional design flexibility and can be readily fabricated into highly porous scaffolds with different structures and sizes to meet the needs of a specific tissue-engineering application. Unfortunately pure polyesters, however, generate an acidic environment during degradation which can induce inflammatory tissue response and result in osteolytic reactions or delayed bone healing/fusion. Ceramics are also widely used as implements and fillers of the bone therapies as bone is formed from approximately 8% water, 22% proteins, and 70% mineral (Einhom, 1996). The mineral component of bone is a form of calcium phosphate known as calcium hydroxyapatite. Being similar to the major inorganic component of natural bone, bioceramics, including hydroxyapatite (HAP) and tricalcium phosphate (TCP) are widely used as scaffolding materials for bone repair (LeGeros, 2002). However, the main limitation for the use of ceramics is their inherent brittleness and difficulty of processing. Therefore, for an ideal bone tissue scaffold, it is a reasonable strategy to combine two or more materials into a composite. In the ceramic-polymer composites, dissolved phosphate ions buffer the acidity of the carboxylic end groups (produced by the polyester chain cleavage) while the polyester provides the composites with the appropriate mechanical properties. Consequently the composites degrade more slowly and maintained their shape longer than the pure polymer. The pH of the surrounding media remains stable for longer periods of time for the composites than for the pure polyesters.

Indeed, various animal studies have shown the capacity of bone tissue engineering to produce bone. Surprisingly however, until recently, no convincing success has been achieved in humans (Rose and Oreffo, 2002). The main challenges of bone tissue engineering, which prevents bone tissue engineering from clinical applications, are 1) perhaps the biggest challenge for all of tissue engineering is how to ensure angiogenesis in a timely fashion within the scaffold construct; 2) the heterogeneous cell growth has been observed in many experiments which can result in inadequate overall mechanical properties (Sengers *et al.*, 2007); and 3) polymer degradation products reduce the local pH and induce a local inflammation (Sengers *et al.*, 2007).

Some papers can be found in the literatures on modelling the interactions in tissue engineering to address the issues highlighted above. Mathematical modelling plays an important role in facilitating growth factor release system design by identifying key parameters and molecule release mechanisms. Mathematical models for controlled molecule release from hydrogels have been developed and reviewed recently (Lin and Metters, 2006). Spatio-temporal distributions of proteins and scaffold are simulated so that one can control the rate of release and degradation to provide a better growth factor delivery system. A mathematical model has been developed by Lewis *et al.* (2005), which considers the interplay between nutrient transport, oxygen diffusion, oxygen uptake and cell growth in a simple diffusion and consumption equation. This model helps to gain an understanding into the heterogeneous phenomena of tissue growth and guides scaffold design. Computational modelling has the potential to improve the bone tissue engineering to meet the clinical requirement. The existing models, however, are not matured enough to directly guide the scaffold or the release system design. The development of an integrated modelling framework therefore becomes the most important challenge.

The models reported in the literature are phenomenological which can be used in calculating oxygen profile for example but cannot be used for scaffold or drug loading design. For instance, the model by Lewis *et al.* (2005) describes the interplay between the nutrient transport and cell growth. However it assumes a constant diffusion coefficient for the nutrient diffusion. In reality the diffusion coefficient depends on the concentration of the nutrient, the concentration of the cells and the microstructure of the scaffold. Ignoring these issues, the simply diffusion-consumption equation is inadequate to gain insight into the matrix details and better mathematical tools should be used to follow a multi-scale approach. Although many fundamental studies have revealed the basic growth factor release mechanisms from polymeric release devices, the parameters in these models are unknown and their change with time or position needs to be identified in order to accurately predict drug release.

Degradable microspheres

Despite hydrophilic polymer and hydrogels, over the recent twenty five years, research has been focused on degradable polymer microspheres for controlled drug delivery intensively. Polylactides (PLA), Polyglycolides (PGA), Poly(lactide-co-glycolides) (PLGA), Polyanhydrides and Polyorthoesters are utilized (Edlund and Albertsson, 2002). Comparing with non-degradable polymers, bioresorbable polymers break into small oligomers and are readily eliminated by metabolism. The most common formulation for these degradable materials is that of microspheres. The advantages for such system are that the microspheres can be ingested as well as injected; they can be tailored for desired release profile. Mechanisms for drug release from biodegradable polymer release systems include diffusion, biodegradation (hydrolysis reaction) and polymer crystallisation. The interactions among diffusion, biodegradation and crystallisation have been discussed on previous work (Pan *et al.*, 2010; Han *et al.*, 2010; Wang *et al.*, 2008; Han *et al.*, 2009). Diffusion is mainly affected by the matrix degradation, crystallisation while it has influence on degradation rate and crystallisation rate as well. The factors affecting drug release in biodegradation include polymer molecular weight, blends of structurally different polymers, crystallinity, porosity and size of the microspheres (Freiberg and Zhu, 2004).

Some literatures have studied different aspects of microspheres for drug delivery (Edlund and Albertsson, 2002; Freiberg and Zhu, 2004; Uhrich *et al.*, 1999; Mogi *et al.*, 2000). Mogi *et al.*, (2000) have studied the release properties of PLGA microsphere sustained release system which contained four different concentrations (0.15, 0.3, 1.5, 2.25% (w/w): PLGA-0.15, PLGA-0.3, PLGA-1.5, PLGA-2.25) of 17 β -estradiol *in vitro* and in Vitamin D-deficient female Wistar rats. They found *in vitro*, that all the microspheres degraded within 100 days. 17 β -estradiol was released from PLGA-0.15 and PLGA-0.3 for one month with a constant rate. On the other hand 17 β -estradiol was released from PLGA-1.5 and PLGA-2.25 with almost constant rates except the first 5 days. *In vivo* tests also showed that 17 β -estradiol can be delivered with almost zero-order release rate using PLGA microsphere. It was found that the release of estradiol from PLGA microspheres is affected by the three mechanisms: 1) the release of estradiol molecules accompanied with the removal of degraded short polymer chains; 2) the dissolution of estradiol crystals into

polymer matrices and solvent and 3) pore formation in polymer matrices caused by the polymer degradation. Galeska *et al.* (2005) described delivery platforms based on poly(vinyl alcohol) (PVA) microgels containing entrapped dexamethasone-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres or only dexamethasone for controlled delivery over one month. *In vitro* studies indicated that when dexamethasone was incorporated into plain PVA hydrogels, 80%-100% release was attained within two weeks. On the other hand, PLGA microsphere-encapsulated dexamethasone, embedded within PVA hydrogels, resulted in minimal release (approximately 6%) over a period of 1 month. Incorporating polyacids within gels containing PLGA microspheres resulted in an order of magnitude increase in the dexamethasone release rate (to 60% to 75% release over a 1-month period).

Polymer/calcium phosphates composites

Polymer/calcium phosphates composites are at the forefront of developing materials for orthopaedic applications. A resorbed screw often leaves behind a hole in the bone which is unsatisfactory. Composites of resorbable polymers and calcium phosphates such as hydroxyapatite or α -TCP have been developed to overcome the problem. They provide initial load bearing capacity in the body and evolve into porous bioactive scaffolds allowing subsequent cell colonisation. The calcium phosphate therefore encourages bone regeneration into the degrading screw. Careful choice of calcium phosphate can lead to the release of buffering salts which reduces autocatalysis thereby slowing the reaction and counteracting the heterogeneity within the sample. Such composites are also mechanically more suitable for orthopaedic applications and are radiographically visible (Heidemann *et al.*, 2001; Ehrenfried and Cameron, 2008; Ehrenfried *et al.*, 2009).

1.3. HYDROLYSIS BIODEGRADATION MECHANISMS

Biodegradation is defined as a bioactive decomposition process. Huge efforts have been made in the last decades by many researchers (Swift, 1997) in order to understand the complexity of the polymer biodegradations which includes 1) degradation during processing and stocking and 2) degradation during employment.

Physical factors induced degradations, such as mechanical degradation, thermal degradation and light degradation, are usually occurred during polymer processing. Chemical factors induced degradation, such as oxidation degradation and hydrolysis degradation are also detected (Gopferich, 1997).

Biodegradable polymers contain either hydrolysable bonds or oxidizable bonds. Therefore the degradation mechanism during employment is induced by hydrolysis, enzymatic hydrolysis (Gopferich, 1997) and oxidation (Albertsson, 1993; Day *et al.*, 1997; Gu, 2003). Biodegradation induced by enzymatic hydrolysis or oxidation is difficult to predict as well as control while biodegradation induced by chemical hydrolysis is more controllable and predictable.

In this thesis, we focus on the chemical hydrolysis degradation and all models are established based on the early stage of hydrolysis degradation. The hydrolysis degradation is a two-phase process: chemical hydrolysis of the polymer backbone and active metabolism of the degradation products. During the first phase, water penetrates the biodegradable device, attacking the ester bonds and converting the long polymer chains into shorter water-soluble oligomers. This is known as the hydrolysis reaction. In the second phase, enzymes released from white blood cells attack these fragments turning them into natural monomeric acids found in the body, such as lactic acid. These acids enter the citric acid cycle and are excreted as water and carbon dioxide. The first phase process contains several steps which are discussed as following (Galeska *et al.*, 2005):

Stage 1: It is relatively easy for water molecules penetrating into polymer matrix because of the high diffusion coefficient for water molecules compared to that of oligomers. In the first stage, time for water uptake is as short as several days (Li *et al.*, 2000) while time for degradation process is as long as many years (Grizzi *et al.*, 1995). It is then assumed that water molecules are abundant anywhere in the matrix.

Stage 2: In this stage water molecules chop the backbone linkages between repeat monomers. Long polymer chains then become water soluble small oligomers.

Stage 3: Water soluble oligomers diffuse out to the solvent (or body fluid).

Stage 4: Carboxylic acids produced from hydrolysis reaction can accelerate the hydrolysis rate which is known as auto-catalytic hydrolysis. Because of oligomer diffusion, Concentration of carboxylic acids in the center core of a device is higher than that near the boundary from which heterogeneous hydrolysis rate is formed.

Figs. (1-1) to (1-3) are schematic figures which illustrate the first three stages. The shadowed ellipses represent the repeat units (monomer) of a long polymer chain. The chemical hydrolysis reaction is the prevailing mechanism for polyester degradation which is dependent on pH value and can be catalysed by an acid (Cameron and Kamvari-Moghaddam, 2008).

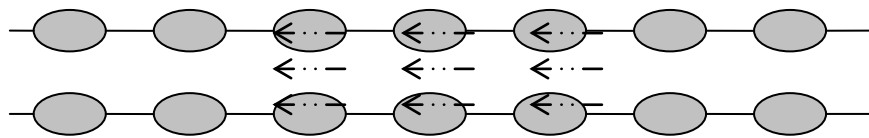
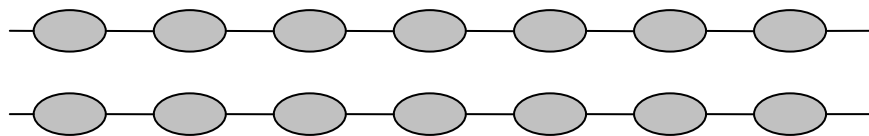


Fig. 1-1 Polymer degradation stage 1: water penetration



Cleavage of backbone linkages between polymer repeat units

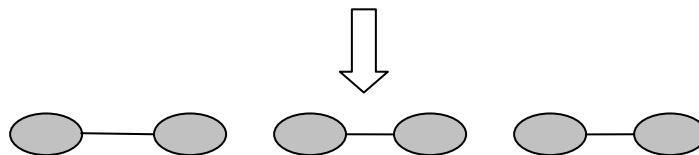


Fig. 1-2 Polymer degradation stage 2

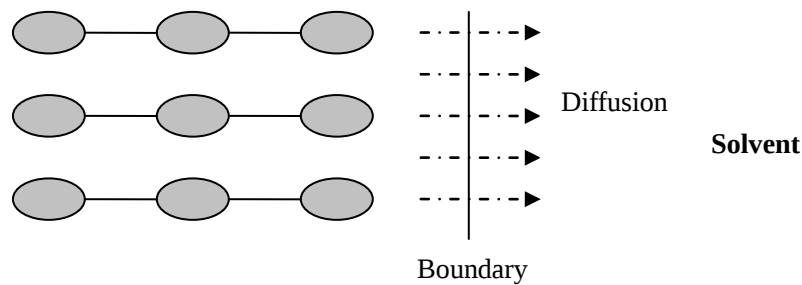


Fig. 1-3 Polymer degradation stage 3: oligomer diffusion

The hydrolysis of polyester molecules produces oligomers with carboxylic acid and alcohol end groups. These acid end groups have a high degree of dissociation and therefore give rise to an acidic environment, which significantly accelerates the hydrolysis rate. The hydrolysis reaction is therefore autocatalytic. If some small and water soluble oligomers can diffuse away, then the acidity of the local environment is reduced. This explains why the surface degrades more slowly than the core of a device. The interplay between oligomer diffusion and the hydrolysis reaction is therefore a central issue that any model must consider. Furthermore the oligomers diffuse in a degrading polymer which has increasing porosity, crystallinity and water content as the degradation progresses. The variation of the effective diffusion coefficient with respect to these factors has to be modelled. Some size effects have been reported by experimental researchers (Grizzi *et al.*, 1995; Li *et al.*, 1990^a; Li *et al.*, 1990^b; Li *et al.*, 1990^c). They showed that clear size effect can be detected for PLLA-co-PGA 50%:50% (PLGA 50).

PGA, PLLA and PCL are all semi-crystalline polymers, although their copolymers are often intrinsically amorphous. The crystalline phase is difficult for water to penetrate and then the rate of hydrolysis reaction is relatively small. The degree of crystallinity increases significantly during biodegradation in both initially amorphous and semi-crystalline polymers. This is because cleavages of the polymer chains provide extra mobility to the chains and lead to further crystallisation. Thus it is necessary to consider the interplay between the hydrolysis reaction and crystallisation. The overall crystallisation mechanisms during degradation contain: nucleation, crystal growth and the secondary crystallisation (which is also known as post-crystallisation). After the nuclei formation the grains begin to grow until they reach an equilibrium stage. Primary crystallization consists of those two

phases above. Primary crystallization happens when some of the controlling factors changes in degradation, such as temperature and chemical environment (pH value for example). Most polymers with high crystallinity will show a spherulitic microstructure of crystals. There are two different kinds of spherulitic morphologies indicated in the fig. 1-4 (Long *et al.*, 1995). In type 1, crystallisation starts from a single nucleus to every direction and then different crystal nucleated separately and independently until it reaches a symmetric spherulitic shape. On the contrary, in type 2, crystallisation develops from a single crystal by continuous growth to every direction until a shape of spherical obtained. Consequently in type 2 only one nucleus is needed for a single crystal while crystal in type 1 is an aggregate of different independent crystals (Long *et al.*, 1995; Albano *et al.*, 2003; Li and Huneault, 2007).

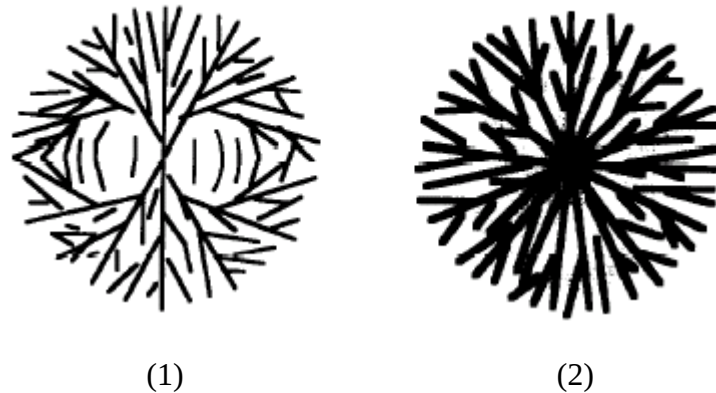


Fig. 1-4 Two types of sphere crystals (Long *et al.*, 1995): (1) type 1 crystallisation; (2) type 2 crystallisation.

If the controlling factors are unchanged when the primary crystallization is completed usually there is no post-crystallization occurred. In biodegradation, water molecules diffuse into amorphous phase and attack back bones of polymer chain. Long polymer chains are then broken into short oligomers from which the chain mobility of the polymer chains is therefore increased. As a result, the disordered repeat units of polymer chains are more likely getting into the ordered ones. The above mechanism can be concluded as secondary crystallization which is constituted by two pathways (Tsuji *et al.*, 2006; Ikejima and Inoue; 2000; Tsuji *et al.*, 2003; Weinberg *et al.*, 1997): water molecules diffuse into the amorphous gap. Via the hydrolysis degradation the long molecular polymers collapse into short

oligomers, thus the chain mobility is increased, which facilitates the crystallization process in the amorphous gap. The secondary crystallization produces thinner and low molecular weight crystal lamellas. Secondly, as water molecules can diffuse through the interlayer of amorphous, the chain scission can lead to the collapse of the polymer chains, causing slightly decrease of the amorphous layer thickness. Fig. 1-5 illustrates the biodegradation induced secondary crystallisation process. The blocks in fig. 1-5 indicate the crystal phase while the disordered lines are amorphous phase.

Number of parameters can be used as evidences of the secondary crystallization shown in Fig. 1-6. They are L (average long period), l_c (average thickness of crystal lamellas), l_a (average thickness of amorphous lamellas).

$$L = l_c + l_a \quad (1-1)$$

These thicknesses are valued from 10 to 100 Å (Zong XH *et al.*, 1999). As aforementioned, in the second stage of secondary crystallisation the amorphous layer thickness l_a decreases slightly while the crystal layer thickness l_c decreases because of the thinner crystal formed during the secondary crystallization (Zong XH *et al.*, 1999). Crystallinity is volume fraction of crystal phase in terms of total polymer system. $\theta = \frac{X(t)}{X_\infty}$ is used to define crystallinity.

Many experiments have been carried out to measure crystallisation using techniques including differential scanning calorimetry (DSC), wide angle X-ray diffraction (WAXD) and small angle X-ray (SAXD) diffraction.

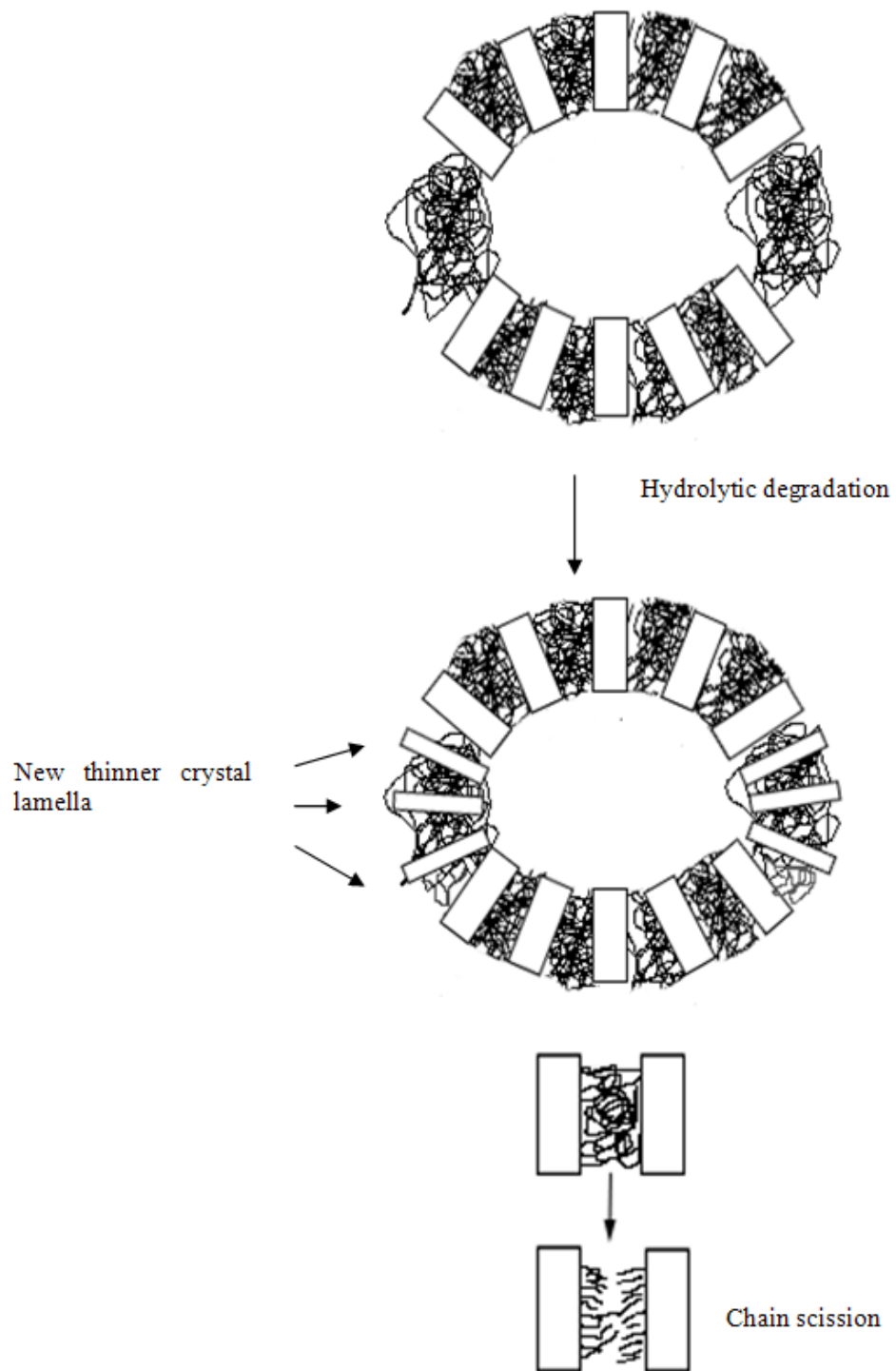


Fig. 1-5 Secondary crystallization in biodegradation

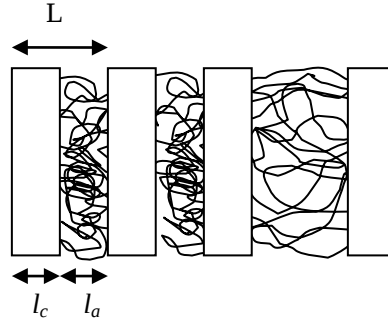


Fig. 1-6 Definitions of parameters for crystallisation

1.4. THE NEED FOR MATHEMATICAL MODELLING

The mechanisms of biodegradation are complicated which include hydrolysis reaction, simultaneous crystallisation, autocatalytic hydrolysis reaction as well as diffusions. This complicated behaviour makes it difficult to optimise the design of the biodegradable implants, tissue engineering scaffold and drug delivery systems. The typical degradation period of an implant can be several years. Hence the trial-and-error approach is problematic. Computational methods have been applied into biomaterial area by various researchers. The diffusion-reaction equations were used to model the coupled hydrolysis reaction and diffusion (Joshi and Himmelstein, 1991). Monte Carlo models were developed and incorporated into the diffusion reaction equations to take into account of the effect of porosity evolution (Zygourakis and Markenscoff, 1996; Gopferich and Langer; 1995; Siepmann *et al.*, 2006). These previous works have laid a solid foundation for modelling biodegradation. However the mathematical equations have been presented in terms of specific reactions, suggesting that they are only valid for a specific polymer system. Furthermore the equations have been solved only for simple one-dimensional cases. In the next chapter, we will discuss the existing models for polymer biodegradation.

CHAPTER TWO - A REVIEW OF EXISTING MATHEMATICAL MODELS FOR POLYMER DEGRADATION

This chapter provides a brief literature review on existing mathematical models for polymer degradation.

2.1. SIMPLE HYDROLYSIS RATE EQUATION

Farrar (2008) provided an overview of the existing analytical models for the degradation of bioresobable polymers. The hydrolysis of polyester molecules produces shorter chains (oligomers) with alcohol (-OH) and carboxylic (-COOH) groups. Pitt and Gu (1987) suggested that the rate of the hydrolysis reaction depends on the concentrations of the ester bonds and water, referred as to C_e and C_w respectively:

$$\frac{dC_{COOH}}{dt} = kC_wC_e \quad (2-1)$$

where k is a reaction constant. The carboxylic end groups have a high degree of dissociation and can act as a catalyst to accelerate the hydrolysis reaction. The hydrolysis reaction of polyesters is therefore autocatalytic (Li *et al.*, 1990^a; Li *et al.*, 1990^b; Li *et al.*, 1990^c) and the reaction rate depends on the concentration of the carboxylic end groups, referred to as C_{COOH} . In this case Pitt *et al.* (1981) suggested that

$$\frac{dC_{COOH}}{dt} = kC_wC_eC_{COOH} \quad (2-2)$$

Siparsky *et al.* (1998) and Lyu *et al.* (2007) made a distinction between the carboxylic end group concentration, C_{COOH} , and the acid catalyst concentration, C_{H^+} and suggested that C_{H^+} should replace C_{COOH} in eqn. (2-2). Using the equilibrium condition for the acid disassociation: $K_a = C_{COOH} / (C_{H^+}C_{COO^-})$, where K_a is the acid disassociation constant, and noticing that $C_{H^+} = C_{COO^-}$, the acid catalyst concentration can be calculated as $C_{H^+} = (K_aC_{COOH})^{0.5}$. Consequently Lyu *et al.* (2007) used

$$\frac{dC_{COOH}}{dt} = kC_w C_e (K_a C_{COOH})^{0.5} . \quad (2-3)$$

For commonly used resorbable polymers such as PLA, PGA and their copolymers, water ingress is much faster than the hydrolysis reaction. It can be assumed that water is always abundant for the hydrolysis reaction and the actual concentration of water does not affect the reaction rate. In the hydrolysis reaction, the concentration of the ester bonds, C_e , reduces due to chain cleavage and oligomer production. Assuming C_e remains constant and noticing that

$$M_n = \frac{M_0 \times C_e}{C_{COOH}} , \quad (2-4)$$

in which M_n is the number averaged molecular weight and M_0 is the molecular weight of a repeating unit of the polymer, eqns. (2-1), (2-2) and (2-3) can be integrated respectively to give three different relations between M_n and time t (Lyu *et al.*, 2007):

$$\frac{1}{M_n} = \frac{1}{M_{n0}} + \frac{1}{M_0} kt , \quad (2-5)$$

$$\log(M_n) = \log(M_{n0}) - kC_{e0}t , \quad (2-6)$$

and

$$\left(\frac{1}{M_n} \right)^{\frac{1}{2}} = \left(\frac{1}{M_{n0}} \right)^{\frac{1}{2}} + \frac{1}{2} \left(\frac{K_a C_{e0}}{M_0} \right)^{\frac{1}{2}} kt . \quad (2-7)$$

The reaction constant k is related to temperature through the Arrhenius relation

$$k = k_0 e^{-\frac{E}{RT}} , \quad (2-8)$$

where R is the universal gas constant ($R = 8.314 \text{ Jmol}^{-1} \text{ K}^{-1}$) and T is the absolute temperature. Once the pre-exponential constant k_0 and activation energy E are determined from the data obtained at elevated temperatures, eqns. (2-5), (2-6) or (2-7) can be used to extrapolate the data to physiological temperatures.

However the analytical relations (2-5)-(2-7) assume that the concentration of ester bonds, C_e , available for the hydrolysis reaction remain constant which is not true for the intermediate and later stages of the degradation as more and more oligomers are being produced. When the change in the ester bond concentration cannot be ignored, equations (2-1)–(2-3) are no longer closed and a relation between the chain scission rate and the oligomer production rate is required to solve these equations. Furthermore even for the early stage of the degradation equations (2-5)-(2-7) are invalid if (a) oligomers diffuse out of the material or (b) the amorphous polymer chains continue to crystallise. It has been well recognised that small and water soluble oligomers can diffuse away during degradation, reducing the acidity of the local environment (C_{H^+}) and hence the rate of the hydrolysis reaction (Li *et al.*, 1990^a; Grizzi *et al.*, 1995). In addition, PGA, PLLA and polycaprolactone (PCL) are all semi-crystalline polymers, although their copolymers are sometime intrinsically amorphous. The degree of crystallinity can increase significantly during biodegradation in both initially amorphous and semi-crystalline polymers (Zong *et al.*, 1999). This is because the cleavage of the polymer chains provides extra mobility to the chains and leads to further crystallisation (Zong *et al.*, 1999). The crystalline phase is difficult for water to penetrate and hydrolyse. Therefore the number of ester bonds available for hydrolysis, i.e. C_e in equations (1) to (3), can be reduced by the crystallisation even at the very early stage of the degradation and should not be treated as a constant.

2.2. REACTION-DIFFUSION MODEL

Joshi and Himmelstein (1991) presented a model for the analysis of the basic physicochemical properties that predicting controlled release of bioactive agents from degradable polymer systems. The following reaction-diffusion equation was applied to the model:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x} D_i(x, t) \frac{\partial C_i}{\partial x} + v_i \quad (2-9)$$

where C_i is the concentration of species i , D_i is the diffusion coefficient of the

corresponding species, x is the distance from the center of the matrix of total thickness $2a$, v_i is the net sum of synthesis and degradation rate of species i and t is the degradation time. The diffusion coefficient was dependent on the concentration of species. v_i can be obtained from the hydrolysis rate equations. Furthermore Gao and Fagerness (1995) provided another expression of concentration dependent diffusion coefficient based on NMR measurements:

$$\frac{D_{s,w}}{D_{w,0}} = k'_w \exp(k_w w_w) \quad (2-10)$$

$$\frac{D_d}{D_{d,0}} = \exp(-k_{d,p} w_p - k_{d,1} w_1 - k_{d,d} w_d) \quad (2-11)$$

where $D_{s,w}$ and $D_{d,0}$ are diffusion coefficients of water and incorporated drug respectively. Parameters k with different subscripts are different constant factors. Obviously, these two diffusion coefficients depend on the concentrations of water, drug and polymer. Applying equation (2-10) and (2-11) to previous hydrolysis reaction model, good agreements between model predictions for polymer and drug release and experimental data were found. The expressions for the diffusion coefficients are however empirical and cannot deal with different polymer systems. Perale *et al.* (2009) developed a polymer degradation model for solid devices by the description of polymer degradation kinetics coupled with the diffusion of water, monomers and oligomers through the polymeric matrix. Their model describes the evolution of the molecular weight distribution function through the device and during time. The considered polyester degradation kinetics of PLLA is opposite to that of polymerization. These models however did not consider the autocatalytic nature of the hydrolysis reaction and the degradation-induced crystallisation.

2.3. MONTE CARLO MODEL

Mohammadi and Jabbari (2006) established a three dimensional Monte Carlo model for the degradation of porous PLA scaffolds. The simulated volume was divided into surface and bulk elements. PLA chains were seeded in the simulation volume using Schultz-Flory

distribution. If degree of polymerization for the polymer chains was smaller than five then this chain was assumed to be soluble in the degradation medium and was not seeded in the simulation volume. Kinetics of autocatalysed hydrolytic degradation of polyester proposed by Cha and Pitt was written as follows (1990):

$$R_d = \frac{d[E]}{dt} = \frac{d[COOH]}{dt} = k_d [COOH][H_2O][E] \quad (2-12)$$

where R_d and k_d are hydrolysis reaction rate and its corresponding rate constant, respectively. $[COOH]$, $[H_2O]$ and $[E]$ are the concentrations of carboxylic end group, water and ester bond. According to Gillespie's kinetic Monte Carlo algorithm for chemical reactions (Gillespie, 1976), the degradation process can be simulated by randomly splitting an ester bond in a time interval dt . Kinetic rate equations for surface and bulk element are therefore given by:

$$R_{d,Bulk} = k_d ([COOH]_s + [COOH]_{RO})[H_2O][E] \quad (2-13)$$

$$R_{d,Surface} = k_d [COOH]_s [H_2O][E]_s \quad (2-14)$$

The Monte Carlo model can calculate carboxylic group concentration, ester bonds concentration, oligomer release, mass loss, pH values and molecular weight *et al.* as functions of time for polymers of various porosities. By using the Monte Carlo method, one can examine the intrinsic relations among all the variables. The diffusion mechanism was based on arbitrary rules and they didn't validate the model with experimental data.

2.4. A MONTE CARLO MODEL BY SIEPMANN *et al.* (2002)

Siepmann *et al.* (2002) used the Monte Carlo techniques to simulate the random degradation behaviour of a large population of ester bonds. They used individual, randomly distributed 'lifetimes' to describe polymer erosion/degradation. As soon as an element (they called it a rectangular pixel) contacts with water, its 'lifetime' starts to decrease. After the latter had expired, the pixel was assumed to erode instantaneously. The 'lifetime', $t_{lifetime}$, of a pixel was calculated as a function of the random variable $\mathcal{E}$ which was a integer between 0 and 99 (2002):

$$t_{lifetime} = t_{average} + \frac{(-1)^\varepsilon}{\lambda} \ln\left(1 - \frac{\varepsilon}{100}\right) \quad (2-15)$$

where $t_{average}$ is the average ‘lifetime’ of the elements and λ is a material constant depending on the physicochemical properties. In addition, they simulated drug release process using Fick’s second law for the axisymmetric geometry:

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial r} \left(D \frac{\partial c}{\partial r} \right) + \frac{D}{r} \frac{\partial c}{\partial r} + \frac{\partial}{\partial z} \left(D \frac{\partial c}{\partial z} \right) \quad (2-16)$$

The diffusion coefficient D in Fick’s second law was taken to depend on time, direction and positions of a pixel:

$$D(r, t) = D_{crit} \varepsilon(r, t) \quad (2-17)$$

$$D(z, t) = D_{crit} \varepsilon(z, t) \quad (2-18)$$

where D_{crit} represents a critical diffusion coefficient, being characteristic for a specific drug-polymer combination. This model can also capture the porosity of the system. The model captured the following major mechanisms including: drug diffusion, polymer degradation, polymer porosity analysis, nonconstant diffusion coefficient and three-dimensional geometry.

2.5. MOLECULAR DYNAMICS MODEL FOR CRYSTALLISATION

Larini and Leporini (2006) presented a molecular dynamics (MD) simulation of the crystallisation process of a single polyethylene (PE) chain with 500 monomers. The behaviour of a single PE chain in solution was simulated by means of a united-atom model. The solvent was mimicked by suitable friction and random forces acting on the monomers. The bond length distance, the bond angle and the torsional barrier were defined for every quadruplet of the adjacent beads. Lennard-Jones potential was applied to pair of beads not interacting with any of the preceding potentials. The time and temperature unit were given by 2.21ps and 56.3K respectively. They concluded that from the results the folding process involved intermediate metastable crystalline states and ended up in an equilibrated lamellar with ten stems. Though MD simulation is indeed more realistic than other models that

depend on a set of assumptions, it cannot simulate diffusion mechanism and whole degradation process because of its limitations.

2.6. MODELS FOR DRUG RELEASE FROM SWELLABLE POLYMERS

Diffusion models for drug release: Siepmann and Peppas (2001) reviewed various mathematical models for drug release from hydroxypropyl methylcellulose (HPMC) based pharmaceutical devices. Higuchi (1961) developed the very first mathematical equations for release rate of drugs from planar matrix systems. This equation has been extended to different geometries and even porous structures later on:

$$\frac{M_t}{M_\infty} = k\sqrt{t} \quad (2-19)$$

in which k is a constant reflecting the design variables of the system and t is time. Thus, the fraction of drug release is proportional to the square root of time. When applying such equation to drug release system, some conditions must be satisfied, including: 1) the swelling or dissolution of polymer carrier is negligible; 2) the diffusion coefficients of water and drugs are constant. Obviously HPMC based controlled drug release system is highly swellable and polymer chains will dissolve into solvent eventually. Consequently those assumptions are not valid for most controlled drug release system on HPMC. A modified Higuchi equation, so-called power law, was then provided:

$$\frac{M_t}{M_\infty} = kt^n \quad (2-20)$$

where k is constant incorporating the geometric and structural characteristics of device. The power law can be considered as a superposition of two different mechanisms: Fickian diffusion and case-II transport. n , varies from 0.5 to 1 for slab geometry and take other values for different geometries. Although power law is more complicated than the simple Higuchi equation, the constant diffusion coefficient is its limitation. HPMC swells to a significant extent volume, the diffusion coefficients of water and drugs are strongly concentration dependent. A different empirical model was developed by Peppas and Sahlin (1994):

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (2-21)$$

In this relationship, k_1 , k_2 and m are constants. This equation can be applied in controlled drug release system with partially coated HPMC (Peppas and Sahlin, 1994). But similarly it would lose accuracy from constant diffusion coefficients. Additionally, some comprehensive mechanistic models have been developed. Ju *et al.* (1995^a, 1995^b, 1997) developed a mathematical model to describe the HPMC-based drug release profile incorporating the effects of swelling and dissolution behaviours. The major improvement of this model is the introduction of a polymer disentanglement concentration to describe polymer dissolution.

Models for polymer swelling: One of the significant properties of HPMC based controlled drug release tablet is its high swellability. Narasimhan and Peppas (1997) used molecular theories in a continuum framework. Moving boundary theory, free volume theory, Flory-Rehner equation and disentanglement rate of polymer were all applied to their models, in which polymer molecular weight, glassy transition temperature, and water/polymer interaction parameters were molecular parameters which cannot taken into account in previous phenomenological models. They also concluded that the predictions agreed with experiment data well. No doubt that they have made a progress in modelling the polymer dissolution in drug release system, similarly they did take the diffusion coefficients as constants which is not valid during the release process. However, they provided information that it is necessary to relate the molecular properties, chemistry properties for example, to continuous model. Then it is possible to learn the intrinsically relationships among different components and the most important issue is that all the parameters can be obtained from experiments directly or indirectly. Laaksonen *et al.* (2009) presented a cellular automata model for modelling swelling-controlled drug release. They divided a release device into square cells. Each cell represents one of six states in the domain including water, solid drug, mobile drug, polymer, wet polymer and wet polymer with drug. Cells were allowed to change their states according to certain statistic rules. In their model,

diffusion and swelling mechanisms were modelled by using randomly walk while the kinetics of chemical and physical processes were modelled by the probabilities of conversion from one state to another. Then they studied how different parameters affected release profile. The model parameters could be obtained from control experiment directly. They also compared their prediction with experiment data obtained by Narasimhan and Peppas (1997) to show the validation. Though their cellular automata model provides a new way to design controlled drug release systems, the model parameters they need have to be obtained from control experiments for the specific polymers which limited the model from predicting different controlled release systems, with different chemical structure for example.

2.7. PREVIOUS WORK AT LEICESTER

Ying Wang: In his PhD thesis, Ying Wang presented a phenomenological diffusion-reaction model for the biodegradation of biodegradable polymers. The biodegradation process was modelled using a set of simplified reaction-diffusion equations. These partial differential equations were non-dimensionalised giving two normalised parameters which controlled the interplay between the hydrolysis reaction and oligomer diffusion. The equations are firstly solved for simple cases of plates and pins. The numerical results were presented in the form of biodegradation maps which show the conditions where the biodegradation was controlled by auto-catalysed hydrolysis, non-catalysed hydrolysis, a combination of auto-catalysed and non-catalysed hydrolysis, or a combination of hydrolysis and oligomer diffusion respectively. The degradation maps provided a clear guide for the design of biodegradable fixation devices used in orthopaedic surgeries. Finally the diffusion-reaction equations were solved using the finite element method for strip and square meshes, showing how the model can be used to assist the design of sophisticated fixation devices (Wang *et al.*, 2009).

He also presented a model for the change in Young's modulus of biodegradable polymers due to hydrolysis cleavage of the polymer chains. The model was based on the entropy

spring theory for amorphous polymers. It was assumed that isolated polymer chain scissions and very short polymer chains did not affect the entropy change of a linear biodegradable polymer during its deformation. It was then possible to relate the Young's modulus to the average molecular weight in a computer simulated hydrolysis process of polymer chain sessions. The experimental data obtained by Tsuji (Tsuji, 2002) for poly(L-lactic acid) and poly(D-lactic acid) were examined using the model. It was shown that the model can provide a common thread through Tsuji's experimental data. A further numerical case study demonstrates that the Young's modulus obtained using very thin samples, such as those obtained by Tsuji, cannot be directly used to calculate the load carried by a device made of the same polymer but various thicknesses. This is because the Young's modulus varies significantly in a biodegradable device due to the heterogeneous nature of the hydrolysis reaction. The governing equations for biodegradation and the relation between the Young's modulus and average molecular weight can be combined to calculate the load transfer from a degrading device to a healing bone (Wang *et al.*, 2009).

Lifeng Ding: In his PhD thesis, Lifeng Ding provided a molecular dynamics study on the change in Young's modulus of semi-crystalline biodegradable polymers, such as poly(glycolic acid), due to hydrolysis chain scissions. Using a combination of molecular dynamics and Monte Carlo steps, a molecular model was constructed which consisted of two polymer crystals connected by an amorphous region between them. The polymer chains in the amorphous region were cut randomly. At various numbers of chain scissions, the system was set to be equilibrium and then be subjected to unidirectional deformation in molecular dynamics simulations, which can be regarded as a series of virtual tensile tests. It was found that if the temperature is below the glass transition temperature, the Young's modulus of the system reduces quickly with the chain scissions because the Young's modulus of the semi-crystalline polymer is dominated by the internal energy at such temperatures. If the temperature was above the glass transition temperature, the Young's modulus reduction lagged behind the polymer chain scissions because the Young's modulus was controlled by the entropy of the amorphous phase at such temperatures. The numerical

study therefore provided a molecular understanding in the widely observed behaviours of semi-crystalline biodegradable polymers.

2.8. UN-RESOLVED ISSUES

Mathematical models for the degradation of biodegradable polymer are in their infancy. Many issues are un-resolved including:

- a) The interaction between polymer degradation and crystallisation has never been modelled.
- b) A connection between the molecular model for polymer degradation and macroscopic models for the various diffusion processes is missing.
- c) There exists no model to deal with the temperature effects on polymer degradation.
- d) There exists no model for the inter-play between polyester and tricalcium phosphate during the degradation of these composite materials.
- e) Drug release models from swelling polymer matrix are limited to one dimensional problems.

2.9. PURPOSE AND STRUCTURES OF THIS THESIS

The purpose of this thesis is to address all the issues highlighted above. Because these issues cover a wide range of very different areas, it is decided to organize the thesis around individual chapters, providing an in-depth introduction and literature review at the beginning of each chapter.

Chapter three presents a two-scale model for polymer degradation connecting molecular models for polymer chain scission and macroscopic models for diffusion.

Chapter four presents a model for simultaneous crystallisation and polymer degradation.

Chapter five addresses the effect of temperature on degradation rate

Chapter six deals with the degradation of TCP /polyester composite.

Chapter seven presents a preliminary study on modeling drug release from a swelling polymer matrix.

Chapter eight summarises the major conclusions of this thesis.

CHAPTER THREE – A MULTISCALE MODEL FOR POLYMER DEGRADATION

This chapter presents a computer model for the biodegradation of polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers. The model can take polymer details such as molecular weight distribution, different end and random scission rates and co-polymer ratio as input data. A multi-scale approach is developed: polymer chain scission and oligomer production which occur at the molecular scale are modelled using a kinetic Monte Carlo scheme, oligomer diffusion that occurs at the device scale is modelled using a diffusion equation, and the two are connected at the finite difference nodes of the diffusion equation. The two scale model can be used to predict the temporal evolution and spatial distribution of molecular weight distribution in a device as well as the weight loss as a function of time. It is shown that the kinetic Monte Carlo scheme can accurately predict the effect of copolymer ratio on the degradation rate. Grizzi and his co-workers (Grizzi *et al.*, 1995) observed in their experiments that a PLA film of 0.3 mm thick degrades much slowly than that of 2 mm thick. The numerical study shows that the conceptional reaction diffusion model suggested by Grizzi *et al.* (Grizzi *et al.*, 1995) needs to be extended in order to fully explain the size effect.

3.1.INTRODUCTION AND OUTLINE OF THIS CHAPTER

An intensive effort is being made to develop scaffolds for tissue engineering using these bioresorbable polymers. The scaffolds are typically in the forms of either porous foams or a network of fibbers. They can be used either directly as implant to encourage tissue growth or to culture specific tissue in vitro before being moved into the human body for implantation. In these applications, it is very important to be able to tailor the degradation rate of the scaffold so that the cells can grow and differentiate properly but the scaffold can disappear once it is no longer required. Resorbable fixation devices, such as screws and plates, are being more and more widely used in surgery. One of the advantages of using bioresorbable fixation in comparison with metallic one is that the load can be gradually transferred from the fixation device to the healing bone to stimulate the healthy remodelling of the bone. Taking this advantage requires a good control of the degradation rate of the fixation device which is currently lacking. The current generation of fixation devices is

often over-designed in terms of their life time to be on the “safe-side”. Many studies have been carried out to investigate the degradation mechanism of bioresorbable polymers (Cameron and Kamvari-Moghaddam, 2008). PLA, PGA and their copolymers degrade through bulk erosion. Water penetrates the device and reaches a saturation level throughout the device very quickly in comparison with the polymer degradation (Wiggins *et al.*, 2006). Molecular weight reduction follows immediately the water saturation. Water molecules attack the ester bonds of the polymer chains through hydrolysis reaction causing the cleavage of the polymer chains. It has been generally believed that the chain scission randomly occurs at the ester bonds. However it has been reported that the scission could occur dominantly at the chain ends (Shih, 1995). The degradation rate can be tuned by copolymerisation of different homopolymers such as PLA and PGA with different copolymer ratio. However the degradation rate of the copolymer and the copolymer ratio follows a complicated relation (Miller *et al.*, 1977). The chain cleavage produces carboxylic acid terminal groups as well as alcohol terminal groups. The acid end-groups have a high degree of dissociation resulting in an acidic environment and acid-catalysed hydrolysis. The hydrolysis reaction is therefore autocatalytic. The chain cleavage produces shorter polymer chains and eventually oligomers. The water soluble oligomers can diffuse out of the device reducing the acidity of the hydrolysis reaction. The oligomer diffusion has been used to explain the experimental observation that thick plates degrade faster than thin films and that the hydrolysis reaction occurs faster at the core of a device than at the surface (Grizzi *et al.*, 1995; Li *et al.*, 1990^a; Li *et al.*, 1990^b; Li *et al.*, 1990^c).

The degradation of biodegradable devices is a multi-scale process. Diffusion of the hydrolysis products such as oligomers occurs over the device scale while hydrolysis reactions occur at the molecular scale (Wang *et al.*, 2008; Han *et al.*, 2009; Han *et al.*, 2010). Buehler and Yung (2009) reviewed various multiscale modelling approaches in the context of biomaterials including regenerative medicine. Modelling chemical reactions naturally falls into the field of molecular dynamics such as the reactive models presented by Buehler (2007). However the typical time scale of the hydrolysis reaction is several weeks which are far beyond the time scale that a molecular dynamics simulation can reach. The kinetic Monte Carlo approach provides an effective alternative at the price of losing

some chemical input such as the chemical composition of the polymer. Mohammadi and Jabbari (2006) developed a kinetic Monte Carlo model for the degradation of PLA scaffolds and demonstrated the potential of the kinetic Monte Carlo scheme in gaining insight into degradation behaviour. In such a model the evolution of the molecular weight distribution as well as the weight loss can be followed. Mohammadi and Jabbari (2006) assumed that the weight loss comes from the dissolution of oligomers from a surface layer and did not consider oligomer diffusion in the polymer matrix. In the current chapter the phenomenological hydrolysis reaction equations in previous model by Wang *et al.* (2008) are replaced by a local kinetic Monte Carlo model similar to that used by Mohammadi and Jabbari (2006) for the polymer chain scission. Polymer characteristics, such as the initial molecular weight distribution, degree of crystallinity and copolymer ratio, are considered as the input data. A two scale approach is developed - the macroscopic diffusion equation of oligomers is solved using a finite difference method. At each finite difference node, production of oligomers is computed discretely using a kinetic Monte Carlo scheme. After a number of Monte Carlo steps, the produced oligomers are counted according to a threshold of degree of polymerisation. The chain scission rates depend on the number of oligomers to reflect the autocatalytic effect. The finite difference and kinetic Monte Carlo models are coupled such that the Monte Carlo steps feed oligomer production to the macroscopic diffusion equation while the finite difference steps provide the Monte Carlo model with the local oligomer concentration. The model is then used to study the effect of copolymer ratio on the degradation rate and the size effect and heterogenous degradation.

3.2.A KINETIC MONTE CARLO MODEL FOR POLYMER DEGRADATION

We consider a small representative volume of a polymer system of homopolymer, copolymer or blend of PLA and PGA. The polymer system is characterised by (a) the weight distribution of the polymer chains, (b) the size distribution of the polymer crystals and (c) the distributions of degree of polymerisation of the constituent polymers. In practice only the weight distribution of the polymer chains, the degree of crystallinity and the copolymer ratio are available for many polymer systems. In such case, assumptions have to be made about the unknown distributions. A computer model of the polymer system can then be generated accordingly. The volume of the representative unit is calculated as $V_0 = N_{e0} / C_{e0}$,

where N_{e0} and C_{e0} are the total mole number of ester bonds in the model and the mole concentration of the ester bonds respectively. There could be many different types of ester bonds in the system which have different hydrolysis rates. For example, in a PLA/PGA copolymer, the PGA degrades much faster than the PLA (Cameron and Kamvari-Moghaddam, 2008). In semi-crystalline polymers, the crystallised polymer chains degrade much slower than the amorphous polymer chains (Li *et al.*, 1990^c). The ester bond next to a chain end often degrades much faster than those in the middle of the chain (Shih, 1995). Eqn. (3-1) reflects the fact that the hydrolysis reaction can have a non-catalytic part and an autocatalytic part:

$$\frac{dC_{COOH}}{dt} = k_1 C_e + k'_2 C_e (K_a C_{COOH})^{0.5} \quad (3-1)$$

Eqn. (3-1) can account for limited mobility of the oligomers in the polymer and therefore their localised availability to act as catalyst. It can also accounts for a blend of polymers that hydrolyze differently. The oligomers are water soluble chains with less than 8 degrees of polymerisation (Cameron and Kamvari-Moghaddam, 2008). It is assumed that only the -COOH end groups on the oligomers can act as the catalyst because only these end groups are mobile enough to participate in the hydrolysis reaction. Using C_{ol} to represent the molar concentration of all the chain units of all the oligomers and m to represent the average degree of polymerisation of the oligomers, the molar concentration of the -COOH end groups available as catalyst is given by $(C_{COOH})_{catalyst} = C_{ol} / m$, which leads to

$$\frac{dC_{COOH}}{dt} = k_1 C_e + \frac{k'_2 K_a^{0.5}}{m^{0.5}} C_e (C_{ol})^{0.5} = k_1 C_e + k_2 C_e (C_{ol})^{0.5} \quad (3-2)$$

In the last term of the above equation we have collected three parameters together and defined $k_2 = \frac{k'_2 K_a^{0.5}}{m^{0.5}}$. Using R_s to represent the molar concentration of chain scissions, we have $dR_s / dt = dC_{COOH} / dt$. The scission rate of the i -th type of the ester bonds can be written as (Han *et al.*, 2010)

$$\frac{dR_i}{dt} = k_i C_i + k_i^a C_i C_{ol}^{0.5} \quad (3-3)$$

in which R_i represents the mole number of total chain scissions of the i -th type of ester bonds per unit volume, t is the time, C_i is the mole concentration of the i -th type of ester bonds, C_{ol} is the mole concentration of the oligomers, and k_i and k_i^a represent the rate constants for the uncatalytic and autocatalytic hydrolysis reactions.

3.2.1. The kinetic Monte Carlo Scheme

Following the kinetic Monte Carlo (KMC) scheme (Gillespie, 1976), a chain cleavage of the i -th type of ester bonds occurs if

$$\sum_{j=1}^i \frac{dR_j}{dt} < \xi_1 \times \sum_{j=1}^N \frac{dR_j}{dt} < \sum_{j=1}^{i+1} \frac{dR_j}{dt} \quad (3-4)$$

in which $\xi_1 \in (0,1]$ is a uniform random number and N is the total number of the different types of ester bonds. The corresponding time step length of the chain cleavage is calculated by

$$\Delta t_i = -\frac{\ln(\xi_2)}{\sum_{j=1}^N \frac{dR_j}{dt}} \quad (3-5)$$

in which ξ_2 is another uniform random number. The kinetic Monte Carlo scheme executes one chain cleavage at each time step which is computationally inefficient. Various coarse grained schemes have been proposed. Chatterjee showed that the following coarse grained kinetic Monte Carlo scheme can reduce the computing time by a factor of 10^4 (Chatterjee and Vlachos, 2005):

- (i) Set a time step length by

$$\Delta t_i = \varepsilon \min_{i=1}^N \left(\frac{C_i}{\sum_{j=1}^N \frac{dR_j}{dt}} \right) \quad (3-6)$$

where ε is a small empirical number;

(ii) Calculate

$$P_i = \frac{\frac{dR_i}{dt} \Delta t_l}{\min_{i=1}^N(C_i)} \quad \text{and} \quad \Delta R^{\max} = \min_{i=1}^N(C_i); \quad (3-7)$$

(iii) Sample the number of chain cleavage, ΔR_i , from the binomial distribution of

$$f(\Delta R_i; P_i, \Delta R^{\max}) = \frac{\Delta R^{\max}!}{\Delta R_i! (\Delta R^{\max} - \Delta R_i)!} P_i^{\Delta R_i} (1 - P_i)^{\Delta R^{\max} - \Delta R_i} \quad (3-8)$$

(iv) Update time $t = t + \Delta t_l$ and return to step (i).

Fig. 3-1 shows the calculated average molecular weight as a function of time for a homopolymer using the kinetic Monte Carlo and coarse grained kinetic Monte Carlo schemes respectively. The initial molecular weight distribution is assumed to follow a normal distribution in the log space. In this example, the reaction constants were arbitrarily

taken as $k_{\text{random}} = k_{\text{end}} = 0.003/\text{week}$ and $k_{\text{random}}^a = k_{\text{end}}^a = 0.002 \sqrt{\frac{m^3}{\text{mol}}} / \text{week}$. It can be

observed from the figure that the coarse grained kinetic Monte Carlo scheme converges to the kinetic Monte Carlo one as ε is reduced to 0.003. Our numerical experience showed that ΔR_i calculated using eqn. (3-8) is in fact very similar to the simple deterministic calculation

of $\Delta R_i = \frac{dR_i}{dt} \Delta t$.

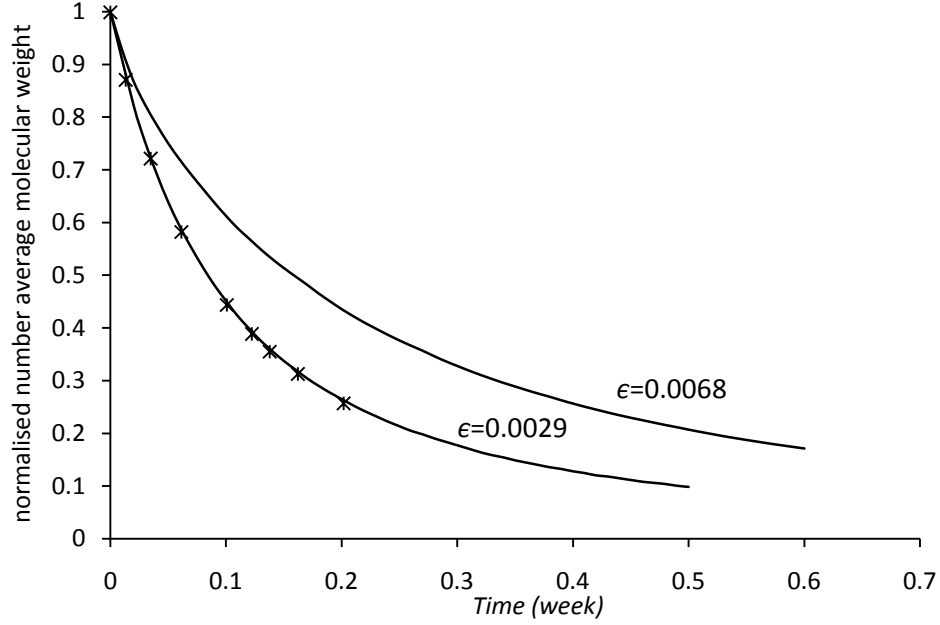


Fig.3-1 Normalised number average molecular weight as a function of time calculated using the KMC scheme (asterisks) and coarse grained KMC scheme with different values of ϵ (solid lines), showing the convergence of the coarse grained KMC scheme.

The chain cleavage produces shorter polymer chains. It is well established that chains shorter than a threshold degree of polymerisation, referred to as m which is usually taken as 8 (Kobayashi and Uyama, 2002), become water soluble and can diffuse in the polymer system. These short chains are referred to as oligomers. If all the chain scissions occur dominantly at the chain ends as suggested by some experimental studies (Shih, 1995), then the oligomer production rate is simply equal to the chain scission rate. If the chain scission occurs randomly, then the ester bond concentration, R_{ol} , of all the oligomers is related to the chain scission, R_s , by (Han *et al.*, 2010)

$$\frac{R_{ol}}{C_{e0}} = \frac{1}{2} \left(m + m^2 \right) \left(\frac{R_s}{C_{e0}} \right)^2, \quad (3-9)$$

in which C_{e0} is the initial mole concentration of ester bonds of polymer chains. Fig. 3-2 shows the $R_{ol} - R_s$ relation obtained using the kinetic Monte Carlo scheme for the end scission controlled case by setting $k_{random} = k_{random}^a = 0$, the random scission controlled case by setting $k_{random} = k_{end}$ and $k_{random}^a = k_{end}^a$, and an intermediate case by setting

$$k_{random} = 0.003 / \text{week}, k_{end} = 0.3 / \text{week}, k_{random}^a = 0.002 \sqrt{\frac{m^3}{mol}} / \text{week}, k_{end}^a = 0.2 \sqrt{\frac{m^3}{mol}} / \text{week}$$

respectively. Eqn. (3-9) is also plotted in the figure. It can be observed that the kinetic Monte Carlo results behave exactly as expected, i.e. providing a linear R_{ol} - R_s relation for the end scission controlled case and following Eqn. (3-9) in the random scission controlled case. It is however interesting to notice that a very small rate constant of random scission can shift the oligomer production to the random scission controlled extreme. This is because the concentration of ester bonds is much higher than that of the chain ends. In the general case, we suggested that

$$\frac{R_{ol}}{C_{e0}} = \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta \quad (3-10)$$

The empirical parameters α and β can be obtained by fitting the numerical results shown in fig. 3-2 using Eqn. (3-10).

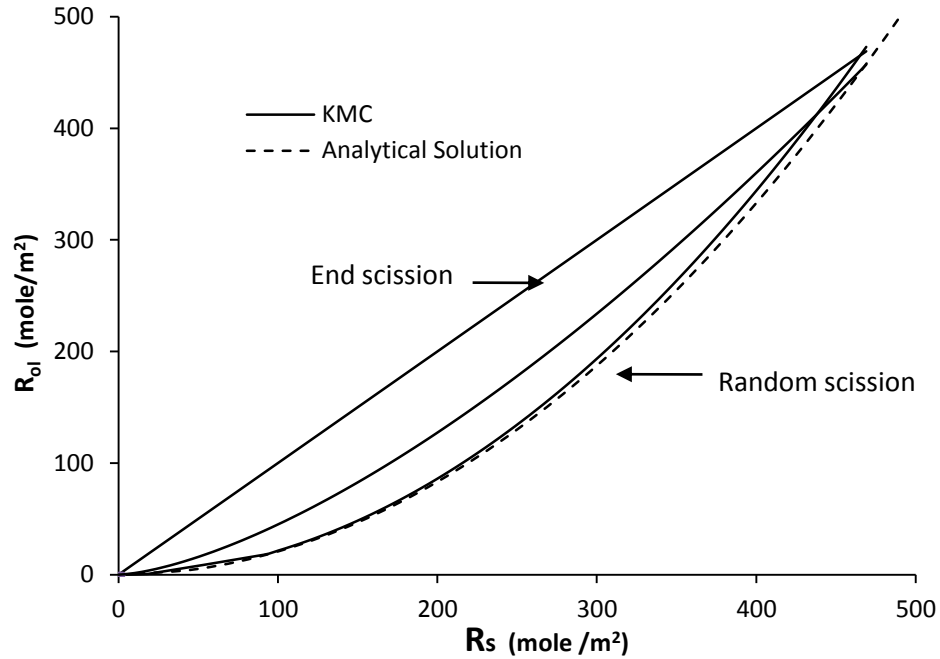


Fig.3-2 Oligomer production as a function of chain scission controlled by end scission, random scission and a very small random scission rate (the middle curve).

3.2.2. Effect of copolymer ratio on the degradation rate Poly(DL-lactic acid) (PDLLA) is the mostly used PLA as a biodegradable polymer due to its well established biocompatibility. PDLLA degrades slower than PGA. By copolymerisation of PDLLA and PGA it is possible to achieve a desired degradation rate. However the relationship between the degradation rate and the copolymer ratio is a complicated one. Fig. 3-3 shows the half degradation time of the copolymer, referred to as PLGA, as a function of the copolymer ratio obtained experimentally (the solid line) (Miller *et al.*, 1977) and by the kinetic Monte Carlo simulations (discrete symbols). The half degradation time is defined as the time taken for the polymer to halve its average molecular weight. In the simulation it is assumed that the PGA monomers are uniformly distributed in the polymer chains. The reaction constants for the PGA and PDLLA are determined by fitting the half degradation times for the pure PGA and PDLLA respectively. The PGA is semi-crystalline and typically increases its degree of crystallinity from 50% to 80% during degradation (Lee and Gardella, 2001). In the fitting it is assumed that the PGA has a constant degree of crystallinity of 70%. The reaction constants obtained from the fitting are provided in Table 3-1 and used to predict the half degradation times for PLGA of four different copolymer ratios. The experimental data in Fig. 3-3 shows that as the PDLLA is firstly introduced into the PGA the half degradation time of the copolymer reduces sharply. This is due to the reduced degree of crystallinity in the copolymer in comparison to that of the PGA. Due to the lack of data in the literature on the degree of crystallinity at different copolymer ratios, we focus the computer simulation on the high percentage of PDLLA where the copolymer is amorphous. At high percentage of PDLLA, introducing more PDLLA in the copolymer increases the half degradation time because the PDLLA degrades slower than PGA. It can be observed that this effect is accurately predicted by the kinetic Monte Carlo model. Fig. 3-4 presents the average molecular weights of PDLLA, PGA and their copolymers as functions of time calculated using the computer simulation. It can be seen that the complicated degradation behaviour of the copolymer is captured by the kinetic Monte Carlo model. Fig. 3-5 shows calculated molecular weight distributions at three different times for the six cases. It can be observed that the distribution remains normal in the log space except for pure PGA which developed a bimodal distribution because the crystalline phase does not degrade. This is further illustrated in Fig. 3-6 which shows the polydispersity index (PDI) as function of time. The

calculated PDIs vary during the degradation from 1.5 to 2 except for pure PGA in consistency with experimental observations (Grayson *et al.*, 2005; Saha and Tsuji, 2006).

Table 3-1. Model parameters used in the case studies

Parameters Case in	D_0 (m^2/week)	k_{random} (1/week)	k_{random}^a ($\sqrt{\frac{\text{m}^3}{\text{mol}}}/\text{week}$)	k_{end} (1/week)	k_{end}^a ($\sqrt{\frac{\text{m}^3}{\text{mol}}}/\text{week}$)	Polymers
Fig.3-1	0	0.003	0.002	0.003	0.002	PLA
Fig.3-2	0	0.003	0.002	0.3	0.2	PLA
Fig.3-3 to 3-6	Diffusion not considered	7×10^{-6}	7×10^{-6}	2.3×10^{-5}	2.3×10^{-5}	PDLLA
	Diffusion not considered	1.9×10^{-4}	1.9×10^{-4}	1.2×10^{-3}	1.2×10^{-3}	PGA
Fig.3-25,3-26	2×10^{-9}	$k = 0.042/\text{week}$		$k^a = 0.001(\sqrt{\frac{\text{m}^3}{\text{mol}}}/\text{week})$		PLA
Fig.3-28 to 3-31	2×10^{-9}	5×10^{-5}	2.5×10^{-5}	0.1	0.1	PLA

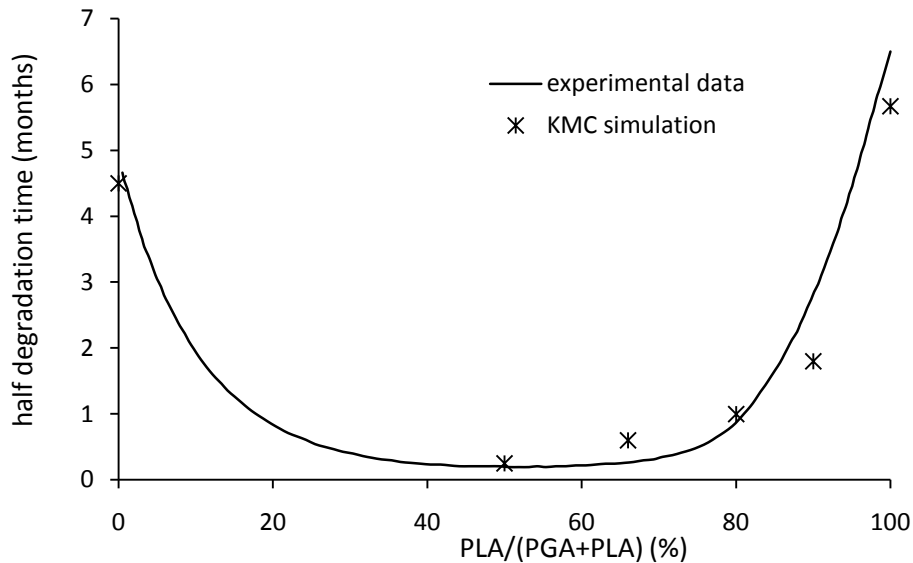


Fig.3-3 The half-life time of PDLLA and PGA homopolymers and their copolymer as a function of the copolymer ratio. The solid line is the experimental data and the discrete symbols are the KMC simulation.

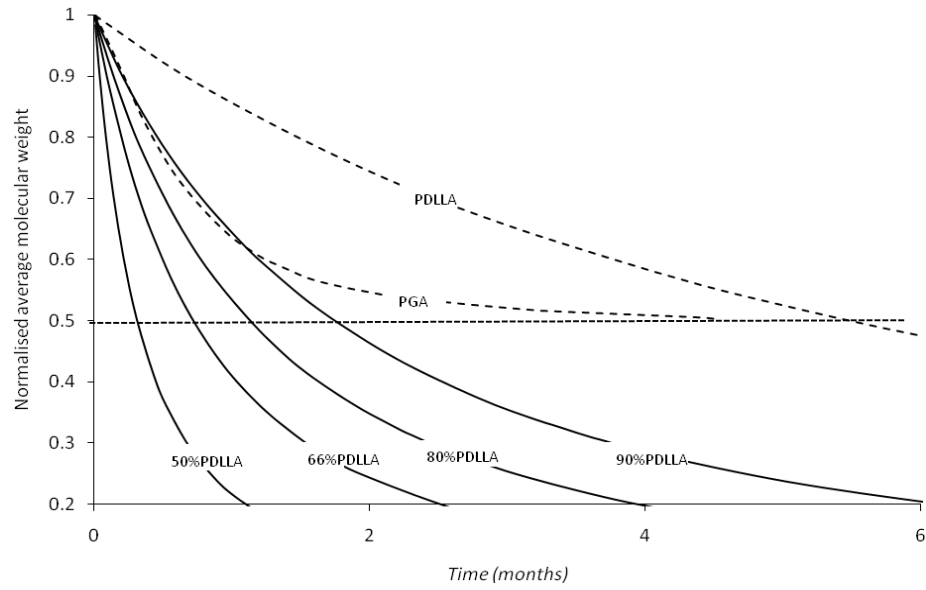


Fig.3-4 Normalised number average molecular weight as a function of time for PDLLA, PGA (solid lines) and their copolymers of different copolymer ratios (dashed lines) from the KMC simulation.

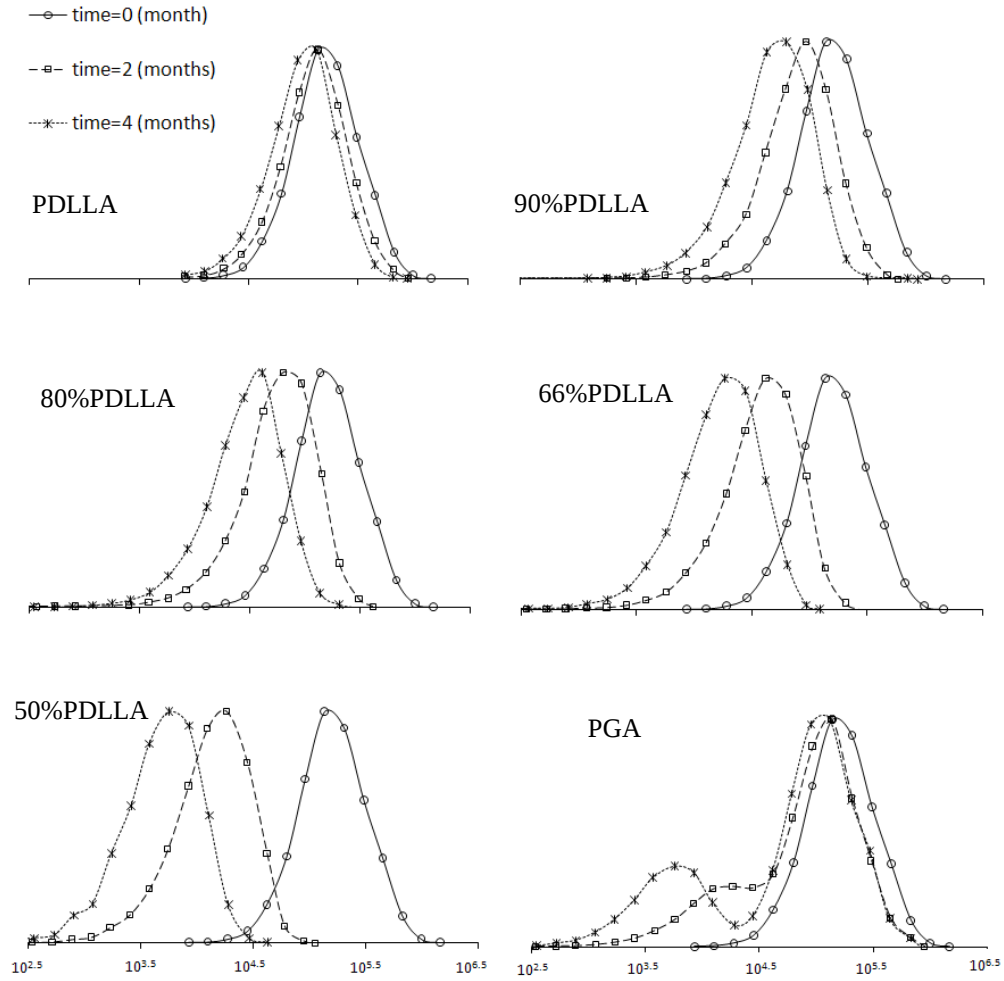


Fig.3-5 Molecular weight distributions of PDLLA, PGA and their copolymers of different copolymer ratio at three different degradation times obtained using the KMC scheme.

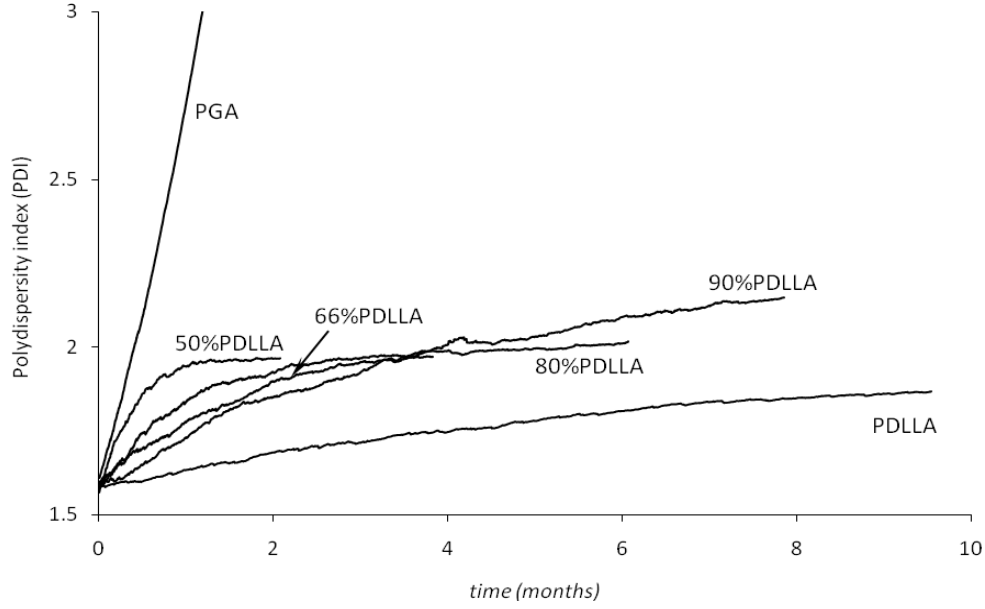


Fig. 3-6 Polydispersity index (PDI) as a function of time for PDLLA, PGA and their copolymers of different copolymer ratio obtained from the KMC simulations.

3.3.A TWO SCALE MODEL FOR DEVICE DEGRADATION

The Monte Carlo simulation in section 3-2 assumes that the oligomers stay in the material. In fact the water soluble oligomers can diffuse out of the device, altering the local pH value and hence slowing down the hydrolysis reaction. In the previous work (Wang *et al.*, 2008) the following governing equation was used to describe the change in the oligomer concentration:

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i} (C_{ol}) \right) \quad (3-11)$$

in which D is the diffusion coefficient of the oligomers that depends on the porosity of the polymer such that

$$D = D_0 + (1.3p^2 - 0.3p^3)(D_1 - D_0) \quad (3-12)$$

where p is porosity given by:

$$p = 1 - C_e / C_{e0} - C_{ol} / C_{e0} \quad (3-13)$$

D_0 the diffusion coefficient of oligomers in non-degraded amorphous polymer, D_1 is the diffusion coefficient of oligomers in liquid-filled pores and C_e is the mole concentration of

the ester bonds of all the polymer chains. Eqn. (3-11) can be discretised using either the finite element method or the finite difference method for a device. At each integration point of the finite element method or the finite difference node, the oligomer production rate in Eqn. (3-11) can be calculated from the kinetic Monte Carlo simulation at that local point. This is achieved by simply counting the number of chains shorter than a threshold degree of polymerisation m at each timestep. On the other hand, the change in the local concentration of oligomers due to the global diffusion can be calculated from Eqn. (3-11). Eqn. (3-3) describes a local process, Eqn. (3-11) describes a global process and the two are coupled at the integration points or the finite difference nodes. Fig. 3-7 shows the two scale model for the degradation of a plate schematically. We consider an infinitively large plate in which the oligomer diffusion occurs only in the thickness direction (marked as a-b). A finite difference scheme is used to discretise the spatial differentiation in Eqn. (3-11) with respect to x . At each finite difference node, tens of thousands of polymer chains are generated according to initial information about the polymer system. The chain scissions are executed using the kinetic Monte Carlo scheme at each node, which provides concentrations of oligomers and the different types of ester bonds on the polymer chains. The change in the oligomer concentration due to global diffusion is calculated using a finite difference representation of the second term of Eqn. (3-11). Direct Euler scheme is used for the time integration. The time step length required by the kinetic Monte Carlo scheme is typically much smaller than that by the global diffusion. Two different time steps are used for the global calculation of oligomer diffusion and the local kinetic Monte Carlo calculation of chain scission respectively. After a number of local time steps, the local concentrations are sent to the global calculation for oligomer diffusion. The changed oligomer concentrations of all the nodes are fed back to the local kinetic Monte Carlo scheme. The kinetic Monte Carlo scheme is then restarted and the entire procedure is repeated. Fig. 3-8 shows the flow chart of the two scale numerical scheme. The left column contains the kinetic Monte Carlo steps for chain cleavage calculation while the right column contains the steps for the global diffusion calculation. The two are interconnected at two interfacing points. The methodology can be readily extended to general 3-dimesional devices using the finite element method for the spatial discretisation of the diffusion equation.

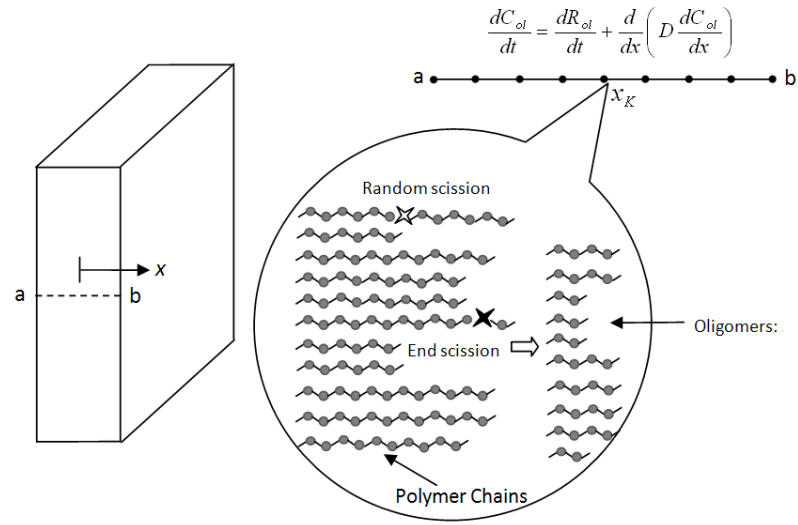


Fig.3-7 Schematic diagram of the two scale model for the biodegradation of a plate in which the diffusion of oligomers occur only in the thickness direction (a-b) of the plate.

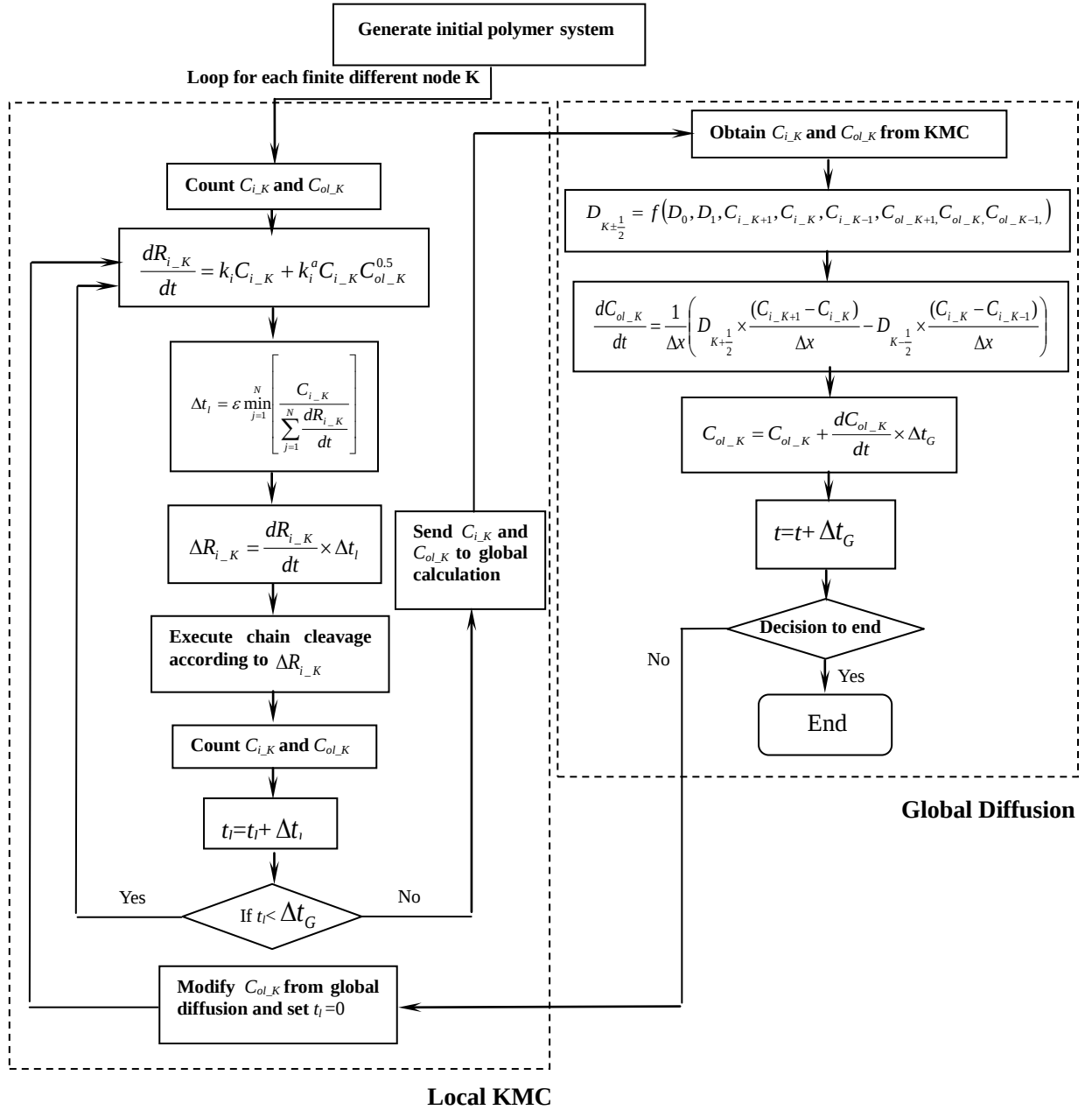


Fig.3-8 Flow chart of the two scale numerical scheme for the degradation of biodegradable polymers.

3.4. NUMERICAL PROCEDURES FOR COMPUTER IMPLEMENTING OF THE MODEL

In this section, details of computer implementing of the model are provided. It is assumed in this model that only end chain cleavage and random chain cleavage occurred in degradation, and we therefore use $a(I)$ and $a(II)$ to present the transition probabilities (reaction rates) for random scission and end scission, respectively. If

$$a(I) < \xi \times (a(I) + a(II)) < (a(I) + a(II)) \quad (3-14)$$

then end chain scission is executed, in which $\xi \in (0,1]$ is a URN (uniform random number). Similarly if

$$0 < \xi \times (a(I) + a(II)) \leq a(I) \quad (3-15)$$

random chain scission is selected. Follow the KMC method $a(I)$ and $a(II)$ are need to be updated using new concentrations. And subsequently another URN ξ_1 is generated; therefore the time is incremented by:

$$\Delta t = \frac{-\ln(\xi_1)}{a(I) + a(II)} \quad (3-16)$$

Assuming that a representative volume is taken into account in this model then we have:

$N_e = C_e \times V_0$: Number of ester bonds in a representative volume V_0

$N_{est} = C_{est} \times V_0$: Number of ester bonds which undergo random chain scission in V_0

$N_{end} = C_{end} \times V_0$: Number of ester bonds which undergo end chain scission in V_0

$N_{COOH} = C_{COOH} \times V_0$: Number of $COOH$ group in V_0 .

N_{m0} : A critical value of degree of polymerisation to define oligomer. ($N_{m0} = 8$)

N_{ol} : Number of ester bonds for oligomers.

Where $V_0 = \frac{N_e}{C_{e0} \times N_A} \text{ (m}^3\text{)}$

Model flow charts: A flow chart which gives a detail of the two scale model is offered in Fig. 3-9. Details of end scission and random scission are given as two flow charts in Fig. 3-10. A code has been developed by using C++ to solve the problem. The Kinetic Monte Carlo model is computing intensive and required supercomputing power. Coarse-grain model which is also known as approximately KMC is developed to save the computing expense. In each time increment for Coarse grain model, each chain scission occurs multiple times. The key point of approximately KMC is to choose the time increment. The time increment is much larger than that in KMC. The Flow chart for approximately KMC is shown in Fig. 3-11.

Model validations: Eqns. 3-17 to 3-22 are specifically modified equations for an extreme case in which polymer chains are randomly attacked by water molecules. This case is only used for model validation by comparing results from KMC model with a continuous model solved by FEMlab. FEMlab is a commercial package used to solve partial differential equations using the finite element method. The dashed line in Fig. 3-12 is the normalised number of polymer chains, N_0 . It is obviously, in Fig.3-12, that predictions from CGMC (Coarse grain Monte Carlo)/KMC and the continuous model do not fit well. From equation (3-16), we know that N_0 is a constant, whereas in CGMC model N_0 is decreasing versus time which is illustrated in the figure. In the very beginning N_0 stays constant which results in a good agreement between molecular weights predictions from KMC and FEMlab. At time=1.5, N_0 begins to decrease and the differentiation appears between both M_n curves simultaneously.

$$\frac{dR_s}{dt} = k_{end} C_{end} + k_{end}^a C_{end} (C_{COOH})^n \quad (3-17)$$

$$R_{ol} = R_s \quad (3-18)$$

$$\frac{dC_e}{dt} = -\frac{dR_{ol}}{dt} \quad (3-19)$$

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i} (C_{ol}) \right) \quad (3-20)$$

$$\text{Where } C_{COOH} = N_0 + C_{ol} \quad (3-21)$$

$$C_{end} = 2 \times N_0 \quad (3-22)$$

(decreases if some chain disappears, but in FEMlab the case is not considered which cause the difference between FEMlab and Monte-Carlo)

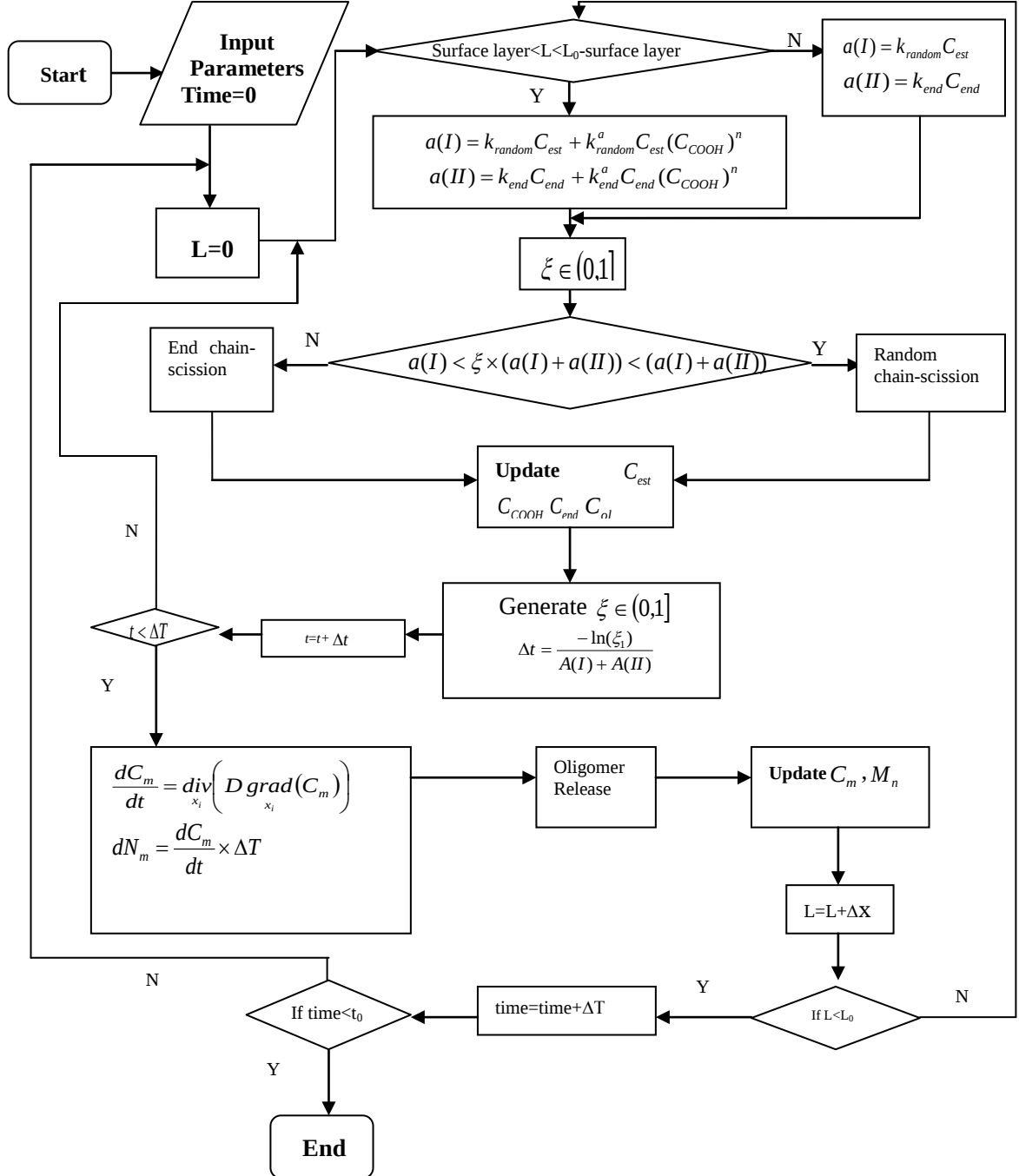


Fig.3-9 Detailed flow chart for two scale model using KMC

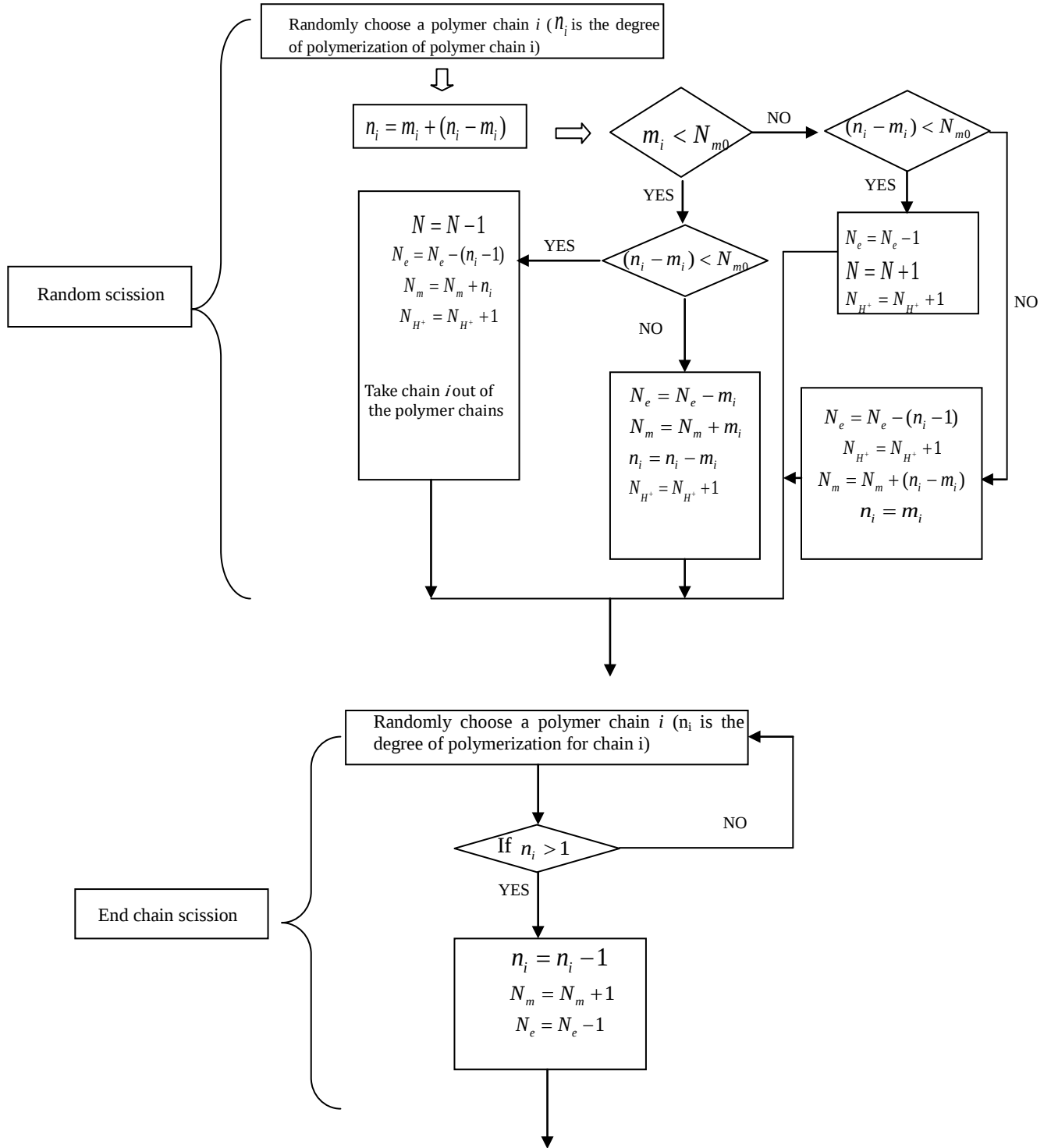


Fig.3-10 Detailed flow chart random scission and end scission respectively

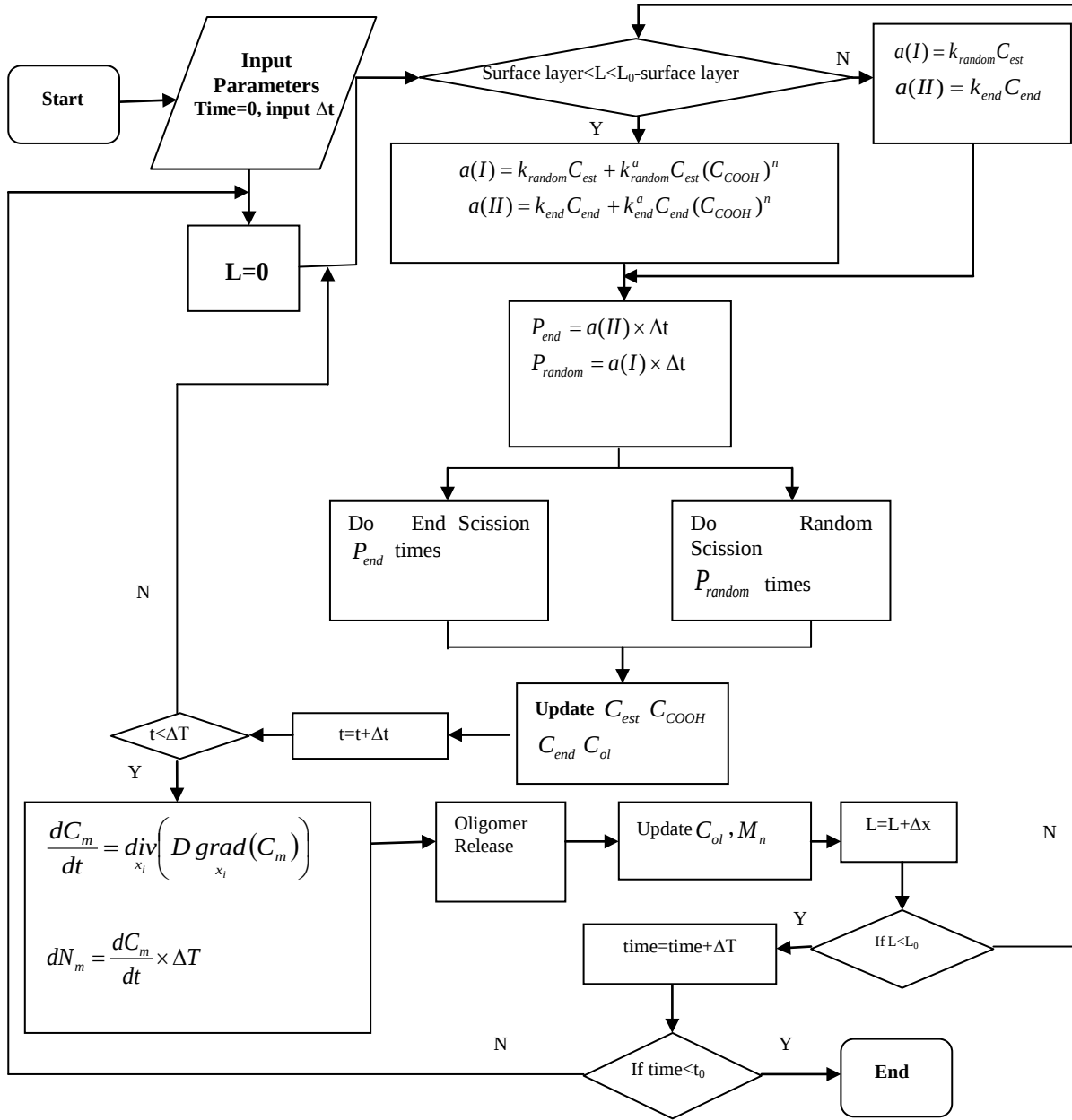


Fig.3-11 Flow chart for two scale model using Coarse grain KMC

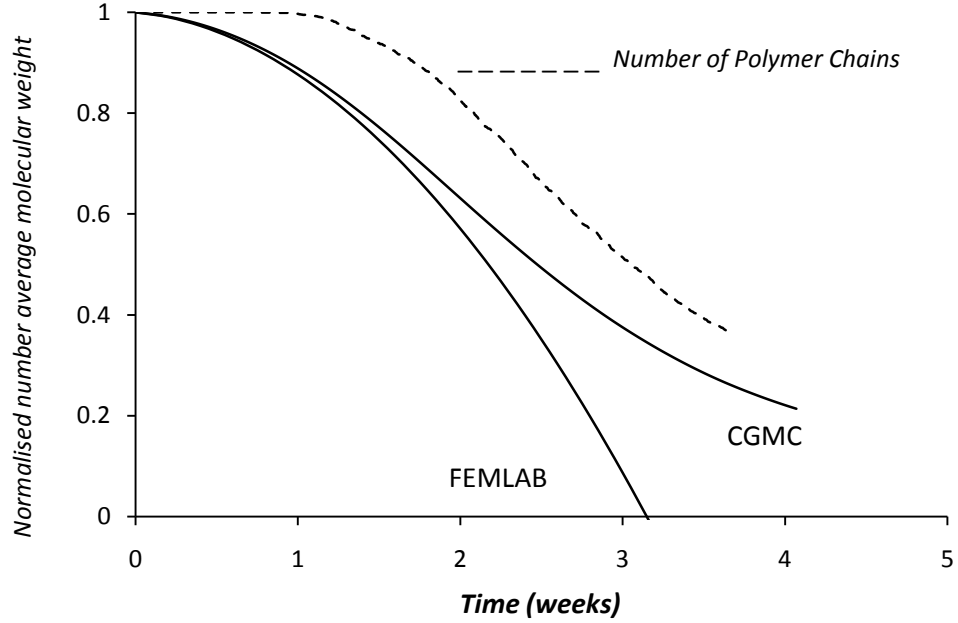


Fig.3-12 Comparison from CGMC and FEMlab: solid lines are normalized molecular weight and the dashed line is number of polymer chains

Eqns. 3-23 to 3-30 are modified governing equations for an extreme case in which water molecules attack the ester bonds of polymer chains randomly. In random scission degradation the chain scission rate for random and end chain scission are set to be the same.

$$\frac{dR_{random}}{dt} = k_{random} C_{est} + k_{random}^a C_{est} (C_{COOH})^n \quad (3-23)$$

$$\frac{dR_s}{dt} = k_{end} C_{end} + k_{end}^a C_{end} (C_{COOH^+})^n \quad (3-24)$$

$$\frac{dR_{ol}}{dt} = -\frac{dR_s}{dt} \quad (3-25)$$

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i} (C_{ol}) \right) \quad (3-26)$$

where:

$$C_{est} = C_e - C_{end} \quad (3-27)$$

$$N = N_0 + R_{random} - N_{ol} \quad (3-28)$$

$$C_{COOH} = N + N_{ol} + R_s \quad (3-29)$$

$$C_{end} = 2 \times N \quad (3-30)$$

N_{ol} is the number of oligomers produced from random scissions. The value of N_{ol} can be obtained from the local simulation directly by counting number in KMC simulation, which is the reason why in continuous model it is unknown. Therefore in FEMlab N_{ol} is set to zero in order to ensure a successful solving. Fig. 3-13 is the plot of N_{ol} versus time from KMC model. Fig.3-14 provides the comparisons between continuous model and KMC model for normalized molecular weight, oligomer concentration and weight loss. Fig. 3-13 illustrates that the gradient of N_{ol} is increasing with time. Because of the effect of N_{ol} , there is a slight difference between the predictions from continuous model and KMC model. The dashed line and the solid line cannot coincide with each other perfectly. Average molecular weight (Fig. 3-14 (a)) gives a better fitting than others. In this case, the decreasing of average molecular rate is modestly depending on random scission. Molecular weight decreases faster for random scission dominated degradation than end scission dominated degradation. Oligomer production rate is faster in end scission dominated degradation than that in random scission dominated degradation. To sum up, end scissions produces oligomers as random scissions reduces the average molecular weight. Therefore, when average molecular weight approaches zero, the concentration of oligomers is still very small in this random scission dominated case.

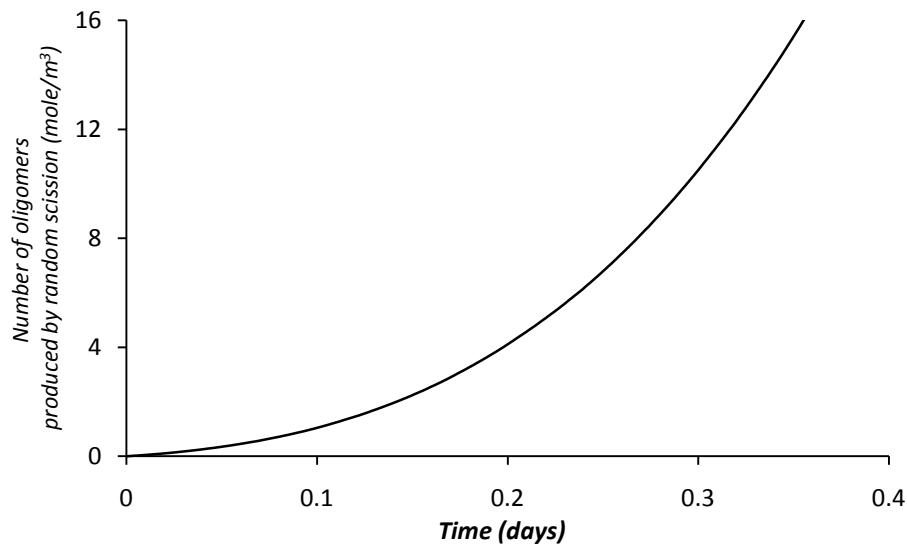
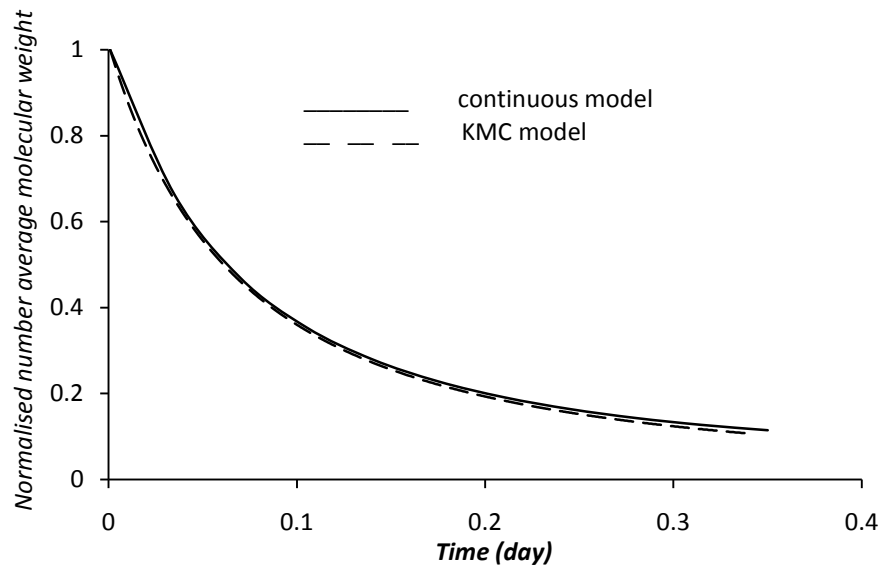
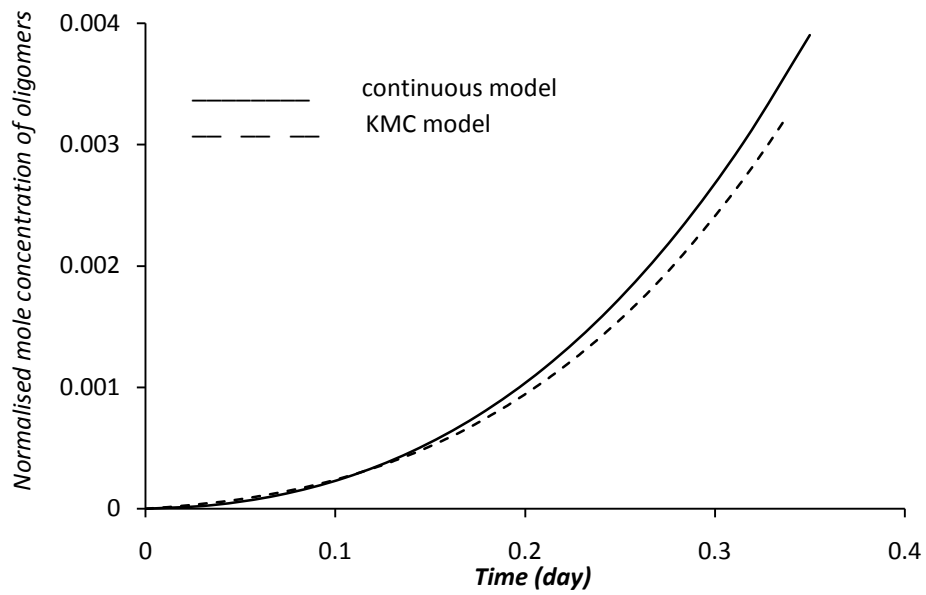


Fig. 3-13 Number of oligomers produced from random scission



(a)



(b)

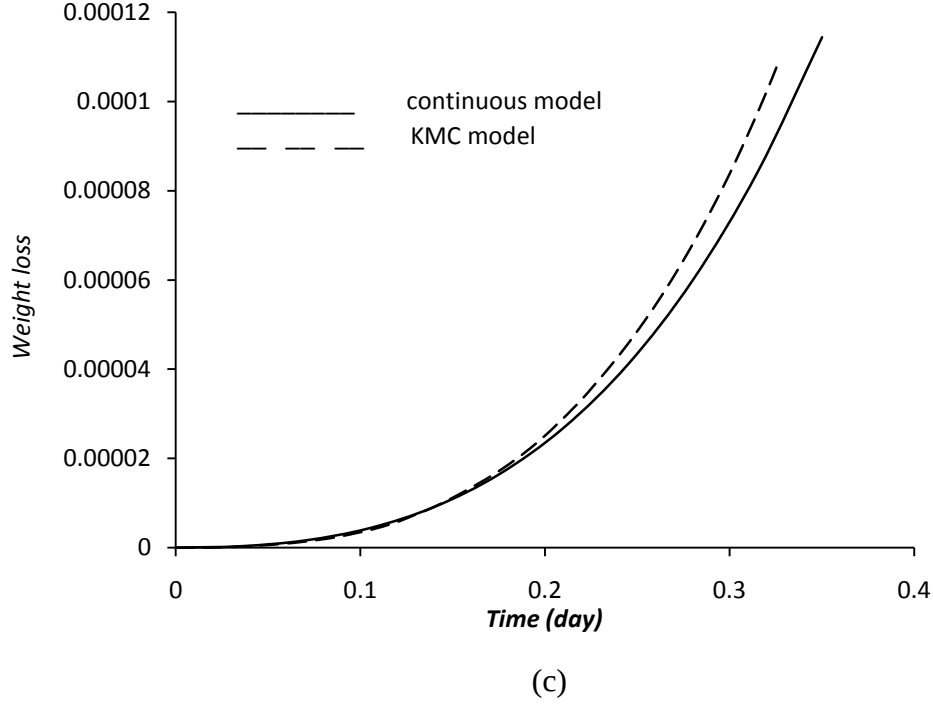


Fig.3-14 Comparisons between the continuous model (FEMlab) and KMC model: Molecular weight (a), concentration of oligomers (b) and weight loss(c) vs. degradation time

If all the polymer chain scissions occur at the chain ends as suggested above, then we have $dR_{ol}/dt = dR_s/dt$. If the chain scission occurs randomly the number of chain units of all the x-mers, R_x , is given by Flory's most probable distribution (Flory, 1955):

$$\frac{R_x}{C_{e0}} = x \left(\frac{C_{COOH}}{C_{e0}} \right)^2 \left(1 - \frac{C_{COOH}}{C_{e0}} \right)^{x-1}. \quad (3-31)$$

The total number of units of all the oligomers shorter or equal to m units is given by

$$\frac{R_{ol}}{C_{e0}} = \sum_{x=1}^m x \left(\frac{C_{COOH}}{C_{e0}} \right)^2 \left(1 - \frac{C_{COOH}}{C_{e0}} \right)^{x-1} \approx \frac{1}{2} (m + m^2) \left(\frac{C_{COOH}}{C_{e0}} \right)^2. \quad (3-32)$$

The last term is obtained by using series expansion and omitting the higher order terms (i.e. assuming $C_{COOH}/C_{e0} \ll 1$). In general the end scission may be faster than the random scission but still cannot completely dominate the oligomer production. We therefore propose to use

$$\frac{R_{ol}}{C_{e0}} = \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta, \quad (3-33)$$

in which α and β are empirical fitting constants. We then have

$$\frac{dR_{ol}}{dt} = \alpha \beta \left(\frac{R_s}{C_{e0}} \right)^{\beta-1} \frac{dR_s}{dt}, \quad (3-34)$$

Fig. 3-15 presents relations between R_s and R_{ol} from eqn. 3-32 and KMC model, respectively. These two plots fit together perfectly which gives a statistic validation of KMC model. In eqn. 3-33 α and β are two fitting parameters show the relationship between R_{ol} and $R_{scission}$. α and β can be obtained directly from KMC model by using equation 3-33. Example is shown in Fig. 3-16. The solid line is a prediction from KMC while the dashed line is a fitting line with $\alpha = 0.007$ and $\beta = 1.75$ in this case.

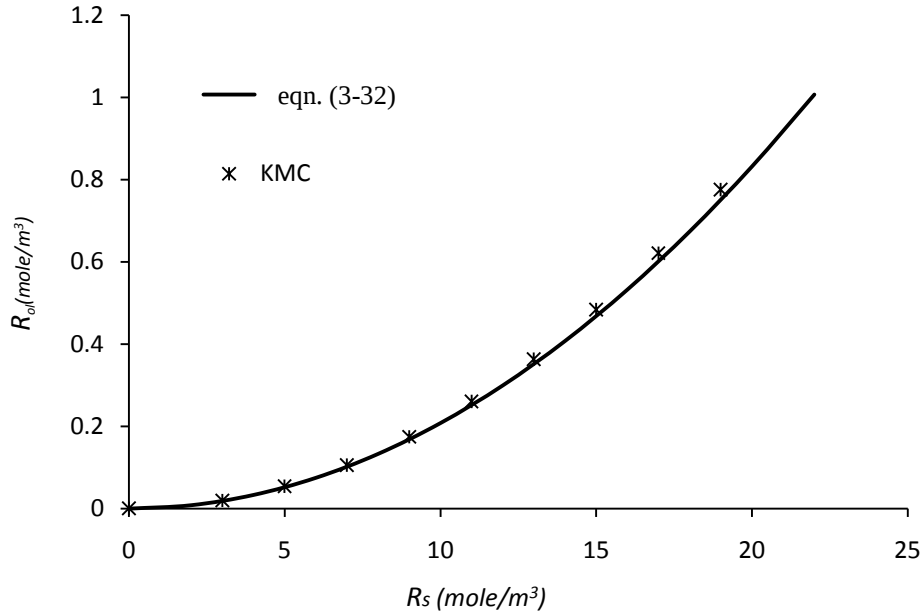


Fig.3-15 A relationship between R_s and R_{ol} predicted from KMC simulation (stars) and equation 3-32

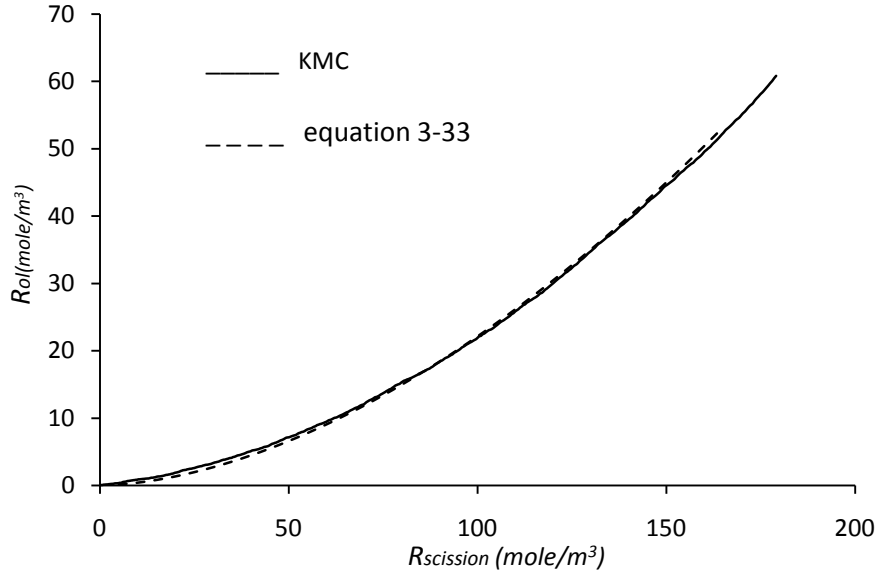


Fig.3-16 Fig.3-15 A relationship between R_s and R_{ol} predicted from KMC simulation (stars) and equation 3-33

3.5. IMPROVED REACTION-DIFFUSION MODEL FOR DEGRADATION

The model outlined in previous work (Wang *et al.*, 2008) can be greatly simplified if (a) the polymer remains amorphous during the degradation, (b) the weight loss in the samples is negligible and (c) the hydrolysis reaction is autocatalytic. Governing equations then become

$$\frac{dR_s}{dt} = k_2 C_e C_{ol}^n \quad (3-35)$$

$$\frac{dC_e}{dt} = -\frac{dC_{ol}}{dt} \quad (3-36)$$

$$\frac{C_{ol}}{C_{e0}} = \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta \quad (3-37)$$

$$\frac{dR_{ol}}{dt} = \alpha \beta \left(\frac{R_s}{C_{e0}} \right)^{\beta-1} \frac{dR_s}{dt} \quad (3-38)$$

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i} (C_{ol}) \right) \quad (3-39)$$

$$M_n = \frac{C_e M_0}{N_{chains0} + (R_s - C_{ol} / m)} \quad (3-40)$$

Three dimensional biodegradation: The biodegradation maps from (Wang *et al.*, 2008) provide a useful guide for material selection and experiment design for plates and pins. However for more sophisticated 3-dimensional fixation devices, the interplay between the oligomer diffusion and hydrolysis reaction is affected by the size and shape of the devices in a more complicated manner. Eqns. (3-35) – (3-40) can be solved using the finite element method for devices of arbitrary geometry. As an example we consider two biodegradable meshes, a strip mesh and a square mesh as shown on the left in Fig. 3-17, which are used in orthopaedic surgery to offer extra support and guiding for bone healing as containment for bone grafts and fragments. It is possible to build a 3-dimensional finite element models for the entire domain. For simplicity we assume that the strip mesh is infinitively long and the square mesh is infinitively large so that only the representative units of the meshes are modelled as shown on the right in Fig. 3-17. The end effect in the strip mesh and the edge effect in the square mesh are therefore ignored. Due to symmetry, the bottom facets of the representative units are on the mid-plane of the mesh. For the representative unit of the square mesh, the shaded facets are free surfaces in contact with the aqueous medium and all the other facets including those cannot be seen are symmetry planes. For the representative unit of the strip mesh, the back facet is also a free surface. The boundary conditions are that the oligomer concentration is set as zero at the free surface and that no flux of oligomer diffusion is allowed across any of the symmetry planes. The initial condition is that the oligomer concentration is zero everywhere in the mesh.

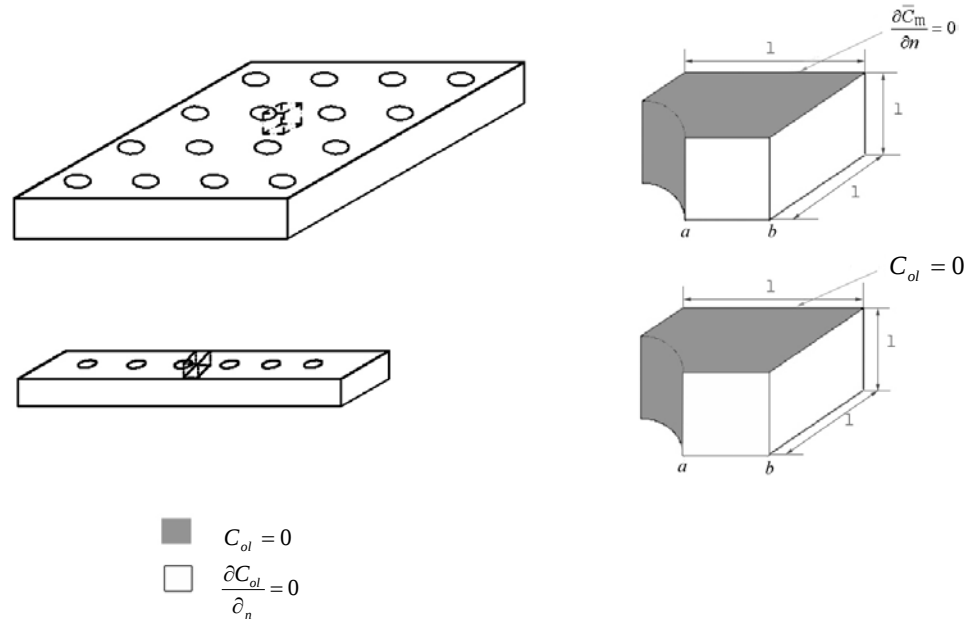
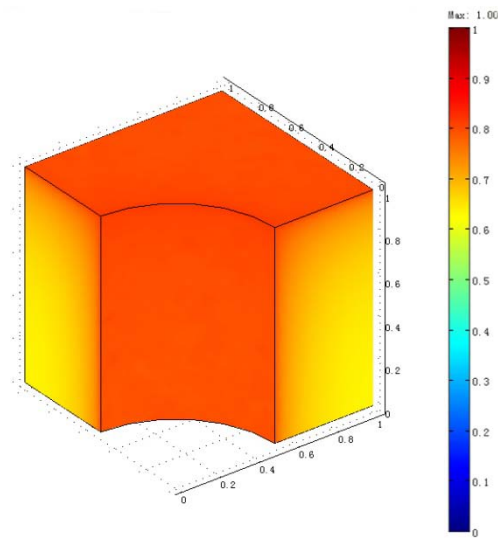
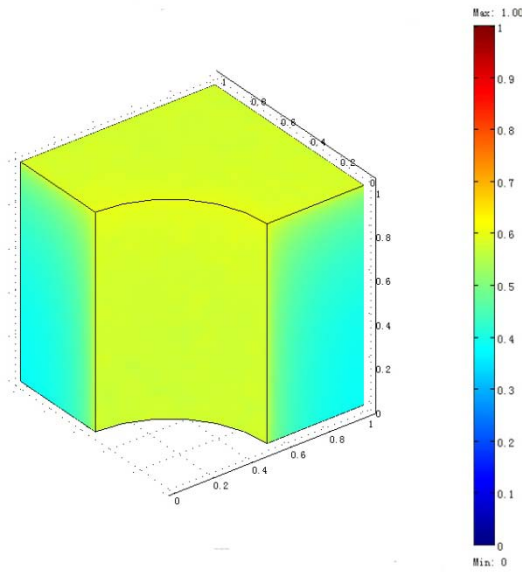


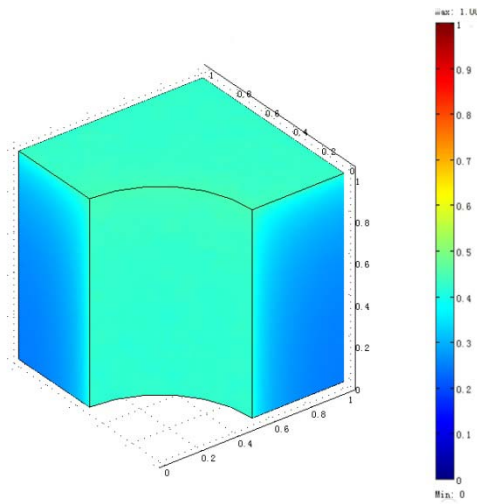
Fig.3-17 Representative units for the square and strip meshes respectively used in the finite element analysis.



(a) $\bar{t} = 2.0$

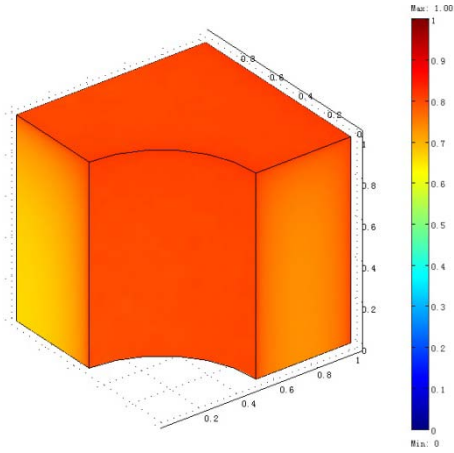


(b) $\bar{t} = 5.0$

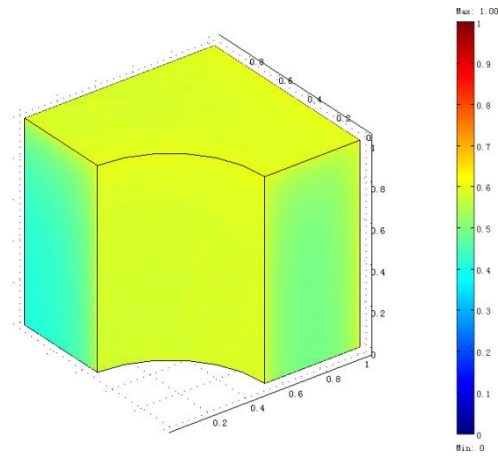


(c) $\bar{t} = 8.0$

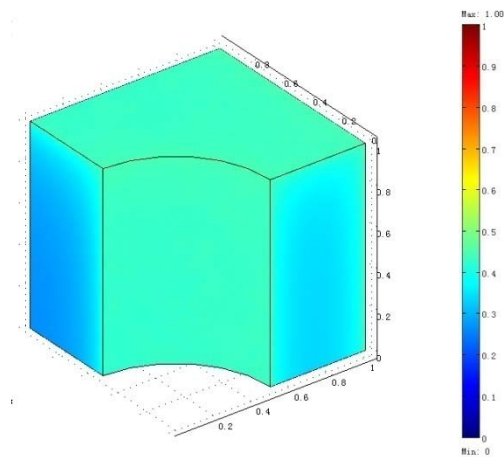
Fig. 3-18 Predicted spatial distributions of ester bond concentration (normalised by its initial value) in square mesh at three different normalised times.



(a) $\bar{t} = 2.0$



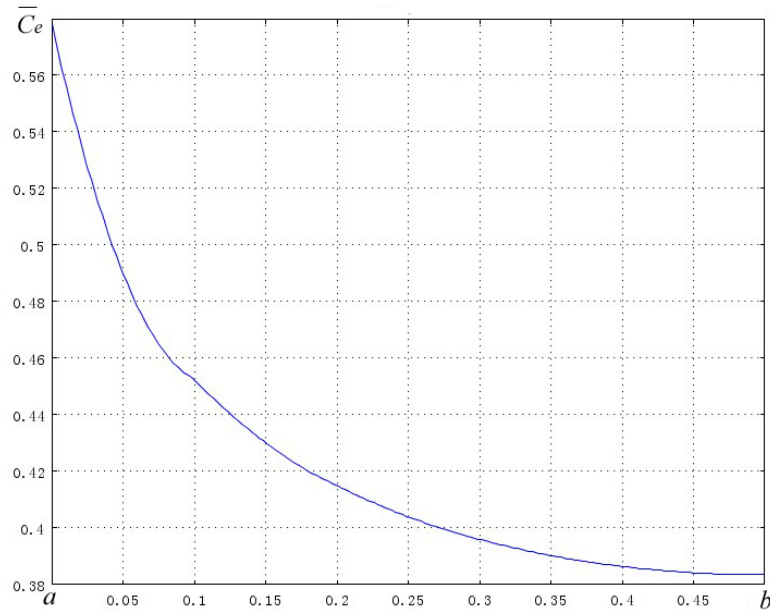
(b) $\bar{t} = 5.0$



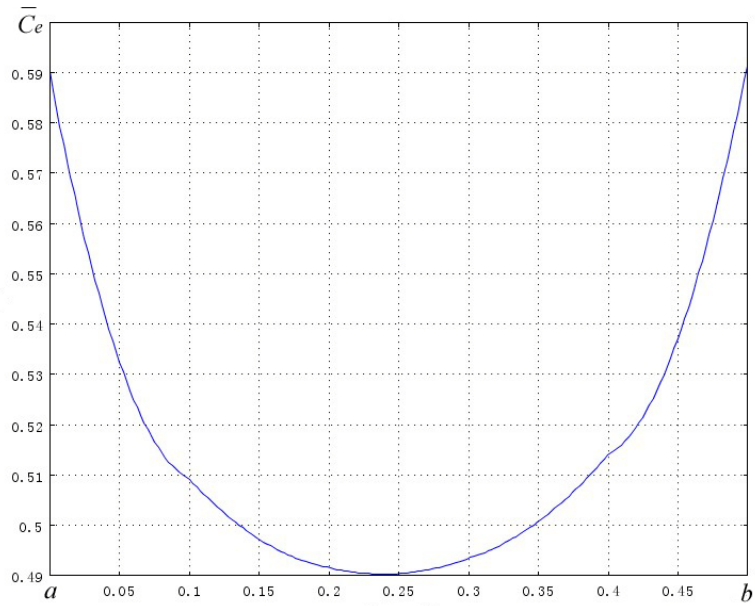
(c) $\bar{t} = 8.0$

Fig. 3-19 Predicted spatial distributions of ester bond concentration (normalised by its initial value) in strip mesh at three different normalised times.

Figs. 3-18 and 3-19 show the snapshots of the normalised concentration $\bar{C}_e$ at three different normalised times for the strip and square meshes respectively. The colours represent different values of $\bar{C}_e$. It can be observed from the two figures that biodegradation is very heterogeneous in the device. The heterogeneous degradation can be seen more clearly in Fig. 3-20 (a) and (b) which show the distribution of $\bar{C}_e$ at $\bar{t} = 5$ along the lines marked by $a-b$ on Fig. 3-17 for the two meshes respectively. Comparison between Figs. 3-18 and 3-19 reveals the major impact that a free surface has on the biodegradation. The free surface is always associated with a layer of much less degraded material, giving the device more strength. Fig. 3-21 provides the $\bar{C}_e$ averaged over the entire volume of the mesh as a function of time for the two different meshes. It can be observed that the strip mesh degrades slower than the square one despite that all the other conditions are identical. Fig. 3-22 shows the averaged $\bar{C}_e$ over the volume of the square mesh as a function of time for holes of three different radii of 0.2, 0.5 and 0.7 respectively. The size effect can be clearly observed in this figure. These quantitative predictions, followed by a stress analysis, can be used to search for the optimised design of a particular device.



(a) Square mesh



(b) Strip mesh

Fig. 3-20 Distribution of ester bond concentration (normalised by its initial value) at $\bar{t} = 5$ along the line $a-b$ marked in Fig 3-17 for the square and strip meshes respectively.

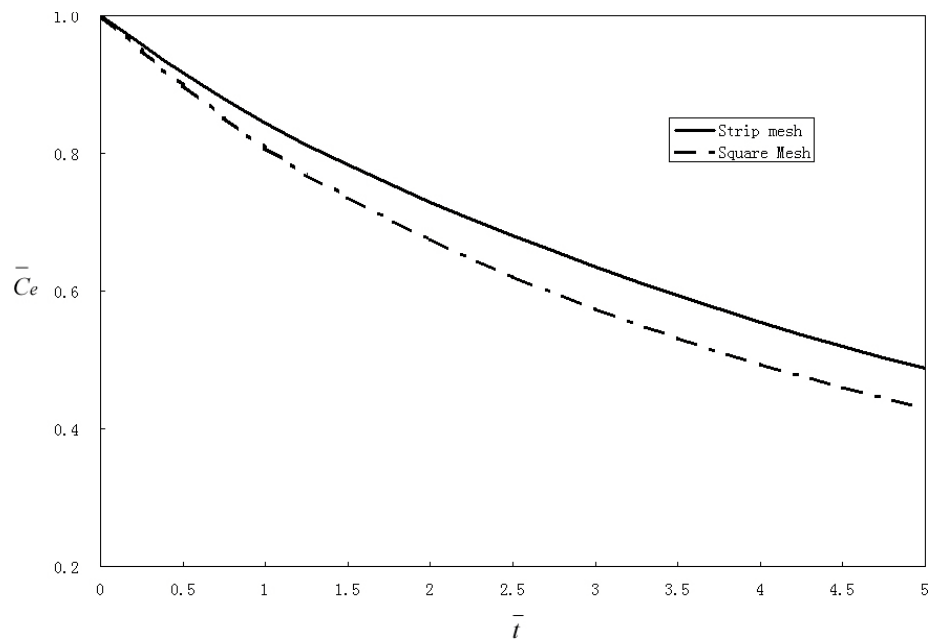


Fig. 3-21 Ester bond concentrations averaged over the entire body as functions of time for the two different meshes respectively.

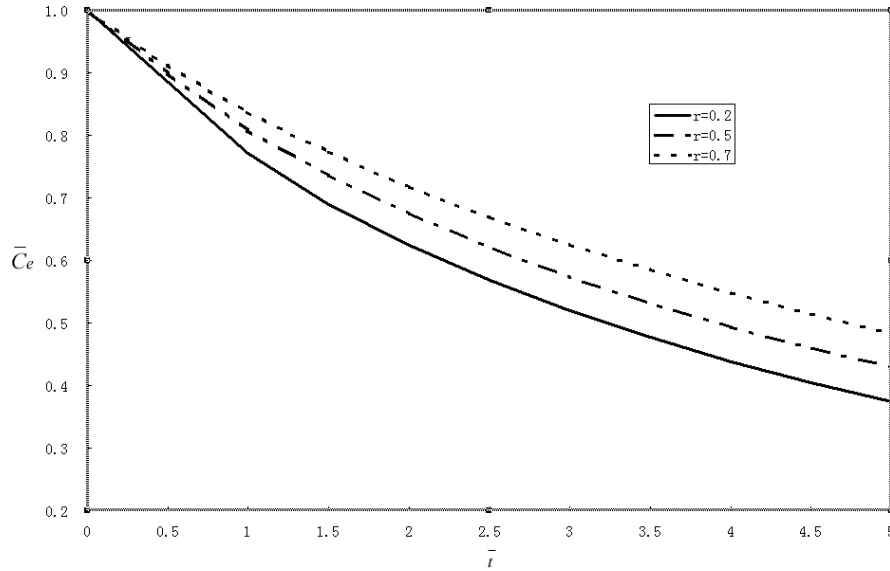


Fig. 3-22 Ester bond concentration averaged over the entire body as a function of time for the square mesh with three different radii of the holes.

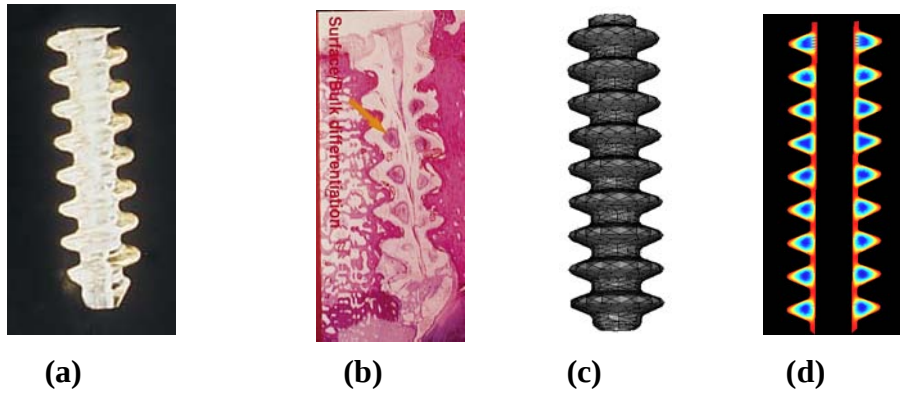


Fig. 3-23 (a) Interference screw made of poly(lactide)s studied by Schacht & Vert (International Journal of Biological Macromolecules, 1999, 25:283); (b) surface/bulk differentiation observed by Schwach & Vert after a period of implantation in sheep; (c) finite element model of the screw; (d) predicted distribution of average molecular weight on the cross-section (the screw is hollow); red indicates high molecular weight and blue indicates low molecular weight.

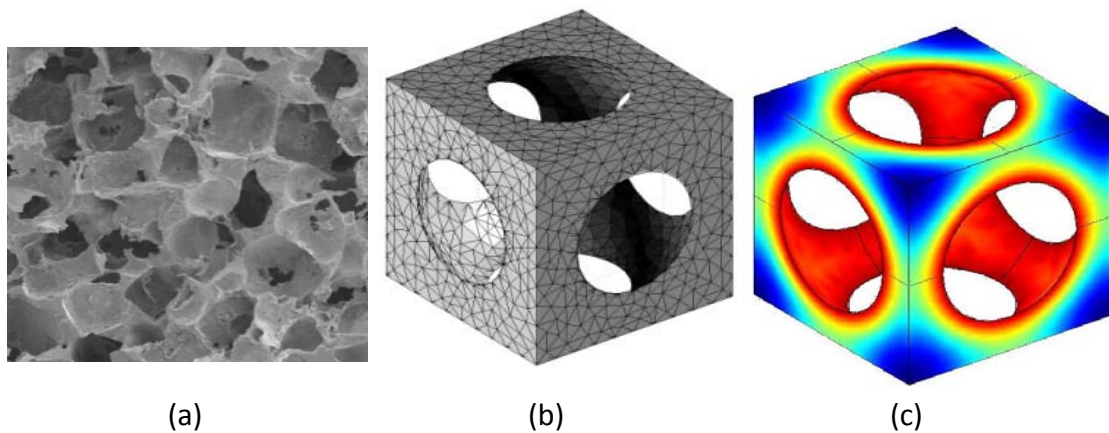


Fig. 3-24 (a) example of scaffolds used in tissue engineering (b) finite element model (mesh) of the scaffold; (c) predicted distribution of average molecular weight; red indicates high molecular weight and blue indicates low molecular weight.

Other sophisticated three dimensional case studies are also carried out. Fig. 3-23 presents a fixation screw made of PLA (a), its *in vivo* study (b), three dimension geometry of the screw modelled by FEMlab (c) and the model prediction (d). Fig. 3-23 (b) illustrates a very clear differentiation between surface and bulk which can be captured by the model showed in Fig. 3-23 (d). In tissue engineering, scaffolds made of degradable polymers can also be modeled. Fig. 3-24 (a) is an example of representative unit for scaffold. We represented it by a cube with a spherical hollow shown in Fig. 3-24 (b) which was solved using finite element method. Fig. 3-24 (c) presents the model prediction. Similarly, differentiation observed between surfaces which contact with solvent molecules and bulk materials.

3.6. REANALYSIS OF THE EXPERIMENT BY GRIZZI *et al.* (1995)

In a series of carefully planned experiments, Li *et al.* (1990^a, 1990^b, 1990^c) demonstrated that the degradation of their disc samples made of PLA and PLGA is highly heterogeneous. The core of the samples degrades much faster than the surface. Grizzi *et al.* (1995) later showed that a thinner film of 0.3mm in thickness degrades slower than a thicker plate of 2mm made of the same PLA. They explained these results using a conceptional diffusion-reaction model. It was suggested that the size effect and heterogeneous degradation are due

to the autocatalytic nature of the hydrolysis reaction. The hydrolysis of a polyester produces shorter chains with acid and alcohol end groups. For PLA, the acid end groups have a high degree of dissociation giving rise to an acidic environment, which significantly accelerates the hydrolysis rate. Therefore diffusion of the shorter chains out of the polymer plays a key role in controlling the overall degradation rate. A thicker plate degrades faster than a thinner one as the short chains with acid end groups in a thick plate cannot diffuse out quickly enough so that an acidic environment is built up at the core of the plate. The core of a thick plate also degrades faster than the surface of the plate. However the size effect and heterogeneous degradation were observed during the early stage of the degradation test when very little weight loss, L-lactic acid release and pH change was measured (Grizzi *et al.*, 1995; Li *et al.*, 1990^a; Li *et al.*, 1990^b; Li *et al.*, 1990^c). This is intriguing because the observed size effect and heterogeneous degradation would require significant oligomer diffusion out of the samples. To demonstrate this point, the conceptional analysis by Grizzi *et al.* (1995) is carried through quantitatively using a diffusion-reaction model (Han *et al.*, 2010). The model in this chapter assumes the polymer remains to be a solid during biodegradation. In the biodegradation tests by Grizzi, Li and their co-workers the core of the polymer discs became viscous in the later stage of the degradation. We therefore limit the numerical analysis to the first 11 weeks of the test. The parameters in the model were obtained by fitting the molecular weight data of the thin film and the thick plate and fitting the weight loss data of the thick plate simultaneously. This procedure gives $k = 0.042/\text{week}$, $k^a = 0.001\sqrt{\frac{\text{m}^3}{\text{mol}}}/\text{week}$ and $D_0 = 2 \times 10^{-9} \text{m}^2/\text{week}$. These parameters are then used to calculate the weight loss of the thin film. Figs. 3-25 and 3-26 show the fitting between the model and the experimental data for average molecular weight and weight loss as functions of time. It can be observed from Fig. 3-26 that significantly more weight loss in the thin film is required by the model to achieve the size effect than the experimental measurement.

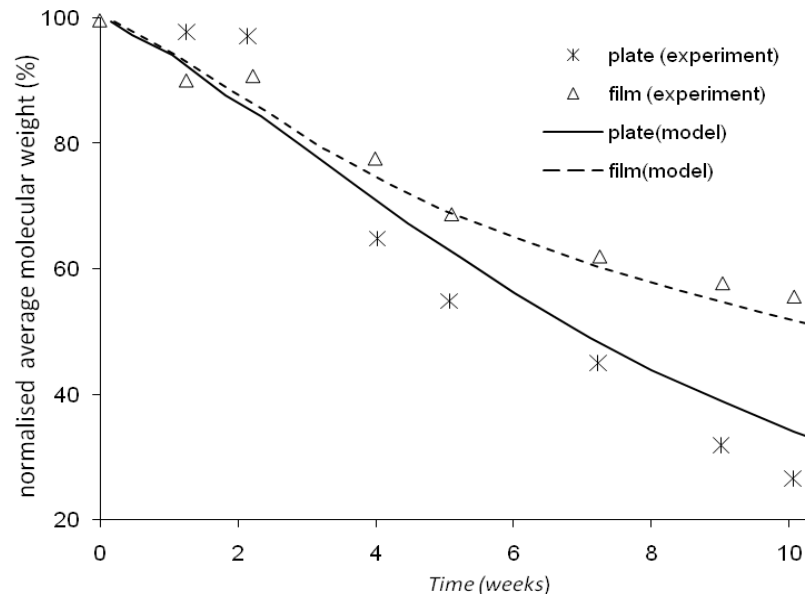


Fig.3-25 Normalised weight averaged molecular weight as a function of time for a PLA plate of 2mm and a film of 0.3mm made of the same PLA. The discrete symbols are experimental data (Li *et al.*, 1990^c) and the lines are fitting using a reaction-diffusion model (Han *et al.*, 2010).

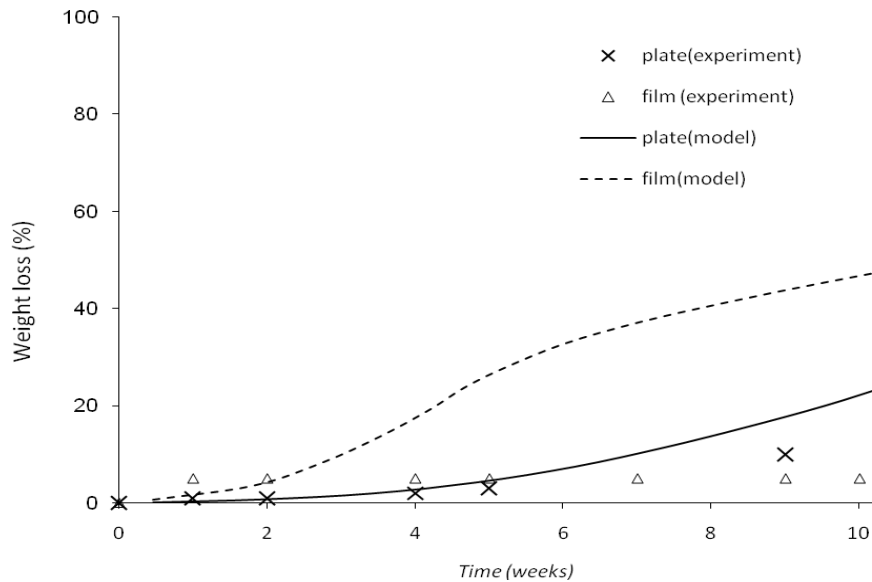


Fig.3-26 Weight loss as a function of time for a PLA plate of 2mm and a film of 0.3mm made of the same PLA. The discrete symbols are experimental data (Li *et al.*, 1990^c) and lines are fitting using a reaction-diffusion model (Han *et al.*, 2010).

The observed size effect without significant weight loss by Grizzi *et al.* (1995) can be achieved in the diffusion-reaction model by introducing a thin surface layer in which the hydrolysis is not autocatalytic as shown in Fig.3-27. The different hydrolysis kinetics in the surface layer can be due to either the neutralisation of the carboxylic end groups at the surface or the instant dissolution of the oligomers into the liquid media. 100 finite difference nodes are used across the thickness of the plate. At each node 20,000 polymer chains are generated following the size-exclusion chromatograms data provided by Grizzi *et al.*(1995). The size-exclusion chromatograms data are transformed into molecular weight distributions by using the linear relationship between the elution volume and log (molecular weight). Following material parameters are found by fitting the experimental data of molecular weight distributions and weight loss at various degradation times:

$$k_{random} = 5 \times 10^{-5} / \text{week} \quad , \quad k_{random}^a = 2.5 \times 10^{-5} \sqrt{\frac{m^3}{mol}} / \text{week} \quad , \quad k_{end} = 0.1 / \text{week} \quad ,$$

$$k_{random}^a = 0.1 \sqrt{\frac{m^3}{mol}} / \text{week} \quad , \quad \text{which represent the non-autocatalytic and autocatalytic}$$

hydrolysis rate constants for random and end scissions respectively, and $D_0 = 2 \times 10^{-9} \text{m}^2 / \text{week}$ which represents the oligomer diffusion coefficient in non-degraded polymer. For the finite difference nodes within the surface layer k_{random}^a and k_{end}^a are set as zero. The thickness of the surface layer is set as 100µm for both plate and film according to Grizzi *et al.* (1995). The model parameters are summarised in Table 3-1. Figs 3-28 to 3-30 show the comparison between the calculated and experimental molecular weight averaged over the thickness of sample, weight loss of the sample and molecular weight distribution averaged over the thickness of the sample as functions of time respectively. It can be observed from the figures that the two scale reaction-diffusion model with surface layer can fit all the experimental data by Grizzi *et al.* (1995) very well. In particular, the size effect is obtained even as the weight losses of the thick plate and thin film are very similar as shown in Fig. 3-29. Fig. 3-30 shows that the model is able to capture the transition from the initial monomodal molecular weight distribution to a bimodal distribution by week 11 in the thick plate, while predicting a monomodal molecular weight distribution in the thin film throughout the degradation process. Fig. 3-31 shows the calculated molecular weight distributions of the central and surface points for the thick and thin samples respectively at 0

and 11 weeks. It can be observed that the thick plate shows much more differentiated degradation than the thin one, exactly due to the slower diffusion of the oligomers out of the thick plate as suggested by Grizzi *et al.* (1995).

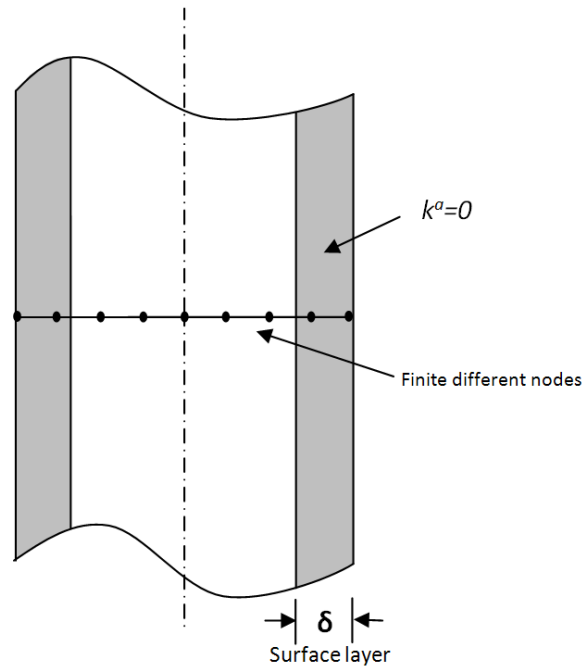


Fig.3-27 A schematic diagram of a plate with a surface layer in which the carboxylic end groups are neutralised.

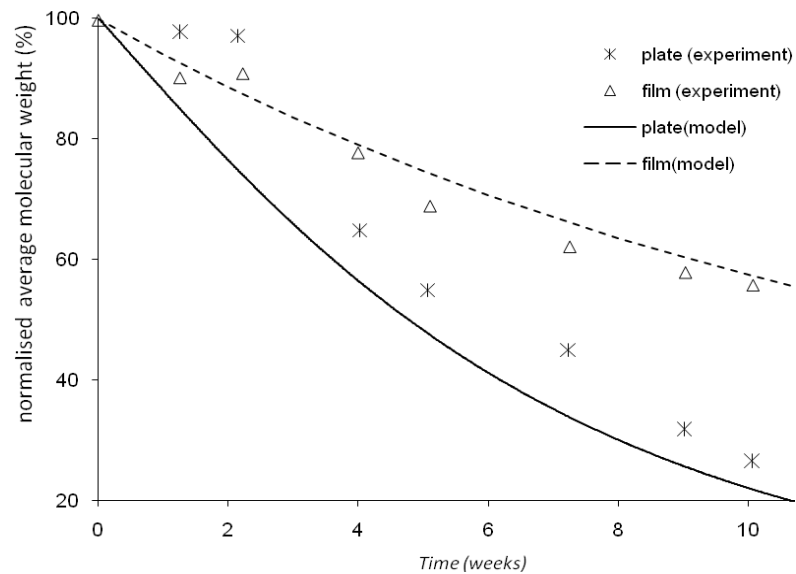


Fig.3-28 Refitting of the data shown in Fig. 3-25 using the two scale model with a surface layer

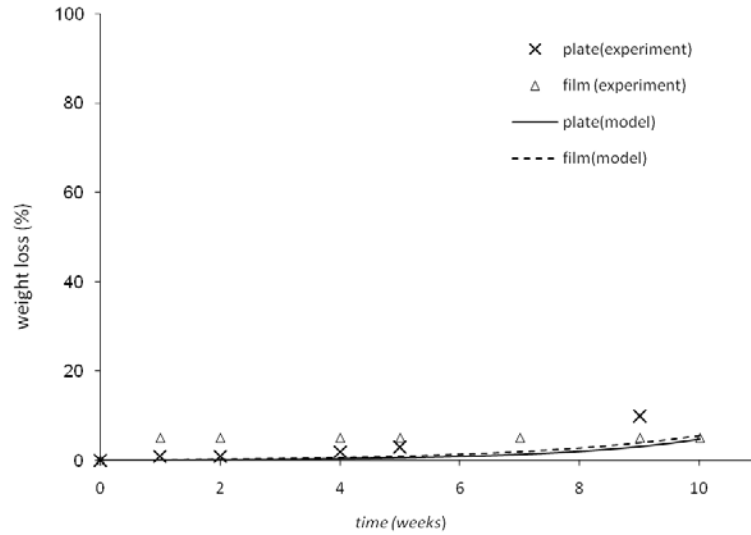
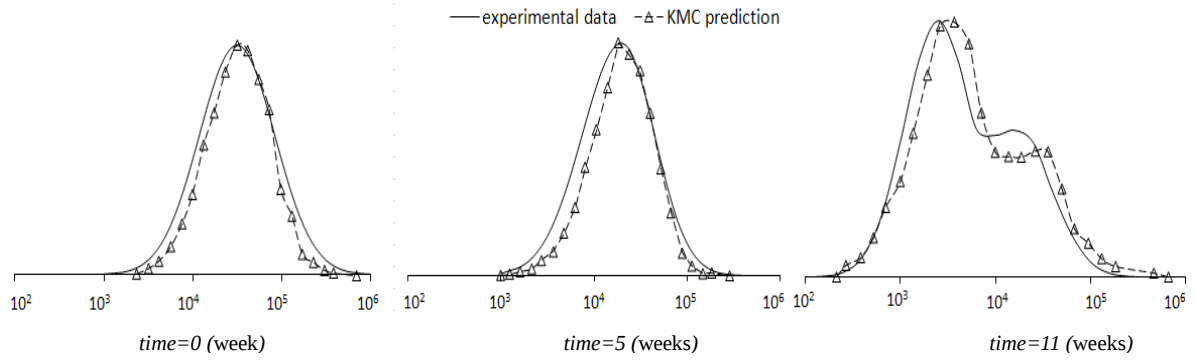
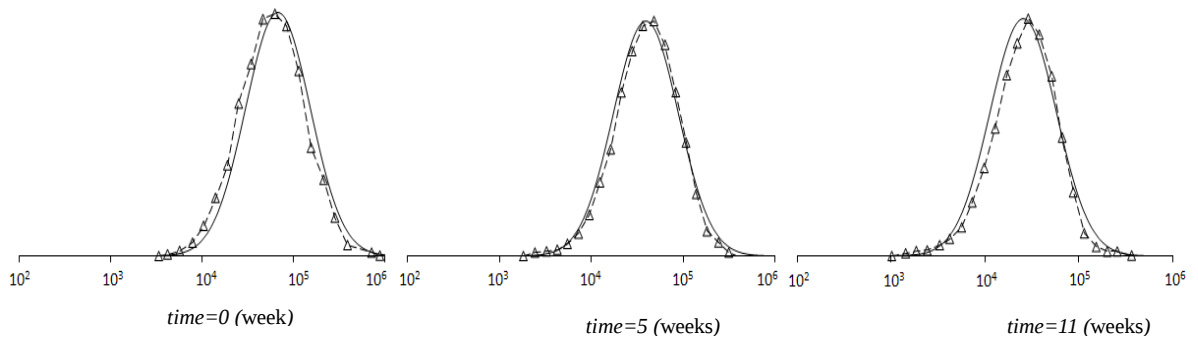


Fig.3-29 Refitting of the data shown in Fig. 3-26 using the two scale model with a surface layer



(a) plate of 2mm



(b) film of 0.3mm

Fig.3-30 Molecular weight distributions averaged over the sample thickness for (a) the plate and (b) the film at different times from the experimental data (Li *et al.*, 1990^c) and the two scale model.

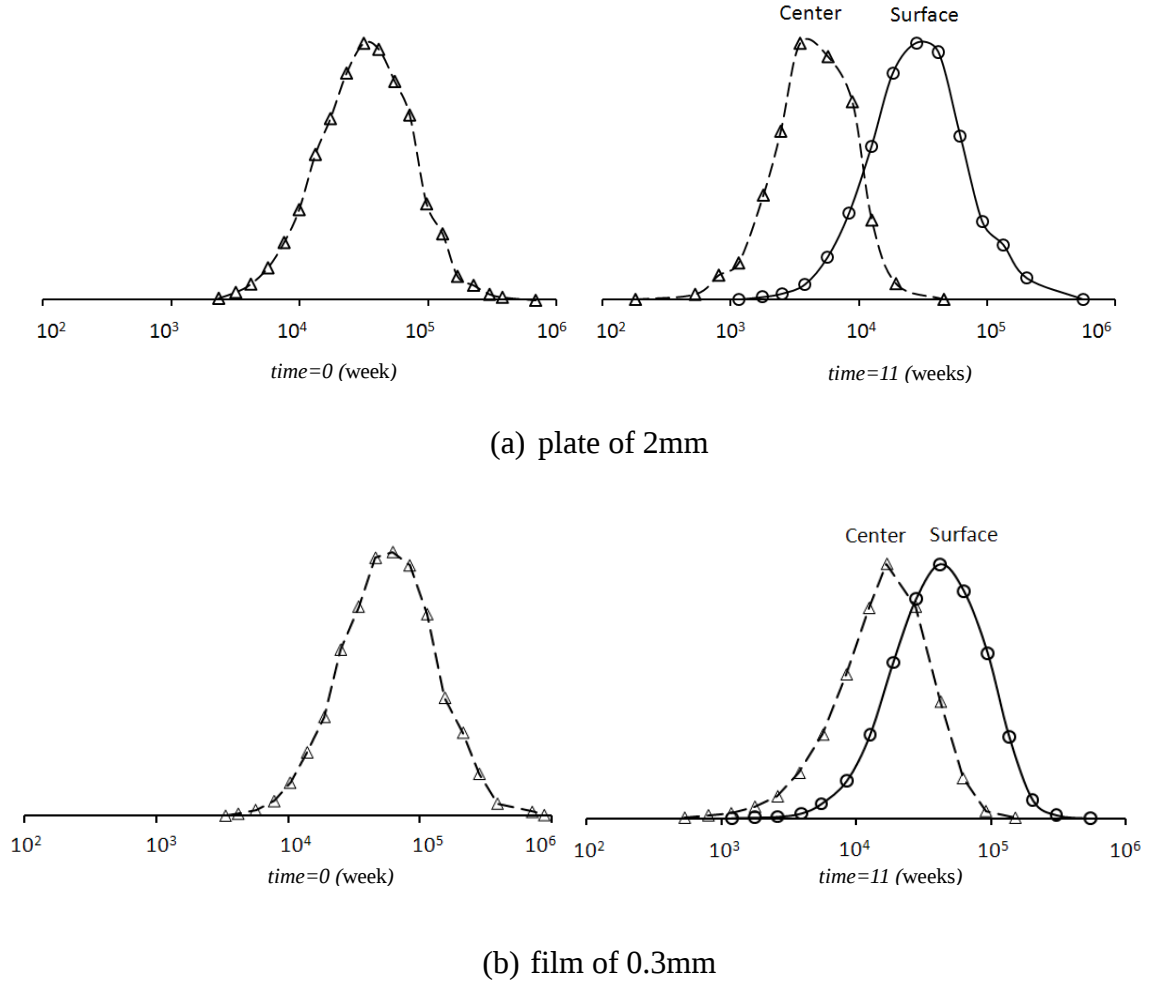


Fig.3-31 Calculated molecular weight distributions of a centre and surface nodes in the finite difference model at the beginning and 11 weeks of the degradation.

3.7. CONCLUSIONS

The two scale reaction diffusion model can be used to predict the temporal evolution and spatial distribution of molecular weight distribution in a device as well as the weight loss as a function of time. Detailed information about the polymer system such as the initial molecular weight distribution, copolymer ratio and degree of crystallinity are part of the input of the model. It is shown that the kinetic Monte Carlo scheme can accurately predict the effect of copolymer ratio between PGA and PDLLA on the degradation rate of the copolymer. The numerical study shows that the conceptional reaction diffusion model

suggested by Grizzi *et al.* (1995) needs to be extended in order to fully explain the size effect and heterogenous degradation observed in the experiment. A possible extension is to introduce a surface layer in which the carboxylic end groups are neutralised. It is shown that such a model can capture all the experimental data well. However, the exact cause of the neutralisation is unclear and remains to be explored in future studies.

For devices of sophisticated shapes, such as an internal fixation screw, the finite element method can be used to perform the global diffusion analysis. The local kinetic Monte Carlo analysis can be connected with the finite element analysis at the integration points of the finite element mesh. One issue that has to be addressed is the demand on the computational time by such a two-scale model. The computer simulation presented in Figs 3-28 to 3-31 took 8 days on a super-computer using a single CPU. A finite element – kinetic Monte Carlo scheme would require parallel processing and some simplification of the kinetic Monte Carlo analysis.

CHAPTER FOUR – A MODEL FOR SIMULTANEOUS CRYSTALLISATION AND DEGRADATION OF POLYMERS

This chapter completes the continuous model of biodegradation for biodegradable polymers that was previously developed by Wang *et al.*(2008). Crystallisation during biodegradation was not considered in the work by Wang *et al.* which is the topic of the current chapter. For many commonly used biodegradable polymers, there is a strong interplay between crystallisation and hydrolysis reaction during biodegradation – the chain cleavage caused by the hydrolysis reaction provides an extra mobility for the polymer chains to crystallise and the resulting crystalline phase becomes more resistant to further hydrolysis reaction. This chapter presents a complete theory to describe this interplay. The fundamental equations in the Avrami's theory for crystallisation are modified and coupled to the diffusion-reaction equations that were developed in the previous work by Wang *et al.*. The mathematical equations are then applied to three biodegradable polymers for which long term degradation data are available in the literature. It is shown that the model can capture the behaviour of the major biodegradable polymers very well.

4.1. INTRODUCTION

Because of their well established biocompatibility, PGA, PLA and their copolymers are the most commonly used biodegradable polymers in medical devices (Wood, 2006; Bell and Kindsfater, 2006; Siepmann *et al.*, 2006; Sengers *et al.*, 2007). However PGA, PLA and their copolymers are not materials easy to work with. Among many other things, two complications have to be considered: (a) the biodegradation of polymers containing PLA is heterogeneous due to the autocatalytic nature of the hydrolysis reaction (Grizzi *et al.*, 1995), and (b) many of these polymers, PGA and PLLA for example, crystallise during biodegradation (Zong *et al.*, 1999; Tsuji and Muramatsu, 2001; Tsuji and Ikada, 2000). A complicated interplay between the hydrolysis reaction, diffusion of the reaction products and crystallisation makes the mechanical and functional properties of the biodegradable devices difficult to predict. So far the development of medical devices made of biodegradable polymers has been almost entirely based on the trial and error approach. The lack of a mathematical framework for the biodegradation process makes it difficult to

extrapolate experience and data obtained in one device to another. Because the biodegradation is dimension dependant, it is even difficult to extrapolate data between same devices of different dimensions (screws of different diameters for example). A mathematical framework is needed for the biodegradation process. In the previous studies by Wang *et al.*, a set of simplified diffusion – reaction equations were established to model the biodegradation (Wang *et al.*, 2008). The model was compared with experimental data and a biodegradation map was presented showing the interplay between the hydrolysis reaction and the diffusion of the reaction products. The heterogeneous nature of the biodegradation was fully considered. However the interplay between crystallisation and biodegradation was not considered in the previous work. The current chapter completes the model by incorporating crystallisation into the diffusion-reaction equations. During biodegradation the chain scissions provide the extra mobility for the polymer chains to crystallise. The resulting crystalline phase becomes more resistant to further hydrolysis reaction. The crystallisation theory due to Avrami (1939, 1940, and 1941) has been shown to be valid for a wide range of materials including polymers. This theory predicts an exponential dependence of the degree of crystallinity on time. However the simple exponential equation cannot be directly applied to biodegradation because it does not consider the interaction between hydrolysis, diffusion and crystallisation. In this chapter, we re-examine the fundamentals in the Avrami's theory and show that the theory can be modified and coupled to the diffusion-reaction equations to model simultaneous crystallisation and biodegradation. It is no longer possible to obtain analytical solutions to the resulting differential equations. Instead, these equations are solved numerically. The model is then applied to three different biodegradable polymers including poly(glycolide-co-L-lactide), poly(L-lactide), and blends of poly(L-lactide) and poly(vinyl alcohol), for which complete biodegradation data are available in the literature (Bell and Kindsfater, 2006; Siepmann *et al.*, 2006; Sengers *et al.*, 2007). Finally parametric studies are carried out using the model to demonstrate the effects of crystallisation rate on the degradation rate and on the biodegradation map.

4.2. GOVERNING EQUATIONS FOR SIMULTANEOUS CRYSTALLISATION AND BIODEGRADATION

It has been widely observed that the degree of crystallinity in commonly used biodegradable polymers increases significantly during both short term and long term degradation (Zong *et al.*, 1999; Tsuji and Muramatsu, 2001; Tsuji and Ikada, 2000). The degradation-induced crystallisation can occur in either initially amorphous or semi-crystalline polymers. Important examples of the biodegradable polymers are PGA, PLLA and their copolymers. PGA is a highly crystalline polymer while PLLA is semi-crystalline. The crystalline phase provides these polymers with the necessary mechanical strength for the medical devices. During biodegradation, the hydrolysis reaction of the ester backbone in aqueous environment leads to cleavage of the polymer chains and produces short oligomers. The oligomers then diffuse out of the material leading to a weight loss of the device. For a semi-crystalline polymer, the chain cleavage occurs preferentially in the amorphous region. Therefore even if the total volume of the crystalline phase remains constant, the observed degree of crystallinity still increases due to the loss of the amorphous phase. More importantly, cleavage of the long and amorphous polymer chains provides higher mobility for the polymer chains, facilitating the crystallisation of the amorphous polymer (Zong *et al.*, 1999). The detailed degradation pathways have been suggested (Zong *et al.*, 1999) and long term experimental data of simultaneous degradation and crystallisation are available in the literature (Tsuji and Muramatsu, 2001; Tsuji and Ikada, 2000). However a mathematical model for the degradation-induced crystallisation does not exist as far as the authors are aware. Avrami's theory (Avrami, 1939; Avrami, 1940; Avrami, 1941) has been shown to be generally valid for polymer crystallisation (Long *et al.*, 1995). It predicts that the degree of crystallinity, X_c depends on time, t , in an exponential manner:

$$X_c = 1 - \exp[-(k_c t)^m] \quad (4-1)$$

in which m is a constant often referred to as the Avrami exponent and k_c is a temperature dependent factor (often taken as an Arrhenius type expression). This equation however does not taken into account of the interaction between polymer chain cleavage and crystallisation, and therefore cannot be directly applied to biodegradation. However it is

possible to modify Avrami's differential equations (Avrami, 1939; Avrami, 1940; Avrami, 1941) led to Eq. (4-1) to model the degradation-induced crystallisation.

Following the previous work by Wang *et al.* (2008), a biodegradable polymer can be viewed as a combination of four species:

- I. amorphous polymer molecules, which can hydrolyse but are too large to diffuse; part of the polymer molecules can also crystallise;
- II. monomers, which are the product of the hydrolysis reaction and can diffuse;
- III. polymer crystals, which are formed and grow but do not hydrolyse;
- IV. water molecules, which are assumed to be abundant anywhere in the device.

The state of a biodegrading polymer can therefore be completely described using

- a) C_e - mole number of ester bonds of amorphous polymer per unit volume of *semi-crystalline polymer*,
- b) C_{ol} - mole number of oligomer ester bonds remained in the material per unit volume of *semi-crystalline polymer*, and
- c) X_c - the volume degree of crystallinity.

It is assumed that the hydrolysis reaction only occurs in the amorphous region despite that the ester groups of polymer chains on the surface of the crystalline region are hydrolyzed. It is then necessary to further define the following variables:

- d) c_e - mole number of ester bonds of amorphous polymer per unit volume of the *amorphous polymer*,
- e) c_{ol} - mole number of oligomer ester bonds remained in the material per unit volume of *amorphous polymer*,
- f) r - mole number of the amount of monomers produced by hydrolysis reaction per unit volume of *amorphous polymer*.

The production rate of monomers by the hydrolysis reaction is given by (Siparsky *et al.*, 1998)

$$\frac{dr}{dt} = k_1 c_e + k_2 c_e c_{ol}^n \quad (4-2)$$

in which k_1 and k_2 are the reaction constants for the non-autocatalytic and autocatalytic hydrolysis reactions. The power n in the second term accounts for the dissociation of the acid end groups. The mole concentrations in the amorphous phase and those in the semi-crystalline polymer are connected by

$$c_e = \frac{C_e}{1 - X_c}; c_{ol} = \frac{C_{ol}}{1 - X_c}. \quad (4-3)$$

Using Eq. (4-3) in Eq. (4-2) gives

$$\frac{dr}{dt} = \frac{1}{1 - X_c} \left\{ k_1 C_e + k_2 \frac{C_e C_{ol}^n}{(1 - X_c)^n} \right\} \quad (4-4)$$

It turns out to be convenient to define a new variable R using

$$\frac{dR}{dt} = (1 - X_c) \frac{dr}{dt} = k_1 C_e + k_2 \frac{C_e C_{ol}^n}{(1 - X_c)^n} \quad (4-5)$$

R represents the moles of monomers produced per unit volume of the semi-crystalline polymer. It also reflects the total number of chain cleavages per unit volume of the semi-crystalline polymer. The reduction in the ester bond concentration in the amorphous phase originates from two parts: (a) hydrolysis of the polymer chains and (b) crystallisation of the mobile polymer chains, which can be expressed as

$$\frac{dC_e}{dt} = -\frac{dR}{dt} - \frac{C_e}{1 - X_c} \frac{dX_c}{dt} \quad (4-6)$$

The second term on the right hand side in Eqn. (4-6) represents the loss of amorphous polymer phase due to crystallisation.

Assuming Fick's law for oligomer diffusion, we have the following governing equation for the oligomer concentration:

$$\frac{dC_{ol}}{dt} = \frac{dR}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i} (C_{ol}) \right) \quad (4-7)$$

in which D is the phenomenological diffusion coefficient. The nomenclature of vector analysis is used to shorten the expression of Eqn. (4-6). The diffusion coefficient D of the degrading polymer is a function of the porosity, p , and degree of crystallinity, X_c . In the previous work by Wang *et al.* (2008) assumed a linear relation between D and p , which was

valid if the porosity was less than 25%. To improve the linear approximation, an effective diffusion coefficient was determined using finite element analysis of a three dimensional representative cubic material. A randomly distributed second phase was gradually introduced into the unit and the effective diffusion coefficient of the two phase material was calculated numerically. Details of the analysis can be found in Jiang *et al.* (2008). The conclusion of the numerical study is that the numerical results can be fitted into the following empirical equation:

$$D = D_{slow} + (1.3V_{fast}^2 - 0.3V_{fast}^3)(D_{fast} - D_{slow}) \quad (4-8)$$

in which D_{slow} and D_{fast} represent the diffusion coefficients of the fast and slow diffusion phases respectively and V_{fast} represents the volume fraction of the fast diffusion phase. Eqn. (4-8) is valid if $D_{fast}/D_{slow} > 10$. For a degrading polymer containing pores which are generated by monomers diffusing out, its effective diffusion coefficient can be calculated using Eqn. (4-8) as

$$D = D_{matrix} + (1.3p^2 - 0.3p^3)(D_{pore} - D_{matrix}), \quad (4-9)$$

in which D_{matrix} and D_{pore} represent the diffusion coefficients of monomers in the polymer matrix and pores respectively. The porosity p can be estimated as

$$p = 1 - \left\{ (\bar{C}_m + \bar{C}_e)(1 - X_{c0}) + X_c \right\}, \quad (4-10)$$

in which $\bar{C}_e = C_e / C_{e0}$ and $\bar{C}_{ol} = C_{ol} / C_{e0}$ where $C_{e0} = C_e(t=0)$; X_{c0} is the initial degree of crystallinity. The polymer matrix consists of an amorphous and a crystalline phase. It can be assumed that the diffusion coefficient of the monomers in the crystalline phase is zero ($D_{slow} = 0$). Using D_0 to represent the diffusion coefficient of monomers in the amorphous polymer, the effective diffusion coefficient of the polymer matrix can be obtained from Eqn. (4-8) as

$$D_{matrix} = \left[1.3 \left(\frac{\bar{C}_{ol} + \bar{C}_e}{\bar{C}_{ol} + \bar{C}_e + X_c / (1 - X_{c0})} \right)^2 - 0.3 \left(\frac{\bar{C}_{ol} + \bar{C}_e}{\bar{C}_{ol} + \bar{C}_e + X_c / (1 - X_{c0})} \right)^3 \right] D_0 \quad (4-11)$$

The effective diffusion coefficient of the degrading polymer can be determined by combining Eqns. (4-9)-(4-11).

The centre piece of Avrami's theory (Avrami, 1939; Avrami, 1940; Avrami, 1941) is the relation between the volume degree of crystallinity, X_c , and a so-called extended volume fraction of the crystalline phase, X_{ext} . This theory is presented in some details here so that further modifications to the theory can be made for the purpose of this chapter. The growth rate G is the same at any direction and the nuclei grow in a matrix shown in Fig.4-1. The radius of one crystal is then given by:

$$r(y, t) = \int_y^t G(x) dx \quad (4-12)$$

In the matrix, r is regarded as a suitably averaged quantity over three directions. G is the direction averaged growth rate which varies with time, temperature and concentration, etc. The volume of a single crystal is then calculated from following equation:

$$V_c(y, t) = \alpha r^3 = \alpha \left(\int_y^t G(x) dx \right)^3 \quad (4-13)$$

where α is a shape factor, which equal to $4\pi/3$ for a sphere. As G is a time independent variable eqn. 4-13 changes to:

$$V_c(y, t) = \alpha r^3 = \alpha G^3 (t - y)^3 \quad (4-14)$$

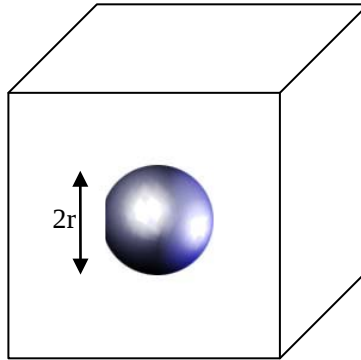


Fig.4-1 Single crystal in three-dimensional matrix.

To mimic a real system for crystallisation, multi grains have to be considered. All the grains are also assumed to have geometrically similar and convex shape. The crystallisation is

occurred in a finite matrix and the grains are randomly distributed (Avrami, 1939; Avrami, 1940; Avrami, 1941) which is shown in Fig. 4-2.

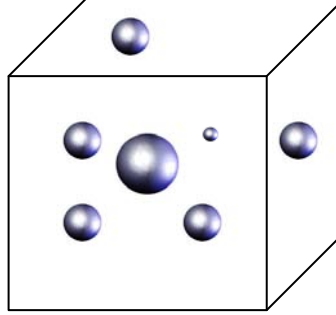


Fig. 4-2 A crystal system in a three-dimensional matrix

Both empirical and theoretical models assume that the crystal phase is nucleated by tiny ‘germ nuclei’ (Avrami, 1939; Avrami, 1940; Avrami, 1941) which are already existed in the amorphous phase and whose effective number are varied by temperature and duration of superheating. In biodegradation, the nuclei are counted only when they meet ester bonds and the growth rate of a crystal is considered independent of time and position. N_0 is referred to the effective number of the nuclei sites at $t=0$ for a given temperature and a specific duration of superheating. $N \equiv N(t)$ is the effective number of nuclei sites at time t . $V_c(y, t)$ represents the volume at time t of any individual grain which began to grow from a nucleus. At time t , the total transformed volume of these nuclei $dN'' = nNdy$ which begin to grow at time y is given as followed:

$$nN(y)dy \times \int_y^t V(y, t)dy = N(y) \times \int_0^t V(y, t)dy \quad (4-15)$$

Considering all the grains which begin to grow from 0 to time t : the integration of equation (4-15) becomes:

$$V_{ext} = \int_0^t nN(y)dy \times \int_0^t V(y, t)dy = \int_0^t V(y, t)nN(y)dy \quad (4-16)$$

where V_{ext} is the total transformed volume at time t neglecting overlapping among grains.

The derivation of $N(t)$ is discussed as below:

At the beginning assuming that the effect number of the germ nuclei is $\bar{N}$ ($t=0$) which only be effects by the temperature and time of superheating, the function $N(t)$ reduced from $\bar{N}$ at $t=0$ by two ways:

1. Some of the germ nuclei become active growth nuclei which have already grew (whose number is represented by $N' \equiv N'(t)$). Give a new concept $n \equiv n(t)$, which represent the probability of a single germ nuclei per unit time which can jump over the boundary in consequence of free energy fluctuation. Therefore $\frac{dN'}{dt} = n \times N$. $n(T)$ may be calculated as a function of temperature then it will has a general form:

$$n(T) = Ke^{-Q+A(T)/RT} \quad (4-17)$$

Where Q is activation energy per gram molecule, R is the gas constant, and $A(T)$ is the work per gram molecule required for forming a growth nucleus at temperature T .

2. The second way of consuming nuclei is through being swallowed by growing grains of the new phase. Let $N'' \equiv N''(t)$, then we have

$$N(t) = \bar{N} - N'(t) - N''(t) \quad (4-18)$$

The rate of nucleus changing is therefore denoted by

$$dN = -dN' - dN'' \quad (4-19)$$

According to (Avrami, 1939; Avrami, 1940; Avrami, 1941), rates for nucleus changing by two ways are given by eqn. 4-20 and 4-21, respectively.

$$dN' = nNdt \quad (4-20)$$

$$dN'' = \frac{N}{1-V_c} dV_c \quad (4-21)$$

Substitute 4-19 and 4-20 into 4-18,

$$dN + \xi Ndt + \frac{N}{1-V_c} dV_c = 0 \quad (4-22)$$

An example of calculating N is given in Fig.4-3. The initial $N(t=0) = A \times B$. After a small time interval Δt , the number of growth nuclei is 10 and the number of swollen nuclei

is 20. Therefore when $t = \Delta t$, $N(t = \Delta t) = A \times B - 10 - 20$.

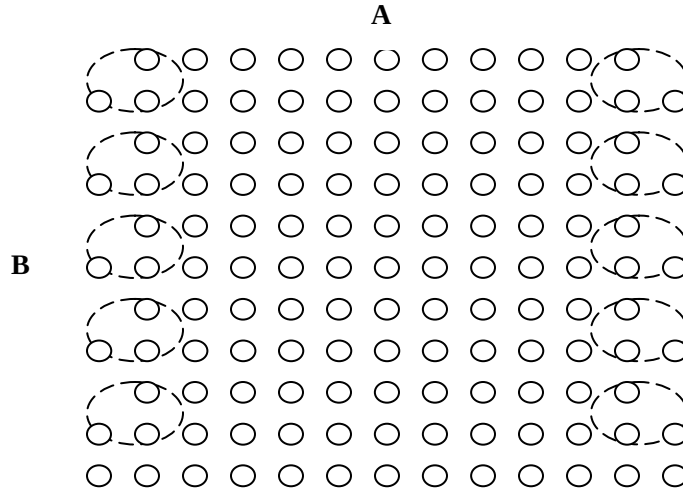


Fig. 4-3 An example of decreasing of number of nuclei sites: in this case

$$N(t = 0) = A \times B, \quad N' = 10, \quad N'' = 30, \quad N(t = \Delta t) = A \times B - 10 - 20$$

Follow Avami's theory, V_c can be expressed in terms of a so-called extended volume fraction of the crystalline phase :

$$\frac{V_c}{V_0} = 1 - e^{-\frac{V_{ext}}{V_0}} \quad (4-23)$$

Eqn. 4-23 can be rewritten as:

$$X_c = 1 - e^{-X_{ext}} \quad (4-24)$$

Eqn. 4-24 provides a relationship between extended volume fraction and the actual volume fraction of crystal phase. The derivation is being discussed as bellows. In actual pattern of grains (see Fig. 4-4 for reference), the overlapping regions are calculated only once to get the real crystallisation volume. V'_1 denotes the volume of nonoverlapping-grain regions, indicated by white areas in Fig. 4-4; V'_2 denotes the volume of double grain regions indicated by light grey regions in Fig. 4-4, V'_3 denotes the volume of triple grain regions indicated by dark grey regions in Fig. 4-4, etc. Since we have V'_m which should be counted m times to get the total extend volume V_{1ex} :

$$V_{1ex} = V'_1 + 2V'_2 + 3V'_3 + \dots + mV'_m + \dots \quad (4-25)$$

the real transformed volume is:

$$V_1 = V'_1 + V'_2 + V'_3 + \dots + V'_m + \dots \quad (4-26)$$

Similarly, according to ref (Avrami, 1939; Avrami, 1940; Avrami, 1941) we have:

$$V_{kex} = \sum_{m=k}^{\infty} C_k^m V'_m \quad (4-27)$$

$$V_k = \sum_{m=k}^{\infty} V'_m \quad (4-28)$$

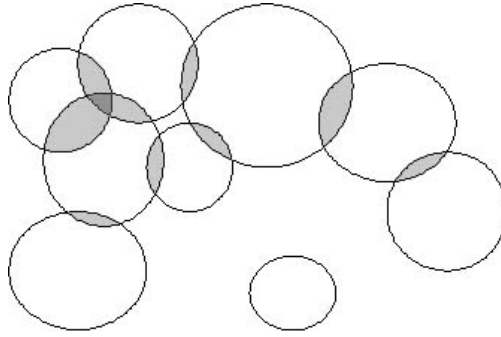


Fig. 4-4 Overlapping of growing crystals

It is V_{kex} rather than V_k that is more easily calculated from eqn. 4-24. Therefore it is important to find an expression for V_1 in terms of the V_{kex} which is derived from Avrami's theory:

$$V_c = V_1 = V_{1ex} - V_{2ex} + V_{3ex} + \dots + (-1)^{m+1} V_{mex} \dots \quad (4-29)$$

If G is time independent, equation 4-16 changes to:

$$V_{1ex} = \int_0^t V(y, t) N(y) dy = \alpha \sigma^3 \int_0^{\tau} (\tau - z)^3 N(z) dz \quad (4-30)$$

where $\frac{G}{n} \equiv \sigma$. Similarly, for two dimensional and one dimensional growth, equation 4-16 becomes:

$$V_{lex} = \alpha' \sigma^2 \int_0^{\tau} (\tau - z)^2 N(z) dz \quad (4-30')$$

$$V_{lex} = \alpha'' \sigma \int_0^{\tau} (\tau - z) N(z) dz \quad (4-30'')$$

Using eqn. 4-29 and 4-30 we have:

$$X_c = 1 - e^{-Bt^k} = 1 - e^{-X_{ext}} \quad (4-31)$$

Some analytical solutions of (4-31) are given with conditions:

The exhaustion of the germ nuclei did not occur at the early stage of the transformation when N is large enough. Under such conditions, we may consider two extreme cases (Avrami, 1939; Avrami, 1940; Avrami, 1941),

1. ξ is very large, and then relation between V and t is given by:

$$X_c = 1 - e^{-\alpha G^3 N_0 t^3} \quad (4-32)$$

2. ξ is small, and then

$$X_c = 1 - e^{(-\alpha G^3 N_0 t^4 \xi)/4} \quad (4-33)$$

When N is small so that the exhaustion occurs in the beginning of the transformation then a analytical solution becomes

$$X_c = 1 - e^{-\alpha G^3 (N_0 - 1) t^3} \quad (4-34)$$

These analytical solutions are valid for general crystallization with assumptions (Liu *et al.*, 2008; Ruitenberg *et al.*, 2001; Todinov, 2000)

- i) The sample is initially homogeneous,
- ii) Product phases are randomly distributed,
- iii) If nucleation occurs, nuclei are randomly distributed,
- iv) Average growth rates are independent of position in the sample,
- v) The reaction is not influenced by any time-dependent process (defect annihilation/creation, relieving/creation of internal stresses) in the sample which is not directly related to the transformation studied,
- vi) Impingement on objects other than neighbouring domains of the product phase is negligible,

- vii) So-called blocking resulting from anisotropic growth is negligible,
- viii) The equilibrium state is constant, i.e. the amount that can transform does not depend on time.

From eqn.4-24 the relation between X_c and X_{ext} is given by

$$\frac{dX_c}{dX_{ext}} = 1 - X_c. \quad (4-35)$$

The extended volume is a fictitious volume of the crystals imagining that the crystal growth is unimpeded by impingement upon each other. X_{ext} is therefore much easier calculated than X_c . The Avrami's expression of Eqn. (4-1) was directly derived from Eqn. (4-35). In this study, it was quickly realized that Avrami's theory based on Eqn. (4-35) is unable to capture the observed crystallisation behaviour in biodegradable polymers. The first problem is that Eqn. (4-35) always predicts to a significant incubation period for crystallisation which is very short during biodegradation (Zong *et al.*, 1999; Tsuji and Muramatsu, 2001; Tsuiji and Ikada, 2000). The second problem is that Eqn. (4-35) always predicts full crystallisation as time approaches infinity which is invalid for most biodegradable polymers. The following modification to Eq. (4-35) is used to overcome these problems:

$$\frac{dX_c}{dX_{ext}} = [1 - X_c]^\lambda. \quad (4-36)$$

Here λ , or its another form, $\eta = 1/(\lambda - 1)$, is referred to as the impingement parameter in the literature, which was introduced by previous researchers to provide a better fit with experimental data (Starink, 2001).

The next fundamental element in Avrami's theory is the governing equation for the crystallisation nuclei. In Avrami's theory, it is assumed that there exist a fixed number of nuclei at the beginning of the crystallisation and that they are gradually used up as the crystallisation continues. Eqn. (4-22) is subjected to the initial condition that $N = N_0$ at $t = 0$. During cleavage-induced crystallisation, the amorphous polymer chains only start to crystallise where chain cleavage occurs, i.e. a nucleus (a foreign inclusion for example) can only become available if a chain cleavage occurs nearby. In a small time interval of dt , the

increase in chain cleavage is quantified by dR given by eqn. (4-5). Keeping in mind that that N_0 and C_{e0} represent the initial concentrations of the nuclei and the ester bonds respectively, we propose to modify eqn. (4-22) as

$$dN = -\xi N dt - \frac{N}{1 - X_c} dX_c + \frac{N_0}{C_{e0}} dR, \quad (4-37)$$

subject to the initial condition that $N = 0$ at $t = 0$. The newly added term on the right hand side represents the nuclei released by chain cleavage over time interval of dt . In Eq. (4-37), N is the number of nuclei that are made available by polymer chain cleavage. N increases from zero to a maximum number and then decreases as crystallisation continues.

Following (Avrami, 1939; Avrami, 1940; Avrami, 1941), the extended volume fraction of the crystals, X_{ext} , can be calculated as

$$X_{ext} = \int_0^t V_{sing}(t - \tau) \xi N(\tau) n_A d\tau \quad (4-38)$$

in which n_A is the Avogadro's number (6.02×10^{23}) and $V_{sing}(t - \tau)$ is the volume of a single crystal at time t that is nucleated at time τ . Avrami's theory assumes linear growth for a single crystal. For polymers the crystal grows through chain folding which is constrained by the entropic frustration of the participating polymer chains (Muthukumar, 2002). Consequently the crystallised lamellae can only reach a limited size, which is referred to as r_{max} . In this chapter, the linear growth limited by a maximum size is approximated by the following function:

$$r = r_{max} \left(1 - e^{-\frac{G}{r_{max}}(t-\tau)} \right) \quad (4-39)$$

in which G is the linear growth rate. We then have $V_{sing}(t - \tau) = \alpha r^3$ and Eq. (4-38) becomes

$$X_{ext} = \int_0^t \alpha r_{max}^3 \left(1 - e^{-\frac{G}{r_{max}}(t-\tau)} \right)^3 \xi N(\tau) n_A d\tau \quad (4-40)$$

in which α is a numerical constant depending on the shape of the crystal.

As demonstrated in the previous work by Wang *et al.* (2008), it is constructive to use the non-dimensional form of the governing equations. The following non-dimensional variables are introduced:

$$\bar{C}_e = \frac{C_e}{C_{e0}}; \bar{C}_{ol} = \frac{C_{ol}}{C_{e0}}; \bar{R} = \frac{R}{C_{e0}}; \bar{N} = \frac{N}{C_{e0}}; \bar{x}_i = \frac{x_i}{l}; \bar{t} = \frac{t}{(1/k_2 C_{e0}^n)} = \frac{t}{t_0} \quad (4-41)$$

together with the following non-dimensionalised parameters in the model:

$$\bar{D}_0 = \frac{D_0}{k_2 l^2 C_{e0}^n}; \bar{k}_1 = \frac{k_1}{k_2 C_{e0}^n}; \bar{N}_0 = \frac{N_0}{C_{e0}}; \bar{r}_{\max} = \alpha C_{e0} n_A r_{\max}^3; \bar{G} = \frac{t_0 G}{r_{\max}}; \bar{\xi} = t_0 \xi. \quad (4-42)$$

Here C_{e0} is the mole concentration of the amorphous ester bonds at the beginning of biodegradation and l is a characteristic length of device. The governing equations then become

$$\frac{d\bar{R}}{d\bar{t}} = \bar{k}_1 \bar{C}_e + \bar{C}_e \left(\frac{\bar{C}_{ol}}{1 - X_c} \right)^n; \quad (4-43)$$

$$\frac{d\bar{C}_{ol}}{d\bar{t}} = \frac{d\bar{R}}{d\bar{t}} + \text{div}_{\bar{x}_i} \left(\bar{D} \text{grad}_{\bar{x}_i} (\bar{C}_{ol}) \right); \quad (4-44)$$

$$\frac{d\bar{C}_e}{d\bar{t}} = -\frac{d\bar{R}}{d\bar{t}} - \frac{C_e}{1 - X_c} \frac{dX_c}{d\bar{t}}; \quad (4-45)$$

$$\frac{dX_c}{dX_{ext}} = [1 - X_c]^\lambda; \quad (4-46)$$

$$d\bar{N} = -\bar{\xi} \bar{N} d\bar{t} - \frac{\bar{N}}{1 - X_c} dX_c + \bar{N}_0 d\bar{R}; \quad (4-47)$$

$$X_{ext} = \bar{r}_{\max}^3 \bar{\xi} \int_0^{\bar{t}} \left(1 - e^{-\bar{G}(\bar{t}-\bar{\tau})} \right)^3 \bar{N}(\bar{\tau}) d\bar{\tau}. \quad (4-48)$$

Eqns. (4-43) to (4-48) form the governing equations for simultaneous biodegradation and crystallisation. Eqns. (4-43) to (4-45) govern the biodegradation while Eqns. (4-46) to (4-48) govern the crystallisation. The last term in Eqn. (4-45) connects biodegradation with crystallisation in the simple sense that crystallisation reduces the concentration of the amorphous polymers. The last term in Eqn. (4-47) connects crystallisation with biodegradation in the simple sense that an existing nucleus can only become available for crystallisation if a chain cleavage occurs nearby. It is useful to point out the following

issues when comparing the model predictions with experimental data:

- a) As biodegradation approaches its end, most of the amorphous polymer chains are exhausted and the validity of Eqns. (4-37) and (4-39) become questionable. We are however less interested in the last part of the degradation as a device would have broken apart by then.
- b) For simplicity the molecular weight distribution of the amorphous polymer chains has been simplified into a bimodal distribution, which is characterised by C_e and C_m . Assuming the monomers are too small to detect using standard experimental techniques, the measured average molecular weight M can be related to C_e such that $M/M_0 = C_e/C_{e0}$ in which M_0 and C_{e0} are the initial values of the average molecular weight and ester bond concentration respectively. The model does not distinguish between number averaged and weight averaged molecular weights, which is a shortcoming of the simplification. One needs to choose one of the averaged molecular weights. The parameters in the model, k_1 and k_2 , are then defined accordingly.
- c) The volume degree of crystallinity, X_c , does not include the effect of weight-loss which has to be considered when comparing with experimental data. The observed degree of crystallinity is given by, $X_{obs} = X_c/(1-W)$, in which W represents the weight-loss in percentage which can be calculated from knowing the monomers diffusing out of the material.

4.3. MODEL VALIDATION

A computer programme is developed to solve the equations (4-43) to (4-48) numerically for infinitively large plate of thickness $2l$. At the surface of the plate, it is assumed that any

oligomer arriving at the surface is immediately taken away by the aqueous medium. The numerical details are presented in a flow chart Fig. 4-5. Finite difference method is used to solve differential equations. However to demonstrate the robustness of the numerical procedure and to check the computer code, the numerical model is reduced to Avrami's theory by switching off biodegradation and diffusion. A initial value, N_0 , was set for the number of nuclei and a very large value was used for $r_{\max}$. Analytical solutions to Avrami's theory are given by (Avrami, 1939; Avrami, 1940; Avrami, 1941).

Fig. 4-6 shows the comparison between the numerical and analytical solutions (4-32) and (4-33). It can be seen from the figure that the current model can be successfully reduced to the Avrami's theory. The degradation and diffusion parts of the numerical model have been validated in the previous work against finite element solution obtained using a commercial package (Wang *et al.*, 2008).

Tsuji and his co-workers carried out a series of long term biodegradation experiments and published complete sets of data of average molecular weights, weight loss, degree of crystallinity and mechanical properties as functions of time for a range of PLA and its copolymers. The first case that we examined here is their experiment on pure PLLA and two blends of PLLA and poly(vinyl alcohol) (PVA) (Tsuji and Muramatsu, 2001). The degradation data were collected over a period of 12 months. PVA was introduced as a hydrophilic water-insoluble polymer to accelerate the biodegradation. In the blend films, PLLA and PVA were phase-separated and both the PLLA and PVA phases were continuous and dispersed. The two blends have weight percentages of PLLA of 80% and 60% respectively. In all the films the PLLA phase was initially amorphous while the PVA phase was semi-crystalline. The introduction of PVA complicates the degradation behaviour, hence provides a test for the flexibility of the mathematical framework proposed in this chapter. To take account of the PVA phase in the model, Eqns. (4-43) to (4-45) are modified to ensure that hydrolysis reaction only occurs in the amorphous region of the PLLA. This is achieved by adding the volume fraction of PVA to X_c in Eqns. (4-43) and (4-45). The crystalline phase of the PVA was excluded as well as the crystalline phase in the PLLA

when calculating the effective diffusion coefficient. Fig. 4-7 shows the fitting between the model and the experimental data for weight percentage of PLLA of 100% (Fig. 4-7(a)), 80% (Fig. 4-7(b)) and 60% (Fig. 4-7(c)) respectively. Table 4-1 shows the parameters used in the model to fit the experimental data which will be discussed together with other cases at the end of this section.

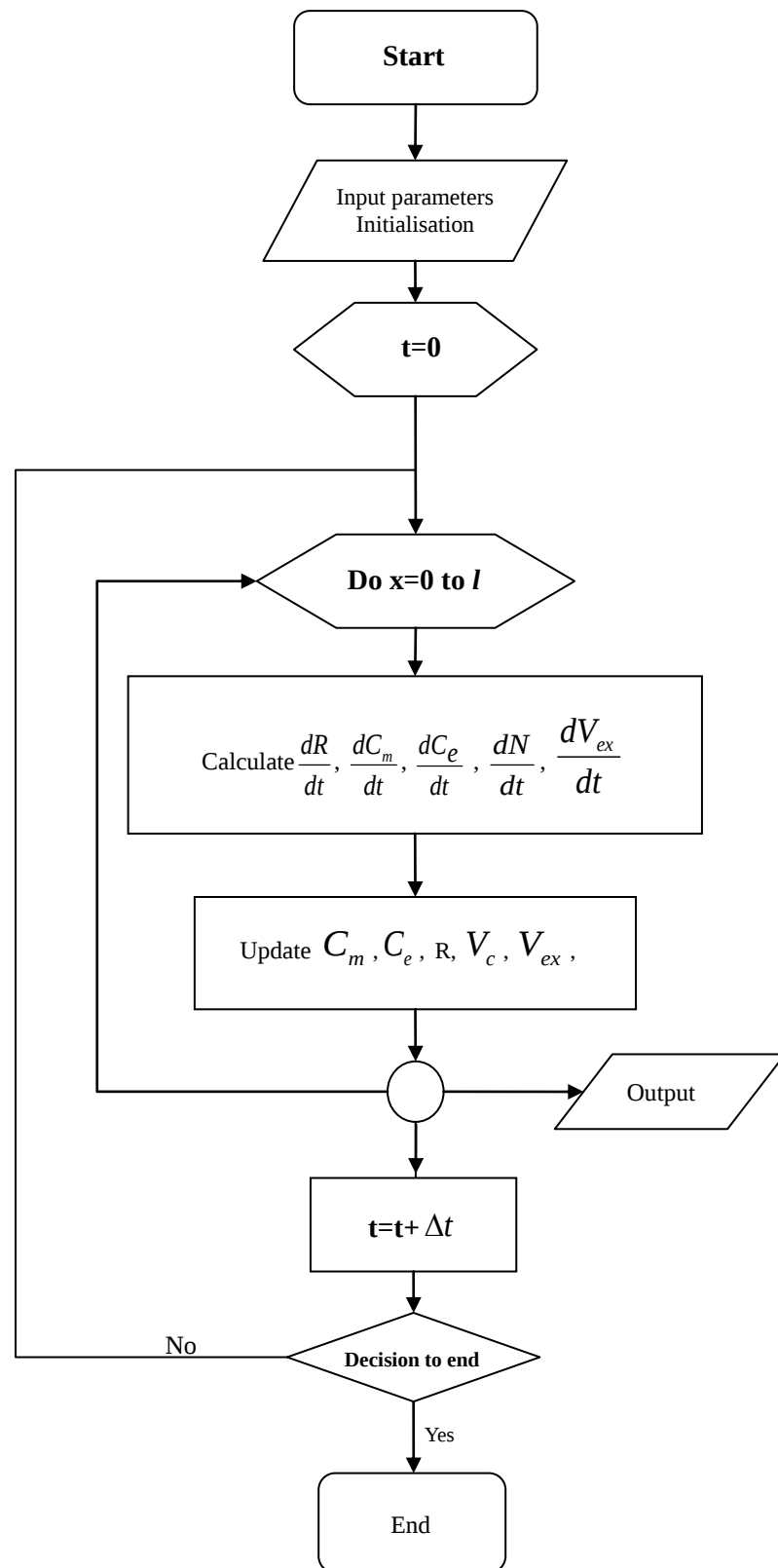


Fig. 4-5 Flow chart for the model

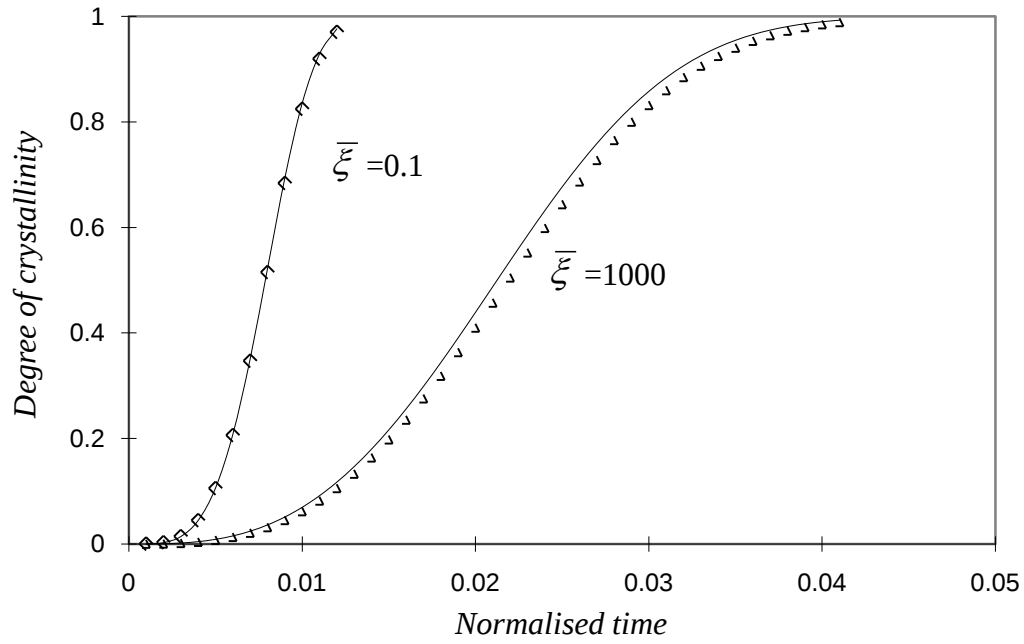
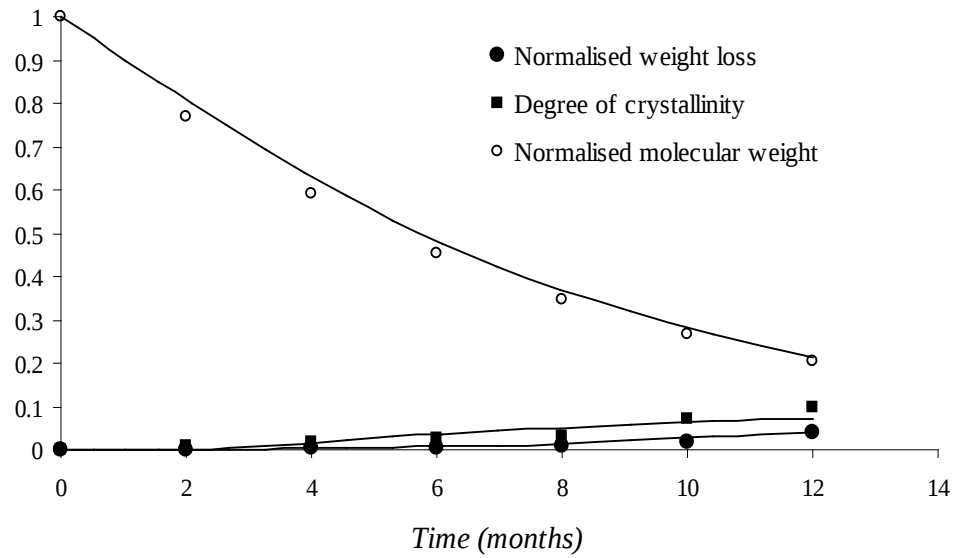


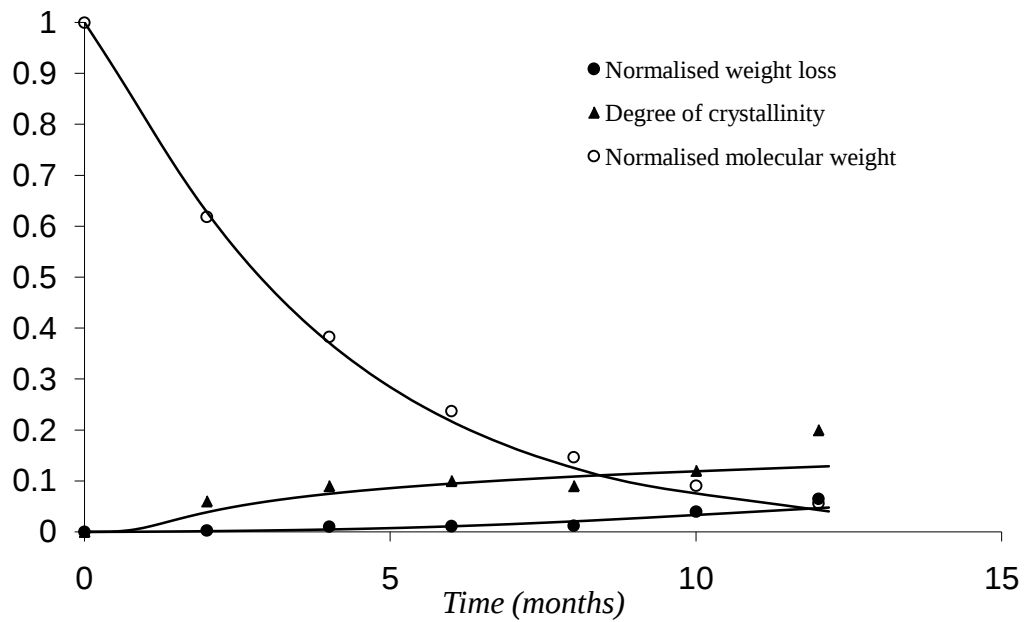
Fig. 4-6 Degree of crystallinity as a function of time for large and small values of $\bar{\xi}$ - a comparison between the analytical solutions of the Avrami's theory (solid lines) and the numerical solutions (discrete symbols) of the simultaneous degradation and crystallisation model when it is reduced to the Avrami's theory. $\bar{N}_0 = 1$; $\bar{G} = 1$; $\lambda = 1$; $\bar{r}_{\max} = 4\pi/3 \times 10^8$.

Table 4-1: Parameters used in the model to fit the experimental data for the different cases.

Parameters Materials		$\bar{D}_0$	$\bar{k}_1$	$\bar{N}_0$	$\bar{r}_{\max}$	$\bar{G}$	$\bar{\xi}$	η	t_0 (week)
PLLA/PVA	$V_{PLLA}=100\%$	0.00 2	2	1	$4\pi/3 \times 10^5$	0.05	1000	0.015	94.54
	$V_{PLLA}=80\%$	0.00 05	2	1	$4\pi/3 \times 10^5$	0.1	1000	0.015	49.52
	$V_{PLLA}=60\%$	0.00 5	2	1	$4\pi/3 \times 10^5$	1	1000	0.015	40.8
PLLA	$X_{c0}=0.4$	0.00 2	1	1	$4\pi/3 \times 10^5$	0.3	1000	0.08	109.1
	$X_{c0}=0.47$	0.02	1	1	$4\pi/3 \times 10^5$	0.7	1000	0.08	94.23
	$X_{c0}=0.54$	0.02	5	1	$4\pi/3 \times 10^5$	1	1000	0.125	312
PLA-co- PGA		1	2	1	$4\pi/3 \times 10^5$	2	1000	0.1	14.29



(a) 100% PLLA



(b) 80% PLLA

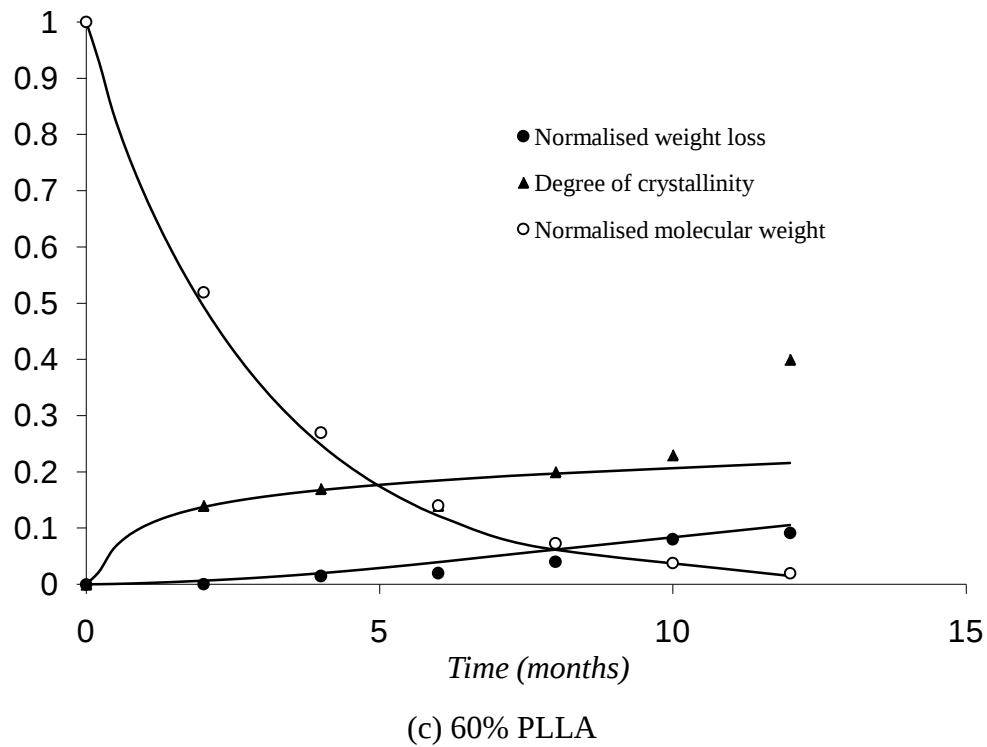
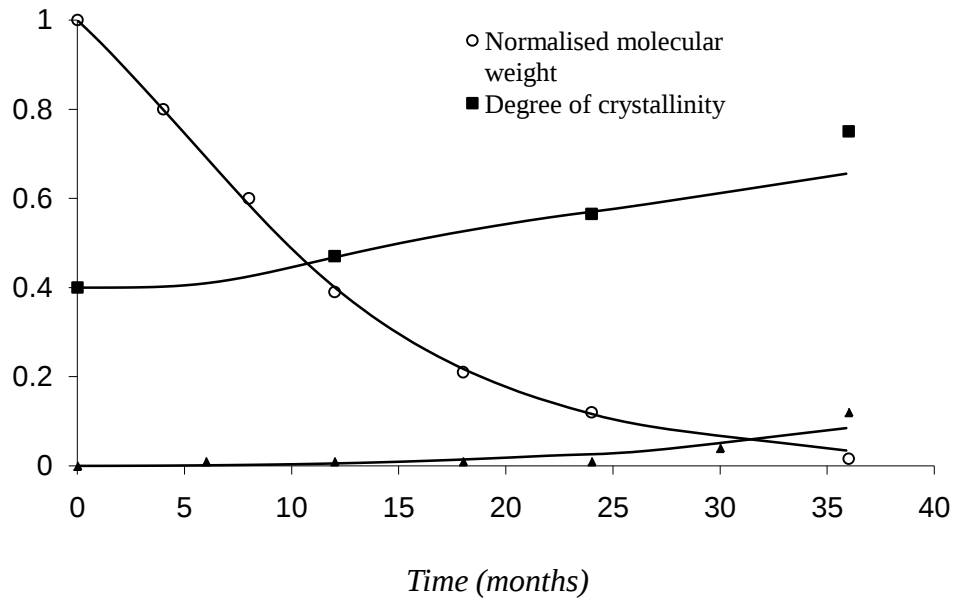


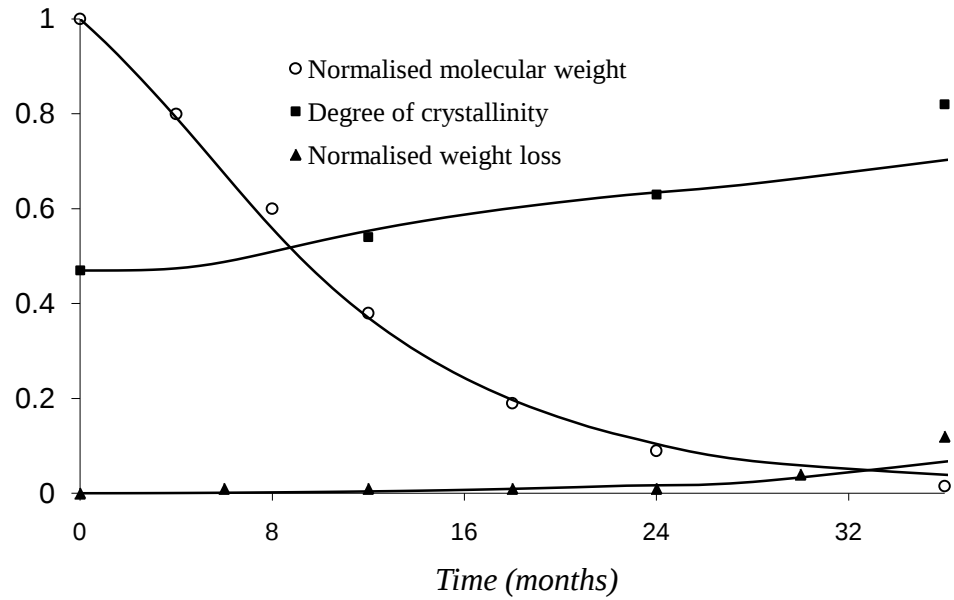
Fig. 4-7 Comparison between the model and the experimental data obtained by Tsuji and Muramatsu (2001) for average molecular weight of PLLA, volume degree of crystallinity of PLLA and weight loss of the film as functions of time for volume percentage of PLLA = 100% (a), 80% (b) and 60% (c) respectively. The continuous lines represent the model prediction while the discrete symbols are the experimental data. The parameters used in the model are given in Table 4-1.

The second case that we studied is their experiment on pure PLLA films with different degrees of initial crystallinity (Tsuji and Ikada, 2000), which were achieved by annealing the PLLA films at different temperatures. The experimental data were collected over a period of 36 months. The actual morphology of the semi-crystalline PLLA is complicated. There are different dimensional and spacing parameters of the crystalline lamellae as well as the size of the crystalline spherulites. There are also amorphous phase inside and outside the crystalline spherulites. All these structural details are ignored in this model and the degree of crystallinity is the only parameter used to describe the crystalline phase. This case, therefore, provides a test for the simplification in the model. Fig. 4-8 shows the fitting

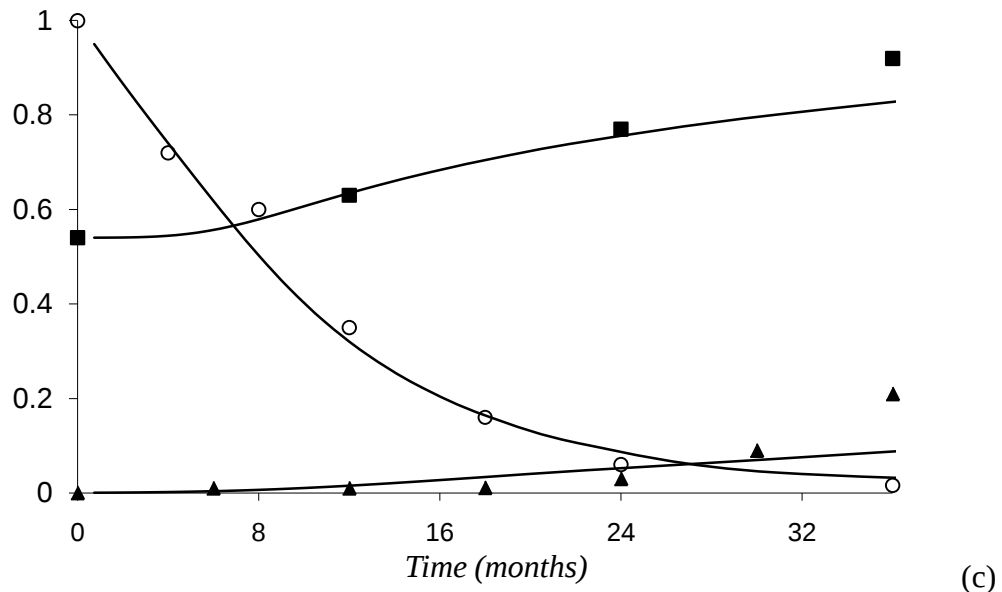
between the model and the experimental data for PLLA with initial degree of crystallinity of 40% (Fig. 4-8(a)), 47% (Fig. 4-8(b)), and 54% (Fig. 4-8(c)) respectively. Table 4-1 shows the parameters used in the model in order to fit the experimental data. The third case that we examined is the poly(glycolide-co-L-lactide) studied by Zong *et al.*(1999). Fig. 4-9 shows the fitting between the model and the experimental data. Again the parameters used in the model are given in Table 4-1. This is a fast degradation case which took just two weeks to complete. Similar to the second case, the crystalline morphology experienced a sophisticated evolution as clearly explained by Zong *et al.*(1999).



(a) $X_{c0} = 40\%$



(b) $X_{c0} = 47\%$



$X_{c0} = 53\%$

Fig. 4-8 Comparison between the model and the experimental data obtained by Tsuji and Ikada (2001) for PLLA films of different initial degree of crystallinity, showing average molecular weight, volume degree of crystallinity, and weight loss as functions of time. The continuous lines represent the model prediction while the discrete symbols are the experimental data by Tsuji and Ikada. The parameters used in the model are given in Table 4-1.

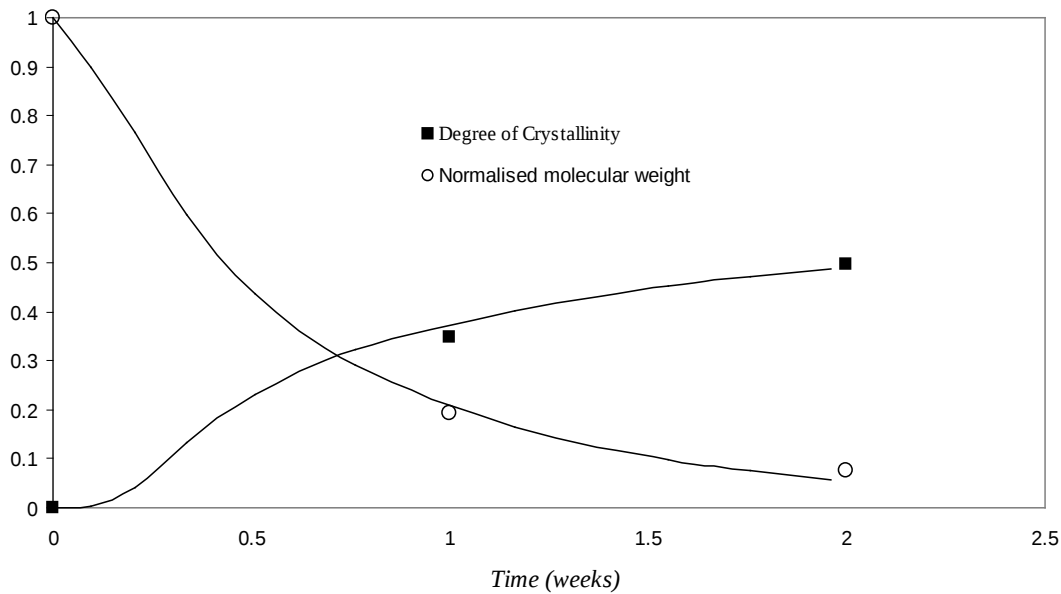


Fig. 4-9 Comparison between the model and the experimental data obtained by Zong *et al.* (1999) for poly(glycolide-co-lactide), showing average molecular weight and volume degree of crystallinity as functions of time. The continuous lines represent the model prediction while the discrete symbols are the experimental data by Zong *et al.* (1999). The parameters used in the model are given in Table 4-1.

It can be observed from Figs. 4-7 to 4-9 that the model fits with all the experimental data very well except for the last data points where the model is invalid. During the biodegradation, the crystallisation, hydrolysis reaction and diffusion of the hydrolysis are highly interconnected. The crystallisation reduces the region where the hydrolysis reaction operates, the hydrolysis reaction encourages further crystallisation and the diffusion process retards the auto-catalytic hydrolysis reaction and leads to weight-loss. Figs 4-7 to 4-9 show that the model developed in this chapter can capture this sophisticated interplay for three very different biodegradable polymers. The material parameters obtained for the three biodegradable polymers are presented together in Table 4-1 so that they can be examined together. The parameters are presented in the non-dimensional form for an easy comparison between the different materials. As will be seen in the following section of this chapter, four

of the crystallisation parameters, including $\bar{N}_0$, $\bar{r}_{\max}$, $\bar{G}$ and $\bar{\xi}$, affect the crystallisation rate as a group. We therefore fixed $\bar{N}_0$, $\bar{r}_{\max}$, and $\bar{\xi}$ for all the materials and only varied $\bar{G}$. $\bar{N}_0 = 1$ means that we have assumed each chain cleavage gives a new nucleation site; Using $C_{e0} = 17300 \text{ mole}/m^3$ for PLLA and $n_A = 6.02 \times 10^{23}$, $\bar{r}_{\max} = 4\pi/3 \times 10^5$ corresponds to a maximum size of the polymer crystals of $20nm$; $\bar{\xi} = 1000$ corresponds to the upper limit of $\bar{\xi}$ in the original Avrami's theory. $\bar{G} = 1$ corresponds to a growth rate at which a crystal reaches its maximum size of $r_{\max}$ at $t = t_0$. The values of $\bar{G}$ in Table 4-1 correspond to rather slow growth but this is because the large values of $\bar{N}_0$ and $\bar{\xi}$ used in the model. The impingement factor, η , is a fitting parameter in the model which has a profound impact on the crystallisation behaviour. It will be further discussed in the following section of this chapter. The intrinsic diffusion coefficient, $\bar{D}_0$, was mainly determined by the weight-loss. $\bar{k}_1$ and t_0 are mainly determined by the reduction rate of the average molecular weight. $\bar{D}_0$, $\bar{k}_1$ and t_0 can therefore be regarded as being measured through the model and the experiments.

4.4. THE INTERPLAY BETWEEN DEGRADATION AND CRYSTALLISATION

It is useful to study what the model predicts in terms of the effect of crystallisation rate on the apparent hydrolysis rate of the material. The apparent hydrolysis rate can be characterised using the time required for $\bar{C}_e$ to reach a fix value, say 0.5. The crystallisation rate can then be characterised using the corresponding value of $X_c - X_{c0}$ at $\bar{C}_e = 0.5$. However there are five parameters in the crystallisation model, including $\bar{N}_0$, $\bar{r}_{\max}$, $\bar{G}$, $\bar{\xi}$, and η , which all affect the crystallisation rate. Fig. 4-10 shows the calculated degrees of crystallinity as a function of time using a wide range of values of the five parameters which all give $X_c = 0.2$ at $\bar{C}_e = 0.5$. It can be clearly seen from the figure that if the

impingement factor η is fixed, then X_c at a fix value of $\bar{C}_e$ almost completely determines the crystallisation behaviour. In other words, $\bar{N}_0$, $\bar{r}_{\max}$, $\bar{G}$, and $\bar{\xi}$, act as a group to control the crystallisation rate. The impingement factor, however, has an independent effect on the crystallisation behaviour which cannot be accommodated into the group. Fig. 4-6 shows the effect of crystallisation rate on the hydrolysis rate. The model predicts that fast crystallisation leads to fast apparent hydrolysis in the amorphous phase. It is often said in the literature that fast crystallisation retards biodegradation. This is obvious because the crystalline phase resists further hydrolysis reaction. However Tsuji and Ikada (2000) carefully distinguished this from the effect of crystallisation on the hydrolysis rate in the amorphous region and observed that the hydrolysis rate was higher in the amorphous region between the crystalline regions than that of the free amorphous region such as in a completely amorphous specimen. The model prediction is therefore consistent with the experimental observation by Tsuji and Ikada (2000). It is interesting to observe from Fig. 4-11 that the effect of crystallisation on the hydrolysis is almost independent of $\bar{k}_1$, the relative rate between the non-catalysed and auto-catalysed reactions.

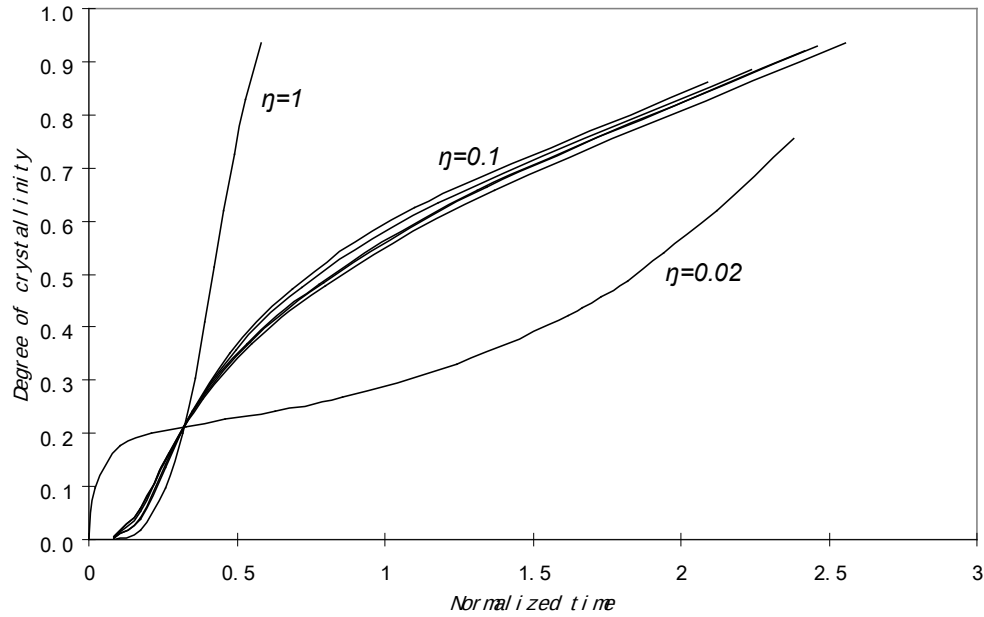


Fig.4-10 Effect of the five parameters in the crystallisation model on the degree of crystallinity as a function of time for a fixed value of $X_c = 0.2$ at $\bar{C}_e = 0.5$. For all the curves $\bar{D}_0 = 0.02$, $\bar{k}_1 = 1$ and $\bar{r}_{\max} = 4\pi/3 \times 10^4$. For the curve of $\eta = 1$, the following parameters were used: $\bar{N}_0 = 1$; $\bar{G} = 0.129$; $\bar{\xi} = 1000$. For the curve of $\eta = 0.02$, the following parameters were used: $\bar{N}_0 = 1$; $\bar{G} = 4.7$; $\bar{\xi} = 1000$. For the curve of $\eta = 0.1$, the following range of parameters were used: $\bar{N}_0 = 0.1$ to 1; $\bar{G} = 0.2$ to 10; $\bar{\xi} = 0.0013$ to 1000.

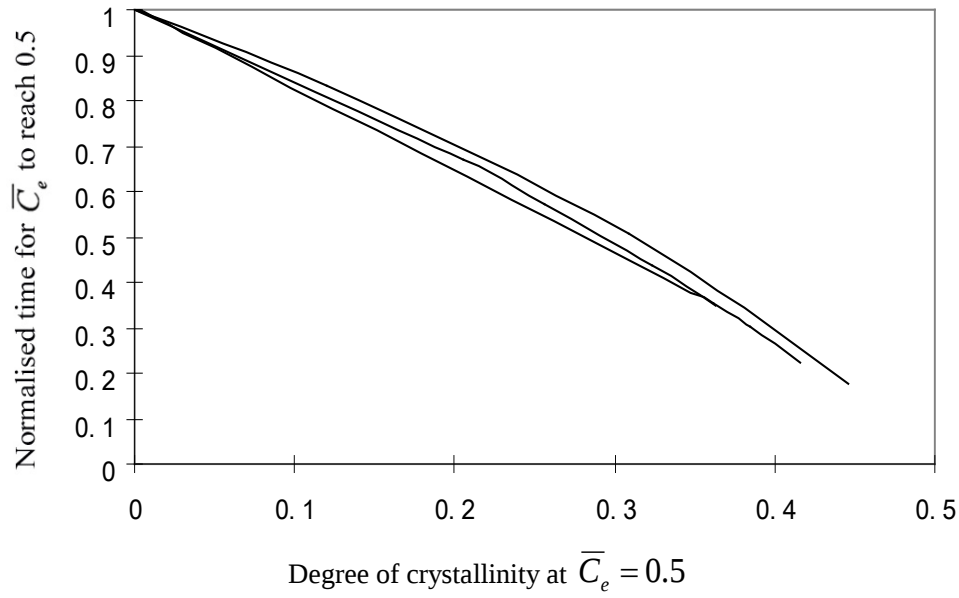


Fig.4-11 Effect of crystallisation rate on the apparent hydrolysis rate showing fast crystallisation leads to fast apparent hydrolysis. $\bar{k}_1 = 1, 100, 1000$ for the three curves respectively; $\bar{D}_0 = 0.02$.

An important concept proposed in the previous work by Wang *et al.*(2008) is the biodegradation map which shows the controlling mechanism for biodegradation in the landscape of $\bar{D}_0$ and $\bar{k}_1$. The map for infinitively large plate is presented in Fig. 4-12 where the dash lines shows the boundaries between the different zones for amorphous polymers. We recall that zone *B* is the fast diffusion zone where the polymer degradation is controlled by the non-catalysed hydrolysis. Zone *C* is the slow diffusion zone where the degradation is controlled by the auto-catalysed hydrolysis. Zone *D* is the fast non-catalysed hydrolysis zone and zone *A* is where hydrolysis and diffusion interact to control the degradation rate. Under the assumption of fast water penetration into the device, biodegradation is spatially uniform except in zone *A*. The shaded region on the map is the newly calculated zone *A* for $X_c = 0.7$ to 0.8 at $\bar{C}_e = 0.3$ to 0.4 . These values reflect a fast crystallisation rate in the biodegradation. The ranges in these values are used because it is difficult to construct the map and control the values of X_c and $\bar{C}_e$ at the same time. The

impingement factor was set as $\eta = 0.5$. Fig.4-12 shows that crystallisation makes it more likely for the biodegradation to be spatially uniform. Most of the biodegradation experiments were performed using thin samples to avoid the accumulation of acid end groups inside the film, i.e. to operate in zone *B*. The map in Fig.4-12 shows that one can use thicker samples for semi-crystallized polymers than those for amorphous polymers, which should make the following mechanical tests easier.

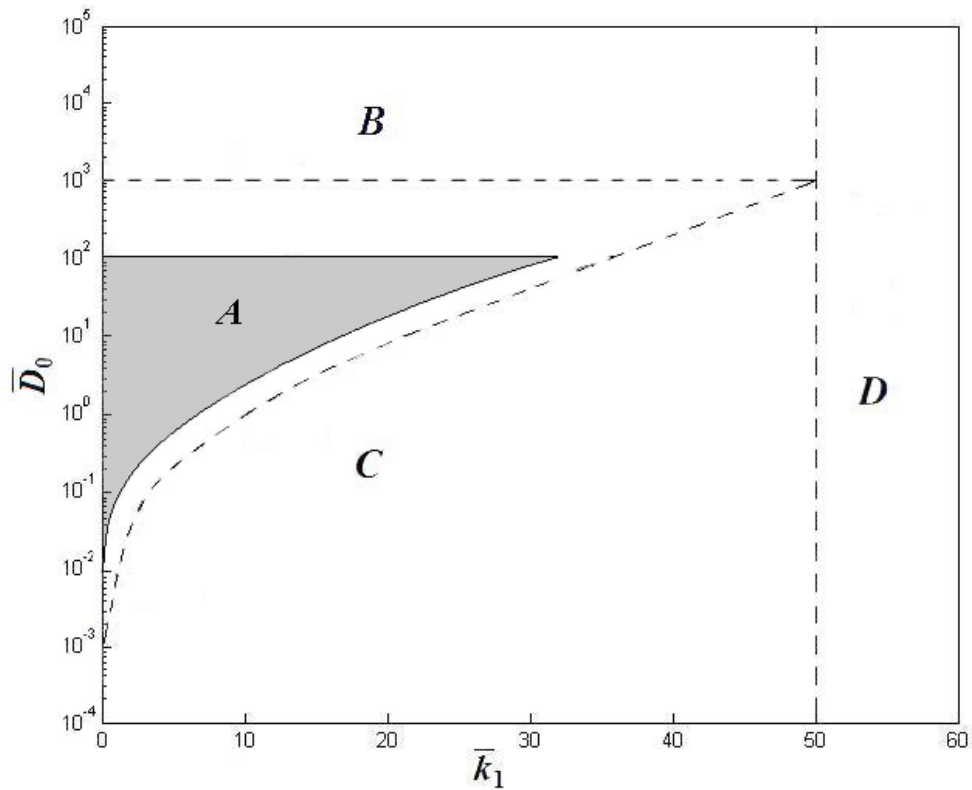


Fig. 4-12 Biodegradation map for infinitively large plate showing the controlling mechanism for biodegradation in the landscape of $\bar{D}_0$ and $\bar{k}_1$. The dash lines show the boundaries between the different zones for amorphous polymers. The shaded area is the newly calculated zone A for semi-crystalline polymers.

4.5. CONCLUSIONS

The typical degradation time for commonly used biodegradable polymers in orthopaedic surgeries can be several years. The trial and error approach in device development is very problematic. The mathematical model developed in the chapter can be solved for any sophisticated device using the modern finite element method (Wang *et al.*, 2008). A significant amount of experimental degradation data have been collected for various existing devices. It is then possible to use the finite element analysis to back-calculated the parameters in the model and to apply them to new device design using the same polymers. This is a powerful approach which will accelerate the development of various biodegradable devices.

CHAPTER FIVE - ANALYSIS OF DEGRADATION DATA OF PDLLA AND PLA OBTAINED AT ELEVATED AND PHYSIOLOGICAL TEMPERATURES USING MATHEMATICAL MODELS

The degradation of resorbable polymeric devices often takes months to years. Accelerated testing at elevated temperatures is an attractive but controversial technique. The purposes of this chapter include: (a) to provide a summary of the mathematical models required to analyse accelerated degradation data and to indicate the pitfalls of using these models, (b) to provide a simple version of the model presented in chapter three with an analytical solution that is convenient to use, and (c) to demonstrate the application of the model in two different PLA systems. It is shown that the simple analytical relations between molecular weight and degradation time widely used in the literature can lead to inadequate conclusions. In more general situations, the rate equations are only part of a complete degradation model. Together with previous works in the literature, our study calls for care in using the accelerated testing technique.

5.1. INTRODUCTION

When using a medical device made of biodegradable polymers, it is important to know the degradation rate of the polymers, which can be determined using *in vitro* or *in vivo* experiments. Samples are retrieved at predetermined time intervals and the molecular weight, degree of crystallinity and mass loss are monitored. However the degradation of the resorbable polymeric devices at physiological temperatures can take months to years. For example the complete degradation of PLLA interference screws in human body has been reported to take four years (Alan Barber *et al.*, 2000). On the other hand, similar polymers took only 25 days to fully degrade at 70°C (Weir *et al.*, 2004). It is therefore a very attractive proposition to obtain degradation data at elevated temperatures and then extrapolate the results to 37°C (Buchholz, 1992). An obvious concern is whether the elevated temperatures alter the mechanism of degradation making the data obtained at elevated temperatures irrelevant to degradation at 37°C. Various researchers have studied the accelerated testing strategy. Bergsma *et al.* (1995) tested homopolymer PLLA and a copolymer PLA96 (96% L4%D lactide) at 90°C in a phosphate buffered solution and

concluded that although the degradation temperature is well above the glass transition temperature and not comparable to physiological temperatures, there seems to be good correlation between the *in vitro* degraded material and physiologically degraded material. Weir *et al.* (2004^a, 2004^b) carried out a series of degradation experiments on PLLA at 70°C, 50°C and 37°C respectively to investigate the potential of accelerated testing. They concluded that the degradation proceeds by a very similar mechanism at the elevated temperatures to that observed at 37°C both *in vitro* and *in vivo*. D'Souza *et al.* (2005) carried out accelerated testing of *in vitro* release of leuprolide from poly(lactide-co-glycolide) microspheres and concluded that short-term *in vitro* release studies offer the possibility of correlation with long-term release. On the other hand, Agrawal *et al.* (1997) tested the degradation of a 50:50 PLA-PGA copolymer over the temperature range of 25°C to 80°C and found that the activation energies for the hydrolysis reaction at temperatures below and above the glass transition temperature were distinctly different. Lyu *et al.* (2007) studied the molecular weight change of Poly(L-lactide-co-L,D-lactic actide) over time between 37°C and 90°C and also found that the activation energies below and above the glass transition temperature were distinctly different. The study by Lyu *et al.* (2007) also showed a further complication in our understanding of the biodegradation - their molecular weight data at various temperatures cannot be fitted by the existing equations for polymer degradation. They attributed this to the lack of mobility of the –COOH chain ends at the early stage of the biodegradation which is not taken into account in the existing theories. Deng *et al.* (2005) also found that the molecular weight change of poly(glycolide-co-L-lactide) fibres does not follow the exponential relation at various temperatures.

There are two major problems in the data analysis of the previous studies in the literatures: (a) the simple analytical relations between molecular weight and time are only valid for the early stage of the degradation; but they were often used for the entire degradation test; and (b) the interplay between the hydrolysis reaction and chain-cleavage induced crystallization was ignored in these analytical relations. Some of the conclusions of these previous studies may therefore be subject to debate. The purpose of this chapter is to resolve these two problems. Firstly the rate equations for the hydrolysis reaction are outlined briefly to show why the simple analytical relations are only valid for the early stage of degradation and

why neglecting the effect of degradation-induced crystallisation can make the data analysis invalid. Secondly the degradation data obtained by Lyu *et al.*(2007) and Weir *et al.* (2004^a, 2004^b) are reanalysed using the full solutions of the mathematical model.

5.2. MATHEMATICAL MODELS FOR DEGRADATION OF BIORESORBABLE POLYMERS

5.2.1 A summary of the mathematical model for biodegradation

The equations of the model are provided here for completion (Han *et al.*, 2009; Wang *et al.*, 2008):

$$\frac{dR_s}{dt} = k_1 + k_2 C_e \left(\frac{C_{ol}}{1 - X_c} \right)^n \quad (5-1)$$

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \text{div}_{x_i} \left(D \text{grad}_{x_i}(C_{ol}) \right) \quad (5-2)$$

$$\frac{dR_{ol}}{dt} = \alpha \beta \left(\frac{R_s}{C_{e0}} \right)^{\beta-1} \frac{dR_s}{dt} \quad (5-3)$$

$$\frac{dC_e}{dt} = -\frac{dR_{ol}}{dt} - \frac{C_e}{1 - X_c} \frac{dX_c}{dt} \quad (5-4)$$

$$\frac{dX_c}{dX_{ext}} = [1 - X_c]^\lambda \quad (5-5)$$

$$X_{ext} = \int_0^t \alpha_0 r_{\max}^3 \left(1 - e^{-\frac{G}{r_{\max}}(t-\tau)} \right)^3 \xi N(\tau) n_A d\tau \quad (5-6)$$

$$dN = -\xi N dt - \frac{N}{1 - X_c} dX_c + \frac{N_0}{C_{e0}} dR_s \quad (5-7)$$

$$D = D_a \left\{ D_{matrix} + (1.3p^2 - 0.3p^3)(D_{pore} - D_{matrix}) \right\} \quad (5-8)$$

$$p = 1 - \left\{ (\bar{C}_{ol} + \bar{C}_e)(1 - X_{c0}) + X_c \right\} \quad (5-9)$$

$$D_{matrix} = \left[1.3 \left(\frac{\bar{C}_{ol} + \bar{C}_e}{\bar{C}_{ol} + \bar{C}_e + X_c / (1 - X_{c0})} \right)^2 - 0.3 \left(\frac{\bar{C}_{ol} + \bar{C}_e}{\bar{C}_{ol} + \bar{C}_e + X_c / (1 - X_{c0})} \right)^3 \right] \quad (5-10)$$

The definitions of symbols are provided in the Nomenclature. Eqn. (5-4) reflects the fact

that the amorphous polymer chains are consumed by a combination of oligomer production (the first term) and chain cleavage-induced crystallisation (the second term). Eqn. (5-5) relates the degree of crystallinity X_c to the extended degree of crystallinity X_{ext} which is fictitious by assuming that the crystals can grow into each other. Eqn. (5-6) calculates the extended degree of crystallinity from the available nucleation sites and the growth rate of a single crystal. Eqn. (5-7) calculates the available nucleation sites for crystallisation by considering (a) sites becoming active growth (the first term), (b) sites swallowed by growing crystals (the second term) and (c) sites generated by chain cleavage (the third term). Eqns. (5-8)-(5-10) are used to calculate the effective diffusion coefficient, D , of the oligomers taking into account the effect of increasing degree of crystallisation, X_c , and increasing free volume for diffusion, p , due to oligomers leaving the system. The number averaged molecular weight can be calculated as

$$M_n = \frac{(C_e + \omega X_c + C_{ol})M_0}{N_{chains}} = \frac{(C_e + \omega X_c + C_{ol})M_0}{N_{chains0} + R_s} \quad (5-11)$$

in which ω is the mole number of the repeating units of the crystalline phase per unit volume. The oligomers are usually too small to be detected by experimental techniques such as gel-permeation chromatography (GPC) and can be taken out from the calculation of the average molecular weight:

$$M_n = \frac{(C_e + \omega X_c)M_0}{N_{chains}} = \frac{(C_e + \omega X_c)M_0}{N_{chains0} + (R_s - R_{ol} / m)} \quad (5-12)$$

The following parameters in the model are temperature dependent:

- k_1 and k_2 – the non-catalytic and autocatalytic hydrolysis rate constants
- D_a – the diffusion coefficient of oligomers in fresh amorphous polymer
- G – the linear growth rate of a single crystal
- ξ – the probability of formation of growth nuclei per nucleus per unit time

We can then use the Arrhenius relations for these parameters:

$$k_1 = k_{10} e^{\frac{E_{k1}}{RT}}, \quad k_2 = k_{20} e^{\frac{E_{k2}}{RT}}, \quad D_a = D_{a0} e^{\frac{E_D}{RT}}, \quad G = G_0 e^{\frac{E_G}{RT}}, \quad \xi = \xi_0 e^{\frac{E_\xi}{RT}} \quad (5-13)$$

to extrapolate degradation data from elevated temperatures to physiological temperatures.

5.2.2 A simple version of the model and its analytical solution

The model outlined in section 5.2.1 can be greatly simplified if (a) the polymer remains amorphous during the degradation, (b) the weight loss in the samples is negligible and (c) the hydrolysis reaction is autocatalytic. Equations (5-1) – (5-11) then becomes

$$\frac{dR_s}{dt} = k_2 C_e C_{ol}^n \quad (5-14)$$

$$\frac{dC_e}{dt} = -\frac{dC_{ol}}{dt} \quad (5-15)$$

$$\frac{C_{ol}}{C_{e0}} = \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta \quad (5-16)$$

$$M_n = \frac{C_e M_0}{N_{chain0} + (R_s - C_{ol} / m)} \quad (5-17)$$

In the case of $\beta = 1$ and noticing that $n = 0.5$, an analytical solution to equations (5-14)-(5-17) can be obtained:

$$\frac{M_n}{M_{n0}} = \frac{1 - \tanh\left(\frac{t}{t_\infty}\right)^2}{1 + \rho \tanh\left(\frac{t}{t_\infty}\right)^2} \quad (5-18)$$

where

$$t_\infty = \frac{2}{\alpha k_2 \sqrt{C_{e0}}} \quad (5-19)$$

which is a characteristic time for the hydrolysis reaction, and

$$\rho = \frac{C_{e0}}{N_{chain0}} \left(\frac{1}{\alpha} - \frac{1}{m} \right) \quad (5-20)$$

in which C_{e0}/N_{chain0} is the degree of polymerisation of the polymer. Eqn. (5-18) is valid for the entire process of the biodegradation. In this section, the model parameters can be replaced by using the Arrhenius relations in section 5.2.1 in order to consider the temperature effect.

5.3. REANALYSIS OF THE DATA OBTAINED BY LYU *et al.* (2007)

Lyu *et al.* (2007) studied the degradation behaviour of Poly(L-lactide-co-L,D-lactic actide)

(70/30) random copolymer using disc samples of 12.5 mm in diameter and 1 mm in thickness cut from compression-moulded sheets. Their degradation was performed by immersing the discs in various testing solutions at various temperatures (37-90 °C), and for various periods up to 500 days. The vials were agitated at a frequency of about 10 turns per min in ovens. The testing solutions were refreshed weekly to monthly to ensure that the pH values of the solutions remained unchanged during the testing. They reported that their degradation data cannot be fitted using any of the equations. Separate equations have to be used to fit the data. They suggested that this is because the –COOH chain ends do not have enough mobility at the early stage of the degradation to fully act as the catalyst for the hydrolysis reaction. A quantitative discussion was made which revealed considerable insight into the diffusion limited hydrolysis reaction for the first time but an alternative model was missing. Here we use this model to reanalyse their molecular weight data for degradation in PBS (pH 7.4). The polymer is amorphous and the weight loss in the samples was negligible until the average molecular weight was reduced to 10% of its initial value. Both oligomer diffusion and crystallisation can therefore be taken out and the simple model presented in section 5.2.2 can be used. The values of M_0 , N_{chain0} and C_{e0} are calculated from the chemical composition, the initial molecular weight and the initial density of the polymer. The average number of repeating units, m , of oligomers is taken as 4 and the acid disassociation factor is 0.5. These values are provided in Table 5-1. Eqns. (5-14)-(5-17) are integrated with respect to time using the direct Euler scheme giving a numerical relation between the average molecular weight M_n and degradation time t .

Table 5-1. Material parameters in eqns. (5-14) – (5-17)

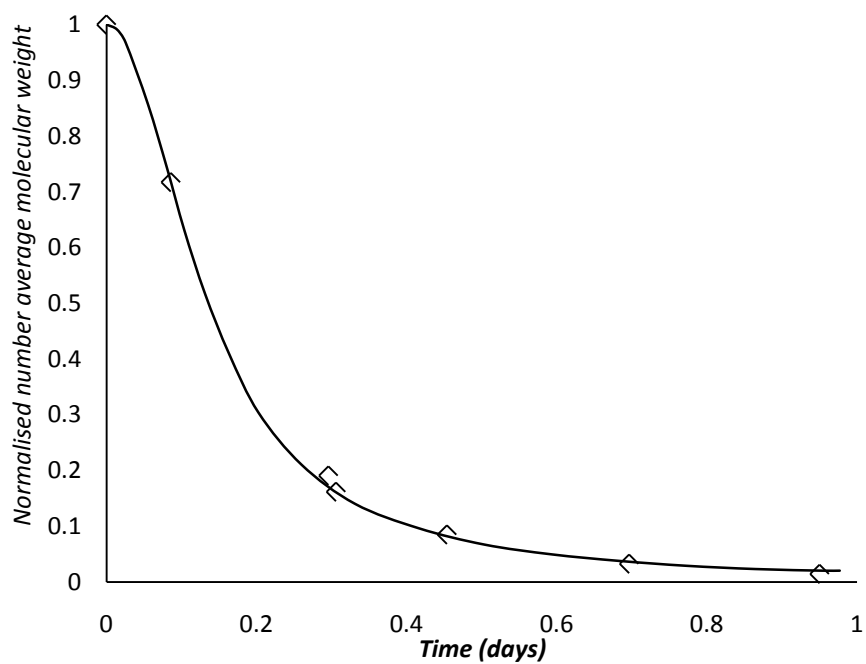
C_{e0}	M_0	N_{chain0}	m	n
17300 (mol/m ³)	72 (g/mol)	4.32 (mol/m ³)	4	0.5

Table 5-2. Model parameters that provide the best fit between eqns. (5-14) –

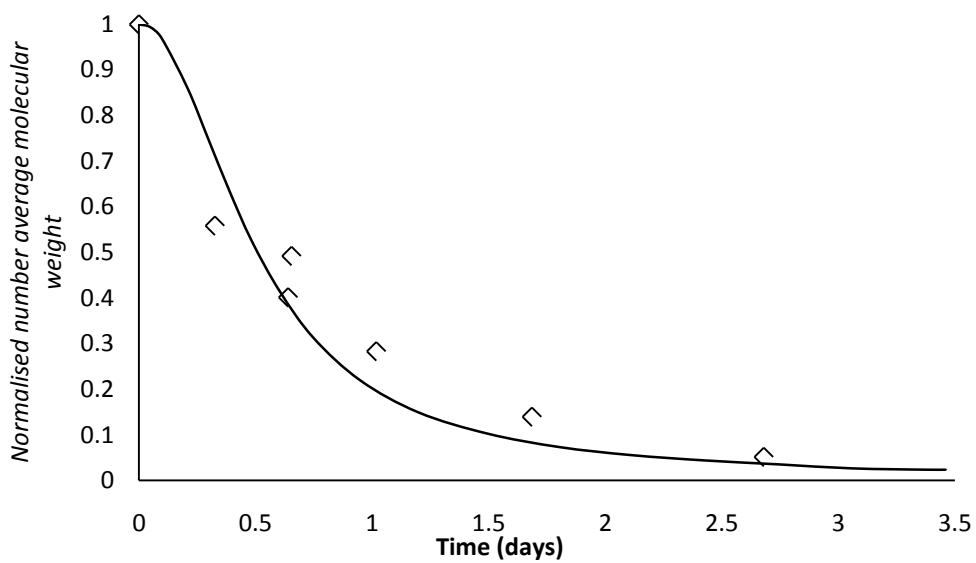
(5-17) and the experimental data for M_n as a function of time obtained by Lyu *et al.* (2007)

	$T = 90^{\circ}\text{C}$	$T = 70^{\circ}\text{C}$	$T = 55^{\circ}\text{C}$	$T = 37^{\circ}\text{C}$
k_2 ($\sqrt{m^3 / mol} / day$)	3×10^{-3}	8×10^{-4}	1.5×10^{-4}	3×10^{-6}
α	0.4			
β	1			

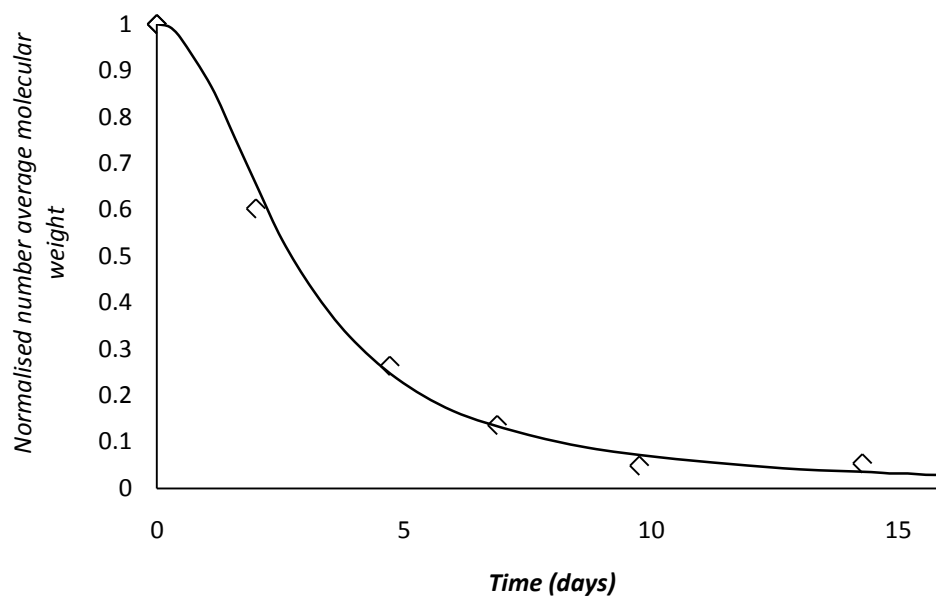
At $t=0$, C_{ol} is set at a very small value of $C_{e0} \times 10^{-12}$ to kick start the hydrolysis reaction. By varying k_2 , α and β systematically, a set of values of k_2 , α and β are obtained that give the best fit between the model prediction and the experimental data. Table 5-2 provides the values of k_2 , α and β that provide the best fit. It can be observed from the table that β is unity, which means the analytical solution of equation (5-17) can be used in this case to replace the numerical solutions. Figs. 5-1(a)–(d) show the fitting for $T = 90^{\circ}\text{C}$, 70°C , 55°C and 37°C respectively. It can be observed from the figures that the current model can fit the degradation data obtained by Lyu *et al.* (2007) without splitting the degradation into different stages. The set of values of k_2 , α and β determined in this way are unique, i.e. the fitting is sensitive to any change in these values. The values of α and β lead to $R_{ol} = 0.4R_s$ which means one oligomer is produced by chance during every ten chain scissions (assuming that the average degree of polymerisation of the oligomers is four). This is quite reasonable. The t_{∞} given by eqn. (5-19) represents the time taken for the average molecular weight to reach absolute zero. The values of k_2 in Table 5-2 lead to $t_{\infty} = 13, 48, 253$ and 12671 days for $T = 90^{\circ}\text{C}$, 70°C , 55°C and 37°C respectively, which are reasonable by examining the trend in Figs. 5-1(a) – (d).



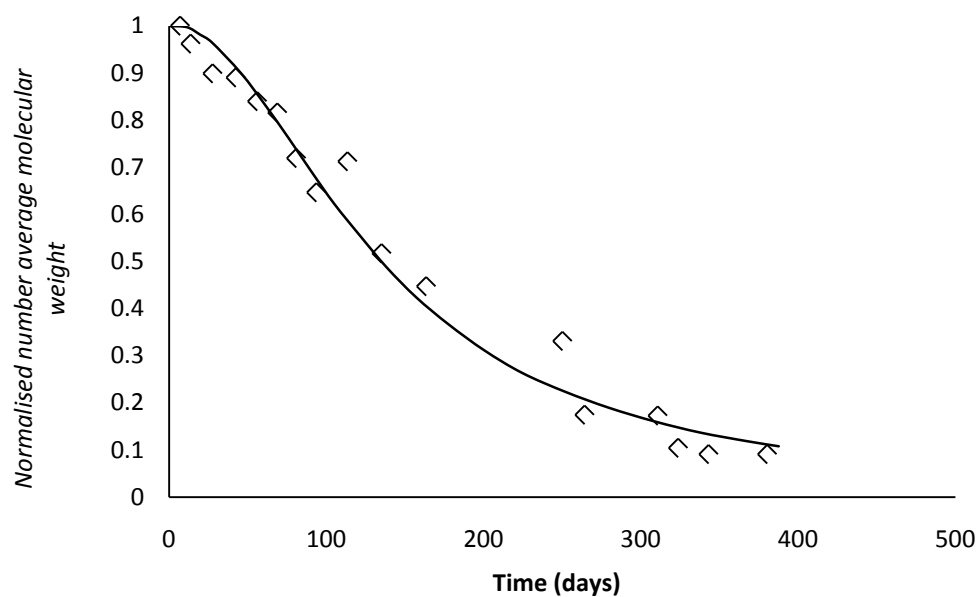
(a) $T = 90^{\circ}\text{C}$



(b) $T = 70^{\circ}\text{C}$



(c) $T = 55^{\circ}\text{C}$



(d) $T = 37^{\circ}\text{C}$

Fig. 5-1 Comparison between eqn. (5-17) (solid lines) and the experimental data (discrete symbols) by Lyu *et al.* (2007) for the number averaged molecular weight M_n as the function of time for (a) $T = 90^{\circ}\text{C}$, (b) $T = 70^{\circ}\text{C}$, (c) $T = 55^{\circ}\text{C}$ and (d) $T = 37^{\circ}\text{C}$ respectively. The parameters used in the model are provided in Tables 5-1 and 5-2.

Lyu *et al.* (2007) reported that their reaction rates, k do not obey the Arrhenius equation over the temperature range of 37°C - 90°C. Fig. 5-2 shows the relation between $\ln(k_2)$ and $1/T$ using the data in Table 5-2. It can be observed that the reaction rate constant does not obey the Arrhenius equation either. Lyu *et al.* (2007) suggested that the Vogel-Tammann-Fulcher (VTF) relation,

$$k = k_0 e^{-\frac{E_k}{R(T-T_s)}} \quad (5-21)$$

should be used, where T_s is a reference temperature. Fig. 5-3 shows $\ln(k_2)$ versus $1/(T - T_s)$ using the data in Table 5-2 and $T_s = 273K$. It can be seen from the figure that the reaction constant indeed follows the VTF relation. By fitting the data in Fig. 5-3, the pre-exponential constant and activation energy for k_2 are obtained as $k_{20} = 1.868 \sqrt{m^3/mol/day}$ and $E_{k2} = 3.66$ kJ/mol. The conclusion by Lyu *et al.* (2007) that there is a change in the activation energy in their degradation tests is therefore confirmed by this study.

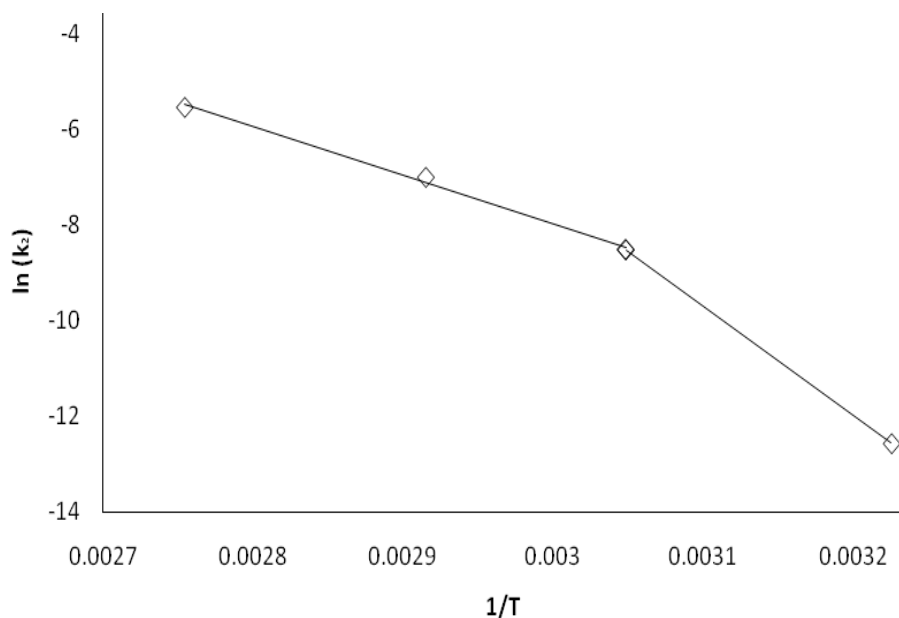


Fig 5-2. Dependence of the reaction constant on the temperature showing that the data do not obey the Arrhenius equation

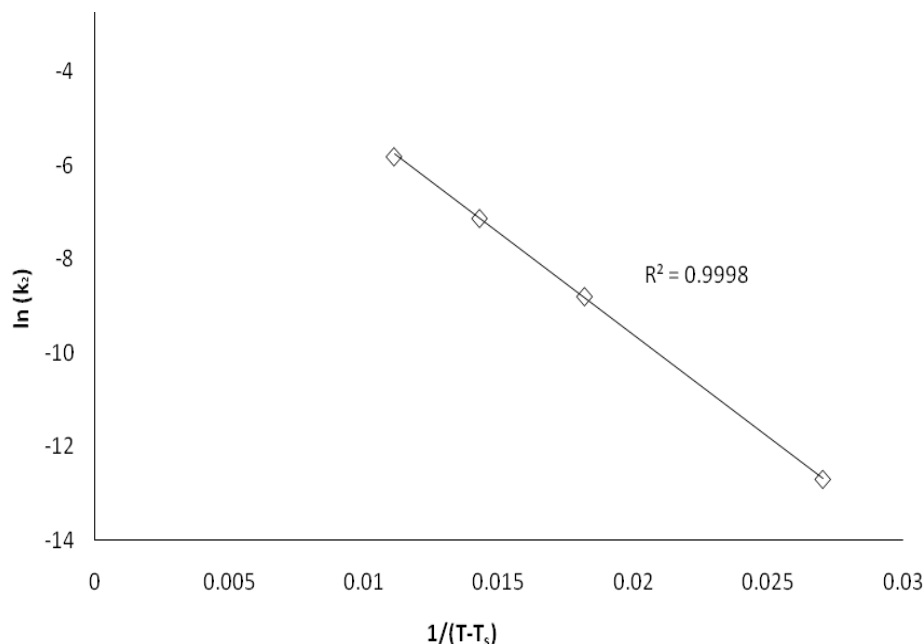
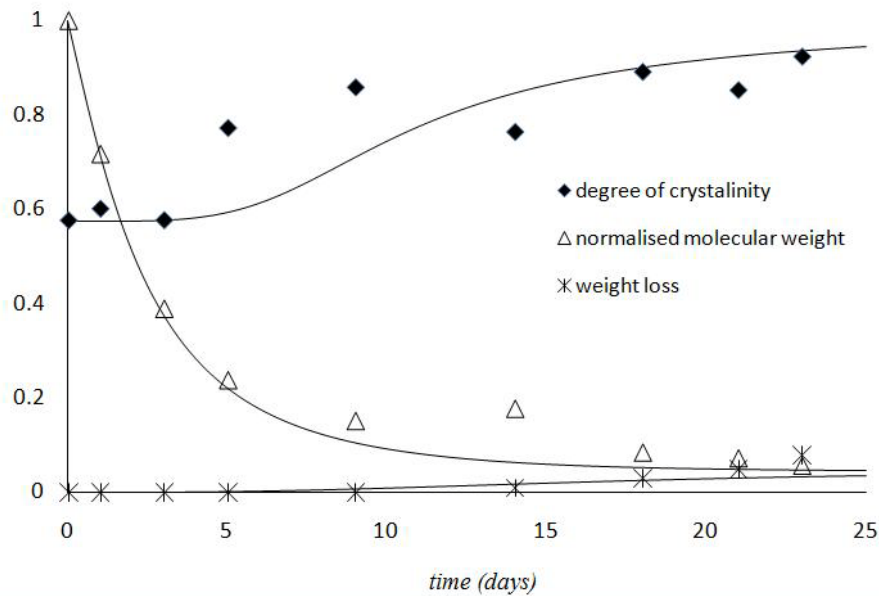


Fig 5-3. Dependence of the reaction constant on the temperature showing that the data obey the Vogel-Tammann-Fulcher relation using $T_s = 273K$.

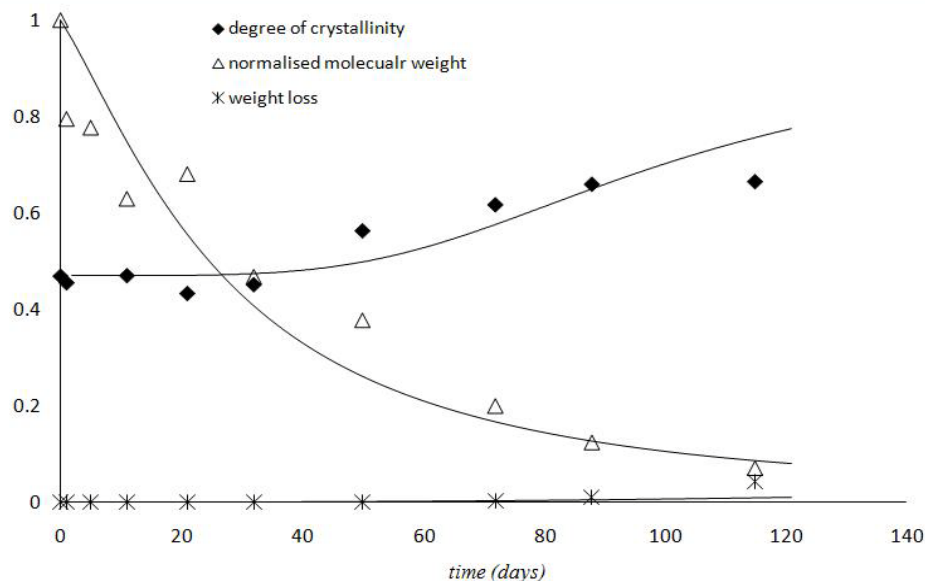
5.4. REANALYSIS OF THE DATA OBTAINED BY WEIR *et al.* (2004^a, 2004^b)

Weir *et al.* (2004^a, 2004^b) carried out a series of degradation tests on PLLA at 70°C, 50°C and 37°C respectively. The PLLA was processed by compression moulding into plates 0.8 mm thick. Tensile specimen were then cut from the plates and placed in 28 ml screw-top glass bottles and immersed in a pH 7.4 PBS. The PBS was not changed during the degradation test. A complete set of data of averaged molecular weights, mass change, degree of crystallinity and ultimate strength were measured at a series of degradation (follow-up) times. It was found that the autocatalytical model, i.e. eqn. (5-14), provides a better fit to the data and that the Arrhenius equation is valid despite that the temperature range went beyond the glass transition temperature (for PLLA $T_g = 56^\circ C$ (Zong *et al.*, 1999; Saad *et al.*, 1999; Yoda, 1998)). Weir *et al.* (2004^a, 2004^b) argued that the actual glass transition temperature may depend on the average molecular weight and the concentration of water in the polymer. The data obtained by Weir *et al.* (2004^a, 2004^b) are ideal to test the model for the interplay between the hydrolysis reaction, crystallisation and mass loss. In the current work, eqns. (5-1)-(5-10) are solved for the thin film numerically. In this case it can

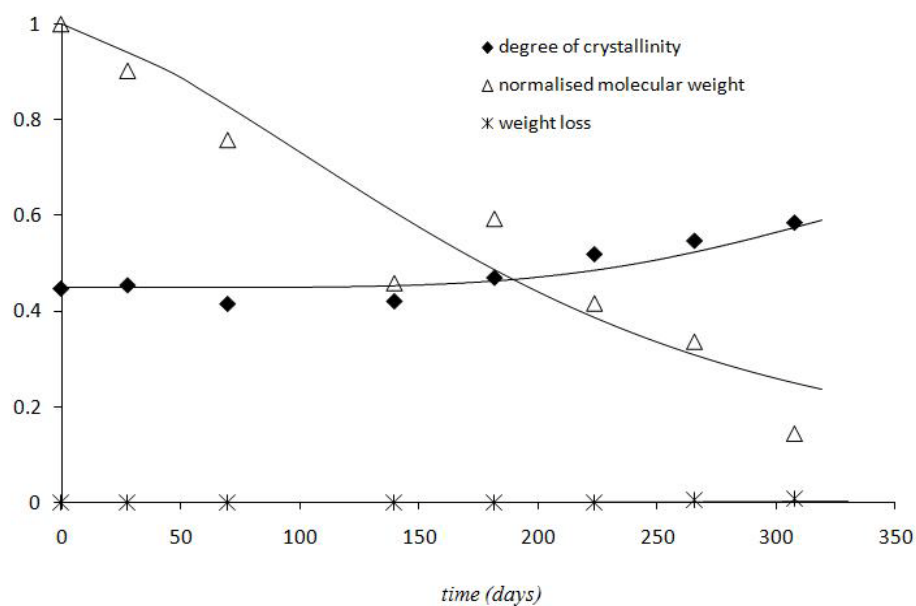
be assumed that the oligomer diffusion occurs in the thickness direction of the film and the problem is reduced to a one-dimensional one. A finite difference scheme is used for the spatial discretisation of the second term on the left hand side of equation (5-2). The integration in equation (5-6) is also carried out numerically. The direct Euler scheme is used for the time integration of all the variables involved. Further details in the numerical scheme are standard and not presented here. The initial conditions are $C_e = C_{e0}$, $X_c = X_{c0}$, $N = 0$, $C_{ol} = 0$, $R_{ol} = 0$ and $R_s = 0$ at $t = 0$. It is assumed that oligomers arriving at the interface between the film and PBS are immediately taken away by the PBS, i.e., a boundary condition of perfect sink, $C_{ol} \equiv 0$, is used at the interface. Figs 5-4(a)–(c) show the fitting between the model prediction and the experimental data for the number averaged molecular weight M_n , degree of crystallinity X_c and weight loss as functions of the degradation time at $T = 70^\circ\text{C}$, 50°C and 37°C respectively.



(a) $T = 70^\circ\text{C}$



(b) $T = 50^{\circ}\text{C}$



(c) $T = 37^{\circ}\text{C}$

Fig. 5-4 Fitting between the model prediction (solid lines) and the experimental data (discrete symbols) obtained Weir *et al.* (2004^a, 2004^b) for the number average molecular weight, volume degree of crystallinity and weight loss of PLLA as functions of the degradation time at (a) $T = 70^{\circ}\text{C}$, (b) $T = 50^{\circ}\text{C}$ and (c) $T = 37^{\circ}\text{C}$, respectively.

The thickness of the film is 0.8 mm. The model parameters used in the analysis are

provided in Tables 5-3 to 5-5. Table 5-3 contains the parameters that cannot be varied in the fitting. X_{c0} were measured by Weir *et al.* (2004^a, 2004^b). N_{chain0} , C_{e0} and M_0 are calculated from the chemical composition, the initial molecular weight and the initial density of the polymer. ω can be calculated from M_0 and the density of the polymer crystals. It should be slightly larger than C_{e0} but is taken as C_{e0} here. The average degree of polymerisation of oligomers is taken as $m = 4$. α_0 is the shape factor of the polymer crystals and is taken as $4\pi/3$ here. The acid disassociation factor n is 0.5. Parameters shown in Table 5-4 can be varied in the fitting. However their ranges of variation are limited as they have to follow common sense and obey certain limits. It is assumed that the oligomer diffusion in the liquid filled pores is much faster than that in the polymer matrix, hence D_{pore} / D_a is set at a very large value. r_{max} represents the maximum size of the polymer crystals which is taken as 13 nanometer. N_0 is the maximum possible number of nucleation sites for crystallisation which is taken as the same as the number of ester bonds. The crystallization behaviour is very sensitive to λ , which was varied in the analysis to provide the best fit. Table 5-5 shows the activation energies and pre-exponential constants for all the kinetic parameters in the model which determine the temperature dependence of the degradation behaviour. These parameters were varied to provide the best fit between the model predictions and the experimental data. Fig. 5-4 shows the fitting between the model predictions and the experimental data obtained by Weir *et al.* (2004^a, 2004^b) for the number average molecular weight, volume degree of crystallinity and weight loss of PLLA as functions of the degradation time at three different temperatures. It can be observed from the figure that this model captures the interplay between the hydrolysis, crystallisation and oligomer diffusion reasonably well. The experimental data points do not always follow a smooth trend making a smoother fitting difficult. It is important to observe that a single set of activation energies can fit all the degradation data in the temperature range. This indicates that the Arrhenius equation is valid for the PLLA as originally concluded by Weir *et al.* (2004^a, 2004^b).

Table 5-3. Material parameters in eqns. (5-1) to (5-10)

T	X_{c0}	N_{chain0}	C_{e0}	M_0	ω	m	α_0	n
37°C	44%	7.85 (mol/m ³)	17300 (mol/m ³)	72 (g/mol)	$= C_{e0}$	4	$4\pi/3$	0.5
50°C	47%	7.5 (mol/m ³)						
70°C	57%	7.5 (mol/m ³)						

Table 5-4. Parameters in eqns. (5-1) to (5-10) that provide the best fit between the model predictions and the experimental data obtained by Weir *et al.* (2004^a, 2004^b).

α	β	λ	D_{pore} / D_a	r_{max} (nm)	N_0
70	1.6	3.5	100	13	$= C_{e0}$

Table 5-5. Activation energies and pre-exponential constants that provide the best fit between the predictions of eqns. (5-1) to (5-10) and the experimental data obtained by Weir *et al.* (2004^a, 2004^b).

E_{k1}	E_{k2}	E_D	E_G	E_ξ	k_{10}	k_{20}	D_{a0}	G_0	ξ_0
161.00 <i>kJ/mol</i>	138.23 <i>kJ/mol</i>	258.53 <i>kJ/mol</i>	90.00 <i>kJ/mol</i>	211.00 <i>kJ/mol</i>	1.62×10^{21} (1/day)	1.61×10^{18} ($\sqrt{\frac{m^3}{mol}}$ /day)	3.03×10^{35} (m ² /day)	1.06×10^{11} (m/day)	9.69×10^{34} (1/day)

At 37°C the corresponding diffusion coefficient of oligomers in a fresh and amorphous polymer is $D_a = 1.157 \times 10^{-14} \text{ m}^2 / \text{s}$ which is within the range of 10^{-14} to $10^{-22} \text{ m}^2 / \text{s}$ provided by Lyu and Untereker (2007). The small diffusion coefficient reflects the fact that a very small weight loss was observed at 37°C (see Fig. 5-4(c)). The fitting is sensitive to the variations in all the parameters in Table 5-5 which means the good fitting between the experimental data and the model prediction is not due to redundant parameters in the model.

5.5. CONCLUSIONS

Care must be taken when using the simple analytical solutions to explain polymer degradation data because these solutions are only valid for the very early stage of the degradation and they exclude the effect of crystallisation and oligomer diffusion. In more general situations the model presented in the current chapter can be used to gain insight into the degradation mechanisms. It is important to point out that the usual non-catalytic and autocatalytic hydrolysis rate equations form part of the model which is able to fit the degradation data for poly(L-lactide-co-L,D-lactic acid) and PLLA without splitting the degradation into different stages. Our studies confirm the conclusion by Lyu *et al.* (2007) that their data on poly(L-lactide-co-L,D-lactic acid) do not obey the Arrhenius relation and the conclusion by Weir *et al.* (2004^a, 2004^b) that their data on PLLA obey the Arrhenius relation. These opposite conclusions for different polymer systems call for care when using the accelerated testing technique. It is necessary to identify an upper limit for the testing temperature under which the Arrhenius relation is valid for different polymer systems.

CHAPTER SIX - A DEGRADATION MODEL OF COMPOSITE MATERIALS MADE OF POLYESTERS AND TRICALCIUM PHOSPHATES

Saturation behaviour has been observed when incorporating tricalcium phosphate (TCP) in various polyesters to control the degradation rate. This chapter presents an understanding of this behaviour using a mathematical model. The coupled process of hydrolysis reaction of the ester bonds, acid dissociation of the carboxylic end groups, dissolution of the calcium phosphates and buffering reactions by the dissolved phosphate ions is modelled together using a set of differential equations. Two non-dimensional groups of the material and chemical parameters are identified which control the degradation rate of the composites. An effectiveness map is established to show the conditions under which incorporating TCP into polyesters is effective, saturated or ineffective. Comparisons are made between the model predictions and existing experimental data in the literature. The map provides a useful tool to guide the design of polyester/TCP composites for tissue engineering and orthopaedic fixation applications.

6.1. INTRODUCTION

An intensive effort is being made worldwide to develop composite materials between biodegradable polyesters and calcium phosphates and use these materials to make internal fixation devices for orthopaedic surgery, implants for bone reconstruction and scaffolds for tissue engineering. Typical examples of the calcium phosphates include hydroxyapatite (HA) and tricalcium phosphate (TCP). Examples of the polyesters are polyglycolic acid (PGA), polylactic acid (PLA) and their copolymers (PLGA). The pure polyesters, however, generate an acidic environment during degradation which can induce inflammatory tissue response, result in osteolytic reactions and delay bone healing or fusion. A fixation screw made of the polyesters can also leave a hole in the bone after full degradation. On the other hand calcium phosphates are ideal materials for healing bone defects because of their biocompatibility and osteoconductivity. TCPs in porous form are suitable for implants used in bone reconstruction or as bone substitutes. They have been used for many years to

replace or complement autologous bone in bone grafts. TCPs are however very brittle and poor in mechanical strength, which limit them to low stress bearing applications. The idea of combining the polyesters with the calcium phosphates is that the composites have good bone-bonding properties due to the osteoconductivity of the calcium phosphates. Furthermore the dissolved phosphate ions buffer the acidity of the carboxylic end groups (produced by the polyester chain cleavage) while the polyester provides the composites with the appropriate mechanical properties. Consequently the composites degrade more slowly and maintained their shape longer than the pure polymer. The pH of the surrounding media remains stable for longer periods of time for the composites than for the pure polyesters. However different researchers have observed very different buffering effects in their experimental studies. Heidemann *et al.* (2001) introduced 76% (molar) tricalcium phosphate (TCP) particles of about 2.2 μ m in diameter in a poly(D,L)lactide (PDLLA) with D/L ratio of 50:50 and weight averaged molecular weight of 220,000g/mol. They tested rod and cube samples in rats for 72 weeks and observed that the average molecular weight of the PDLLA reduces much more slowly in the TCP/PDLLA composite than in the pure PDLLA. It was unclear whether α - or β -TCP particles were used. Niemela (2005) introduced 20wt% β -TCP particles of 50-125 μ m in diameter in a PDLLA with D/L ratio of 4:96 and tested rod samples of 2.7mm in diameter in phosphate buffered saline solution (PBS) at 37°C for up to 104 weeks. They also observed that the average molecular weight of the PDLLA reduces more slowly in the composite than in the pure PDLLA. Ehrenfried *et al.* (2009) fabricated β -TCP/PDLLA composites by infiltrating and in-situ polymerisation of PDLLA respectively in continuous foams of TCP with 75% of porosity. They tested their samples in phosphate buffered saline solution (PBS) at 42°C for up 80 days and observed that the average molecular weight of the PDLLA reduces more slowly in the composite than in the pure PDLLA although the effect is much more significant in the infiltrated samples. Ehrenfried *et al.* (2008) and Yang *et al.* (2009) compared the change in the pH of the dissolution media (PBS) as a function of time between pure Poly(D,L-lactide-co-glycolide) (PLGA) and PLGA/ α -TCP composites of different weight percentages of TCP (Ehrenfried *et al.*, 2009) and different TCP particle sizes (Yang *et al.*, 2009). They observed that the incorporation of α -TCP delays the onset of pH reduction and leads to a higher pH in the solution at the end of the degradation. However their data suggest that

there exists an upper limit of the TCP weight percentage (about 30%) above further improvements in the buffering effect are small (Ehrenfried *et al.*, 2009). The data also show that for the same weight percentage of TCP, changing the particles from micron-sized to nano-sized does not improve the buffering effect in a major way (Yang *et al.*, 2009). On the other hand Ignatius *et al.* (2001) and Jin *et al.* (2006) compared the average molecular weight as the function of the degradation time between pure PDLA and PDLA/ β -TCP composites, and between pure PLGA and PLGA/ β -TCP composites. They observed no significant change in the degradation rate of the polyesters when incorporated with β -TCP of different weight fractions.

The purpose of this chapter is to present a mathematical model for the degradation of polyester/TCP composites and to present an understanding of the saturation behaviour using a mathematical model. The coupled process of the hydrolysis reaction of the ester bonds, the acid dissociation of the $-\text{COOH}$ end groups, the dissolution of the calcium phosphates, and the buffering reactions by the dissolved phosphate ions is modelled together using a set of differential equations. Comparisons are made between the model prediction and existing experimental data in the literature. Two non-dimensional groups of the physical and chemical parameters are identified which control the degradation behaviour of the composites. A TCP effectiveness map is established using the model to show the conditions under which incorporating calcium phosphates into polyesters is effective, saturated or ineffective in terms of changing the degradation rate.

6.2. GOVERNING EQUATIONS FOR POLYESTER DEGRADATION BUFFERED BY CALCIUM PHOSPHATE

Fig. 6-1 shows an example of the bioresorbable devices considered in this chapter.

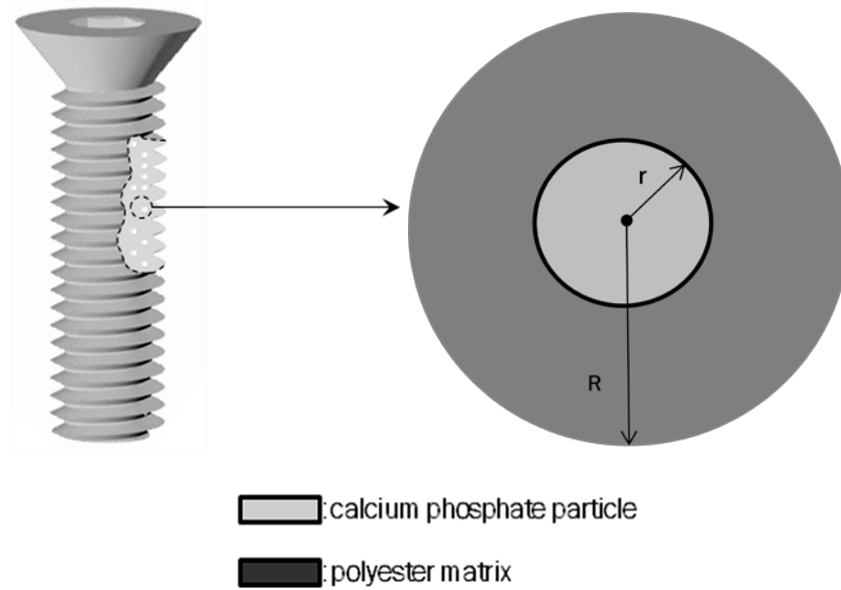
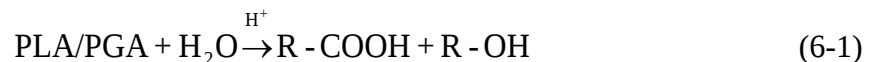
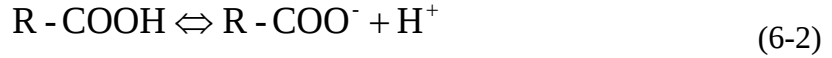


Fig. 6-1 A representative unit of a fixation device made of polyester/tricalcium phosphate composite considered in the mathematic model.

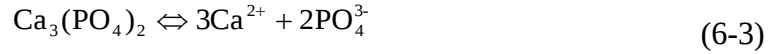
TCP particles are embedded in the polyester matrix. We consider a spherical representative unit of the composite material which contains only one particle and its surrounding polymer matrix. The first step of the biodegradation is the diffusion of water into the device. Although water absorption often continues to increase during the entire process of the device degradation, the water content reaches an abundant level in a few days and further absorption of water has little effect on the degradation rate (Wiggins *et al.*, 2006). It is therefore reasonable to assume that water is always abundant when modelling biodegradation. The hydrolysis reaction between the ester bonds and water is responsible for the chain cleavage of the polyester (Pitt and Shah, 1996; Pitt *et al.*, 1981). The reaction is catalysed by H^+ (Sykes, 1986; Lyu *et al.*, 2007) and produces hydroxyl alcohol and carboxylic acid end groups, which can be schematically described as:



Here we have neglected the actual reaction steps which can be found in (Cameron and Kamvari-Moghaddam, 2008). The carboxylic end groups have a high degree of acid disassociation:



which accelerates the hydrolysis reaction (1). On the other hand, the TCP particles dissolve in the water producing calcium and phosphate ions:



The solubility of TCP particles is rather poor. However the following buffering reactions between PO_4^{3-} and H^{+} , an inverse analogy to the dissolution of phosphoric acid (H_3PO_4) (Wong and Czemuszka, 1995), continuously shift the equilibrium of reaction (6-3) to the right and lead to further dissolution of the TCP:



These buffering reactions reduce H^{+} available as catalyst for the hydrolysis reaction (6-1) and slow down the degradation of the polyester. In solution, Ca^{2+} and PO_4^{3-} ions may also precipitate into hydroxyapatite, octacalcium phosphate, monetite or brushite depending on the pH of the hydrolysis medium (Wong and Czemuszka, 1993; Wong and Czemuszka, 1995; Lin *et al.*, 1999; Durucan and Brown, 2002; Monma *et al.*, 1998; Kanazawa, 1898). The precipitation, if present, however is only likely to occur on the surface of the polymer rather than inside the polymer matrix and is therefore not considered in this work.

Firstly considering the hydrolysis reaction (6-1), following chapter three the scission rate of the polyester chain due to the hydrolysis reaction can be expressed in two terms:

$$\frac{dR_s}{dt} = \frac{dC_{end}}{dt} = k_1 C_e + k_2 C_e C_{H^{+}} \quad (6-7)$$

where the first term on the right hand side represents the un-catalytic hydrolysis and the second term represents the auto-catalytic hydrolysis. In eqn. (6-7) R_s , C_{end} , C_e and $C_{H^{+}}$ represent the molar concentrations of total number of chain scissions, polyester chain ends,

ester bonds of all the polymer chains and H^+ in the system respectively; k_1 and k_2 represent the reaction constants for the un-catalytic and auto-catalytic hydrolysis reactions respectively. The polymer chain scission reduces the average molecular weight and produces oligomers. Following chapter three, an empirical relation between the oligomer production and polymer chain scission can be used:

$$C_{ol} = \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta \quad (6-8)$$

in which C_{ol} represents the molar concentration of all the repeating units of the oligomers, C_{e0} is the initial value of C_e , and α and β are numerical constants. We then have

$$C_e = C_{e0} - C_{ol} = C_{e0} - \alpha \left(\frac{R_s}{C_{e0}} \right)^\beta \quad (6-9)$$

The number averaged molecular weight of the polyester, excluding the oligomers, can be calculated as chapter three

$$M_n = \frac{C_e M_{unit}}{C_{end0} / 2 + (R_s - C_{ol} / m)} \quad (6-10)$$

in which M_{unit} is the molecular weight of a repeating unit of the polymer chain, C_{end0} is the initial value of C_{end} ($C_{end0} = 2C_{e0} M_{unit} / M_{n0}$) and m is the average degree of polymerization of the oligomers.

Secondly considering the acid dissociation of the carboxylic end groups, the equilibrium expression of reaction (6-2) is

$$K_a = \frac{[H^+] \times [R - COO^-]}{[R - COOH]} \quad (6-11)$$

in which K_a is the equilibrium constant. PDLLA and PGA have a disassociation constant of $pK_a = 3.87$. For pure polyesters without the buffering TCP, we have $[H^+] = [R - COO^-]$ and eqn. (6-11) leads to $[H^+] = \sqrt{K_a [R - COOH]}$ or $C_{H^+} = \sqrt{K_a C_{end} / 2}$ which was used by several authors to model the biodegradation (Lyu *et al.*, 2007; Wang *et al.*, 2008; Han *et al.*, 2009; Han *et al.*, 2010; Farrar, 2008). For the polyester/TCP composites considered here,

the hydrogen ions are consumed by the buffering reactions (6-4)-(6-6) and this expression for C_{H^+} is no longer valid. Instead eqn. (6-11) itself has to be used.

Thirdly considering the dissolution of the TCP particles, the solubility product of TCP is written as $K_s = [Ca^{2+}]_{eq}^3 [PO_4^{3-}]_{eq}^2$. At 37°C, $K_s = 3.162 \times 10^{-26}$ (mole/L)⁵ for α -TCP and $K_s = 3.162 \times 10^{-30}$ (mole/L)⁵ for β -TCP (Fernández *et al.*, 1999). The equilibrium is however broken by the buffering reactions (6-4)-(6-11) leading to an undersaturation which can be described by

$$\sigma = \left(\frac{[Ca^{2+}]^3 [PO_4^{3-}]^2}{K_s} \right)^{\frac{1}{5}} - 1 \quad (6-12)$$

This undersaturation provides a driving force for the continuous dissolution of the TCP particles. Defining a dissolution flux J as the mole of TCP molecules dissolved off a unit area of the particle surface per unit time, then J can be related to σ . Many expressions for the J - σ relationship have been proposed depending on the controlling mechanism of the particle dissolution (Bohner *et al.*, 1997; Tang *et al.*, 2001). Here a power law is adopted for its simplicity without losing the general validity because power law is a good approximation of many other expressions:

$$J = A_d |\sigma|^n \quad (6-13)$$

in which A_d and n are material constants.

Next considering the buffering reactions (6-4)-(6-6), the equilibrium expressions for these reactions are given by

$$K_1 = \frac{[H^+] \times [H_2PO_4^-]}{[H_3PO_4]}; K_2 = \frac{[H^+] \times [HPO_4^{2-}]}{[H_2PO_4^-]}; K_3 = \frac{[H^+] \times [PO_4^{3-}]}{[HPO_4^{2-}]} \quad (6-14)$$

in which, $pK_1 = 2.33$, $pK_2 = 6.82$ and $pK_3 = 11.27$ (Karickhoff *et al.*). Finally matter conservation requires

$$[R - COO^-] + [R - COOH] = C_{end} / 2 \quad (6-15)$$

$$([PO_4^{3-}] + [HPO_4^{2-}] + [H_2PO_4^-] + [H_3PO_4]) / 2 = [Ca^{2+}] / 3 \quad (6-16)$$

$$[H^+] + [HPO_4^{2-}] + 2[H_2PO_4^-] + 3[H_3PO_4] = [R - COO^-] + [H^+]_0 \quad (6-17)$$

Equations (6-7) – (6-17) form a complete set of governing equations for $[H^+]$, $[R - COOH]$, $[R - COO^-]$, $[Ca^{2+}]$, $[PO_4^{3-}]$, $[HPO_4^{2-}]$, $[H_2PO_4^-]$ and $[H_3PO_4]$ involved in reactions (6-1) – (6-6). Standard numerical procedure for solving the differential equations are used to provide the time evolution of these concentrations as well as the average molecular weight, M_n , of the polyester. The numerical details are omitted here. To demonstrate the general behaviour of the mathematical model, Figs. 6-2 and 6-3 present the numerical solutions using the material parameters provided in Tables 6-1 and 6-2 for the PDLA/TCP composite used by Heidemann *et al.*(2001).

Table 6-1. Parameters in the model which are common to all the cases in this chapter

$pK_a = 3.87$	$pK_1 = 2.33$	$pK_2 = 6.82$	$pK_3 = 11.27$	$K_s = 3.162 \times 10^{-26} (mol / L)^5$
$\alpha = 0.4$	$\beta = 1.0$	$n = 5.5$	$m = 4$	$C_{e0} = 17300$
$(C_{H^+})_{pH=7.4} = 4 \times 10^{-5}$	$(C_{Ca^{2+}})_{eq} = 2.43 \times 10^{-4}$		$\rho_{cp} = 3.14 g / cm^3$	$C_{cp,solid} = 10123$

Unit for concentrations: mol / m^3

Table 6-2. Parameters in the model for the case by Heidemann *et al.* (2001)

$w_{cp0} = 75.9\%$	$r_0 = 10 \mu m$	$\rho_{poly} = 1.25 g / cm^3$
$(M_{n0})_{composite} = 129000 g / mol$	$(M_{n0})_{PDLA} = 141000 g / mol$	$M_{unit} = 72 g / mol$
$A_d = 8 \times 10^{-5} mol / m^2 week$	$k_1 = 5 \times 10^{-5} / week$	$k_2 = 8 \times 10^{-5} \sqrt{\frac{m^3}{mol}} / week$

We have assumed that α -TCP was used in this work. Fig 6-2 shows the calculated concentrations of H^+ and Ca^{2+} versus time for the PDLA/TCP composite in comparison with the concentration of H^+ in pure PDLA. The buffering effect of the TCP can be clearly observed in the figure. The maximum concentration of hydrogen ion in the composite is about 0.42 mole/m^3 , i.e. $pH=3.38$. Fig 6-3 shows the calculated concentrations of HPO_4^{2-} , $H_2PO_4^-$ and H_3PO_4 versus time. It can be observed that $H_2PO_4^-$ is the most abundant ions in consistence with the pK values of the buffering reactions.

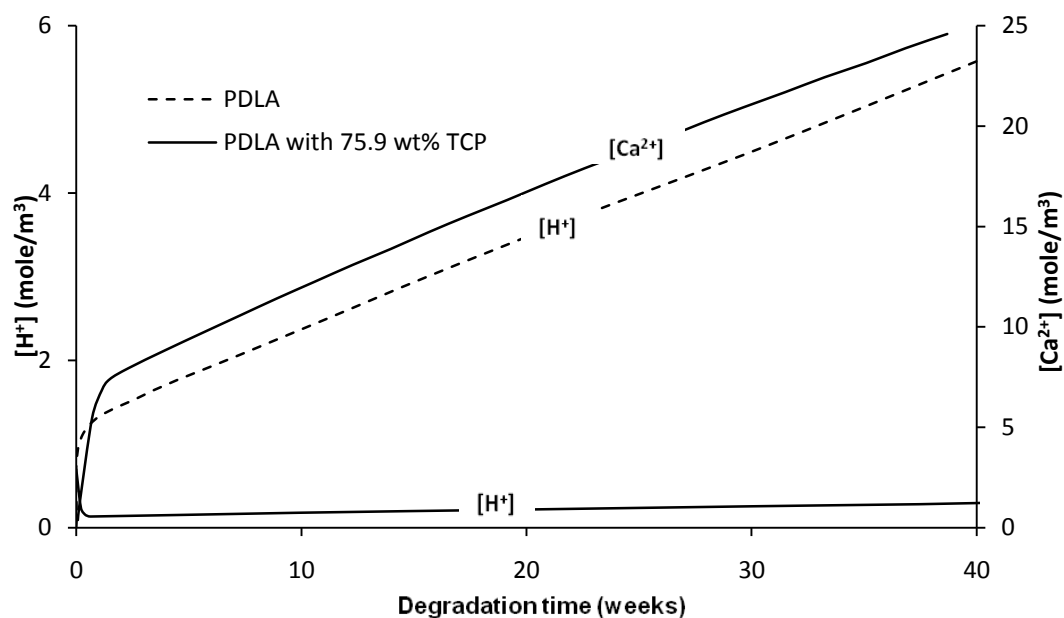


Fig.6-2 Calculated concentrations of H^+ and Ca^{2+} versus time for a PDLA/TCP composite in comparison with the concentration of H^+ in pure PDLA.

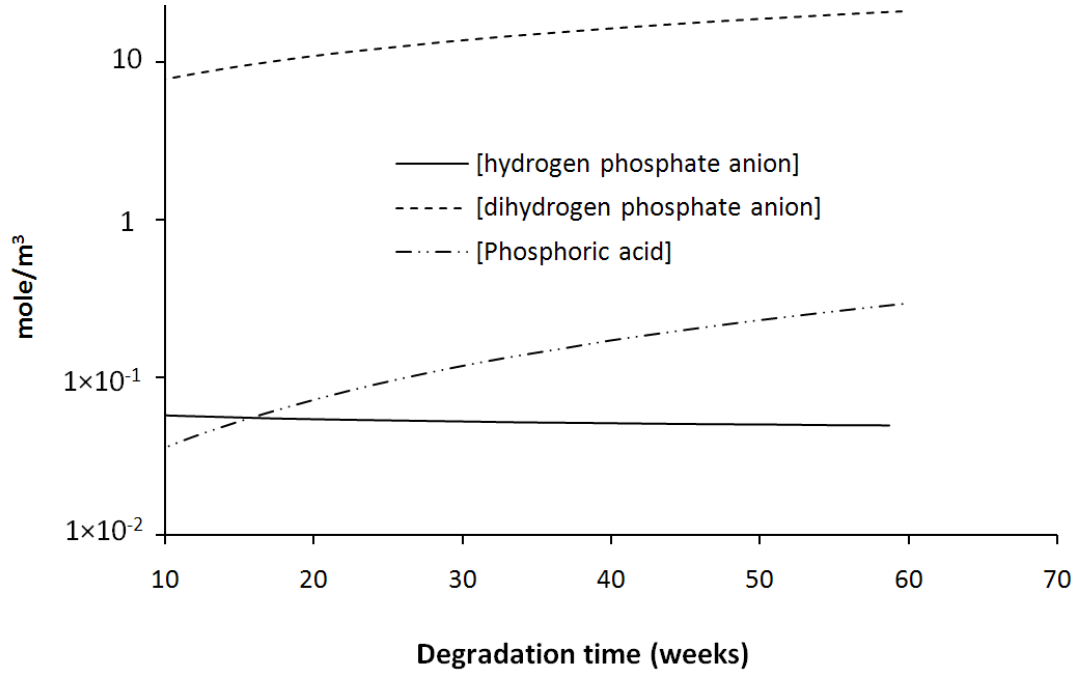


Fig.6-3 Calculated concentrations of HPO_4^{2-} , H_2PO_4^- and H_3PO_4 versus time for a PDLLA/TCP composite.

6.3. EFFECTIVENESS OF INCORPORATING TCP PARTICLES INTO POLYESTERS

The mathematical equations developed in section 2 can be used to establish the conditions under which the TCP particles are effective, ineffective or saturated in terms of changing the degradation rate of the polyester. Using the auto-catalytic hydrolysis as a reference, the rate equations (6-7) and (6-13) can be rewritten into the following non-dimensional formats:

$$\frac{d\bar{R}_s}{d\bar{t}} = \frac{d\bar{C}_{end}}{d\bar{t}} = \bar{k}_1 \bar{C}_e + \bar{C}_e \bar{C}_{H^+} \quad (6-18)$$

and

$$\frac{d\bar{C}_{Ca^{2+}}}{d\bar{t}} = S_{cp} \times |\sigma|^n \quad (6-19)$$

in which

$$\bar{R}_s = \frac{R_s}{C_{e0}}, \quad \bar{C}_{end} = \frac{C_{end}}{C_{e0}}, \quad \bar{C}_{H^+} = \frac{C_{H^+}}{(C_{H^+})_{pH=7.4}}, \quad \bar{C}_{Ca^{2+}} = \frac{C_{Ca^{2+}}}{(C_{Ca^{2+}})_{eq}}, \quad \bar{t} = \frac{t}{t_0} \quad (6-20)$$

where

$$t_0 = \frac{1}{k_2 \times (C_{H^+})_{pH=7.4}} \quad (6-21)$$

Two non-dimensional groups of the material parameters emerged from this analysis:

$$\bar{k}_1 = \frac{k_1}{k_2 \times (C_{H^+})_{pH=7.4}} \quad (6-22)$$

and

$$S_{cp} = \frac{3A_d(A_{cp}/V_{polyester})}{k_2 \times (C_{H^+})_{pH=7.4} \times (C_{Ca^{2+}})_{eq}} \quad (6-23)$$

in which $A_{cp} = 4\pi r^2$ is the surface area of a single TCP particle and $V_{polyester} = \frac{4\pi}{3}(R^3 - r^3)$ is the volume of polyester in the representative unit. The size of the representative unit can be calculated from the initial weight fraction of the TCP particles, w_{cp0} , and the densities of calcium phosphate, ρ_{cp} , and the polyester, ρ_{poly} , such that

$$R = r_0 \left[1 + \left(\frac{1}{w_{cp0}} - 1 \right) \frac{\rho_{cp}}{\rho_{poly}} \right]^{\frac{1}{3}} \quad (6-24)$$

The size of the particle is a function of time and can be calculated from the current molar concentration of Ca^{2+} such that

$$r = r_0 \left[\frac{1 - \frac{C_{Ca^{2+}}}{3C_{cp,solid}} \left(\frac{R}{r_0} \right)^3}{1 - \frac{C_{Ca^{2+}}}{3C_{cp,solid}}} \right]^{\frac{1}{3}} \quad (6-25)$$

in which $C_{cp,solid}$ is the molar concentration of calcium phosphate in the solid state. $\bar{k}_1$ reflects the relative rate of the uncatalytic hydrolysis to the auto-catalytic hydrolysis, which will be referred to as the strength of uncatalytic hydrolysis in this chapter. S_{cp} reflects the relative rate of calcium phosphate dissolution to the auto-catalytic hydrolysis, which will be referred to as the strength of calcium phosphate dissolution.

Defining a half degradation time, $t_{0.5}$, as the time taken for the polyester to halve its average molecular weight, Fig 6-4 shows the calculated $t_{0.5}$ as a function of S_{cp} for a series of values of $\bar{k}_1$.

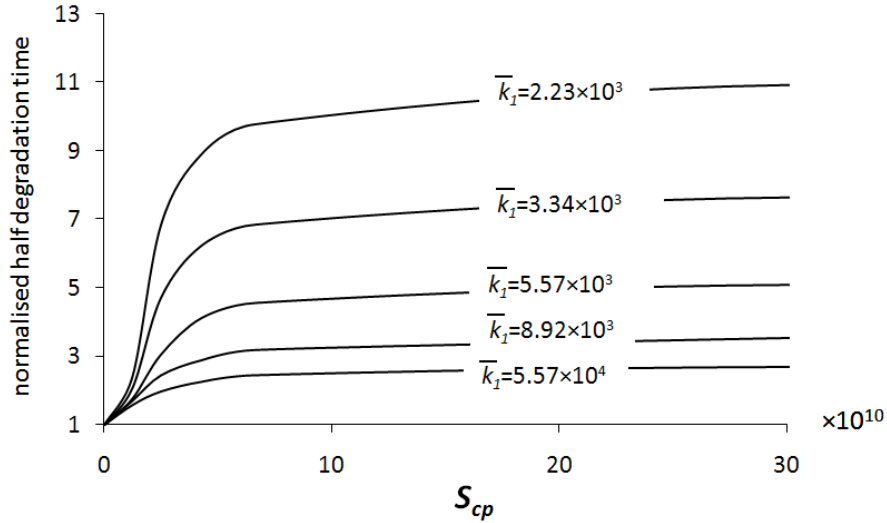


Fig 6-4. Calculated half degradation time for the composite normalized by the half degradation time of the pure polyester as a function of S_{cp} for a series of values of $\bar{k}_1$

The data other than $\bar{k}_1$ and S_{cp} used in these calculations are provided in Table 6-1. It can be observed from Fig. 6-4 that for each value of $\bar{k}_1$ the mathematical model predicts a saturation point for S_{cp} beyond which further increasing S_{cp} cannot further reduce the degradation rate. It can also be observed that the effectiveness of the TCP is strongly controlled by $\bar{k}_1$, the relative strength of uncatalytic hydrolysis reaction to the autocatalytic hydrolysis reaction. Fig.6-5 shows the half degradation time at the saturation (i.e. the maximum half degradation time shown in Fig.6-4 for each value of $\bar{k}_1$) as a function of $\bar{k}_1$. The model predicts a sharp reduction in the effectiveness of TCP as $\bar{k}_1$ is increased. These

understandings can be further illustrated using an effectiveness map as shown in Fig. 6-6 for incorporating calcium phosphates. The horizontal axis is S_{cp} and the vertical axis is $\bar{k}_1$.

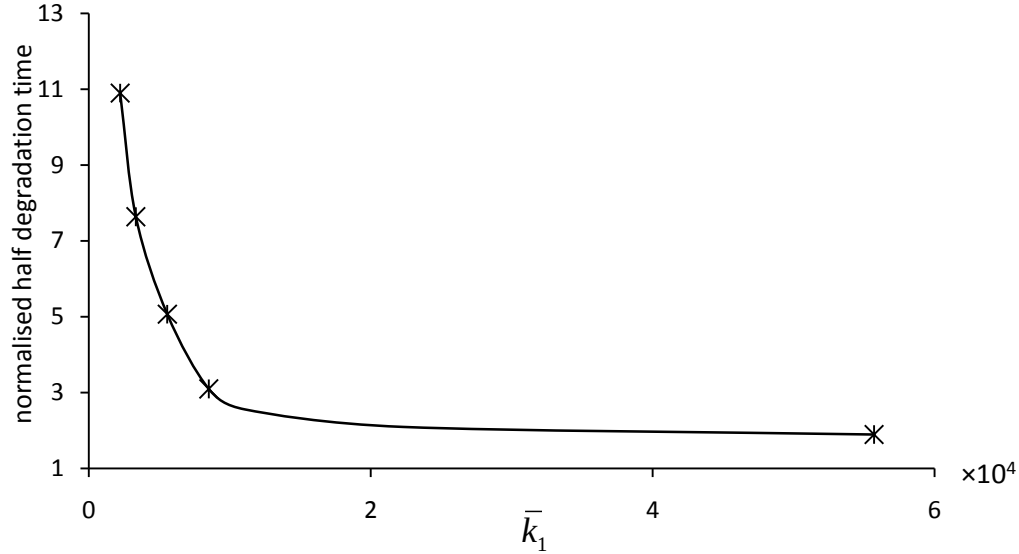


Fig.6-5 Normalised half degradation time at saturation (i.e. the maximum half degradation time shown in Fig.6-4 for each value of $\bar{k}_1$) as a function of $\bar{k}_1$

Roughly speaking, TCP dissolves faster and faster from the left to right of the map and the hydrolysis reaction of the polyester becomes more and more non-catalytic from the bottom to the top of the map. The very top region represents polyesters which degrade by uncatalytic hydrolysis. Incorporating TCP in these polyesters is ineffective because the degradation is insensitive to the local pH. The left bottom region is where the degradation rate can be easily altered by changing S_{cp} , through changing the volume fraction or reducing the particle size of the TCP for example. It is however the saturation region that dominates the map where changing S_{cp} has little further effect on the degradation rate of the polyester. The absolute boundaries between the various regions are somewhat arbitrary. We have used $(t_{0.5})_{saturation} = 2(t_{0.5})_{PDLLA}$ to set the lower boundary for the ineffective region and $t_{0.5} = 0.9(t_{0.5})_{saturation}$ to set the boundary between the sensitive and saturation regions.

Fig.6-7 compares the numbers of chain scissions of the polyester versus time due to the uncatalytic and autocatalytic hydrolysis reactions respectively for the value of $\bar{k}_1$ at the lower boundary of the ineffective region. It can be observed that even at this boundary it is still the autocatalytic hydrolysis that dominates the polymer degradation.

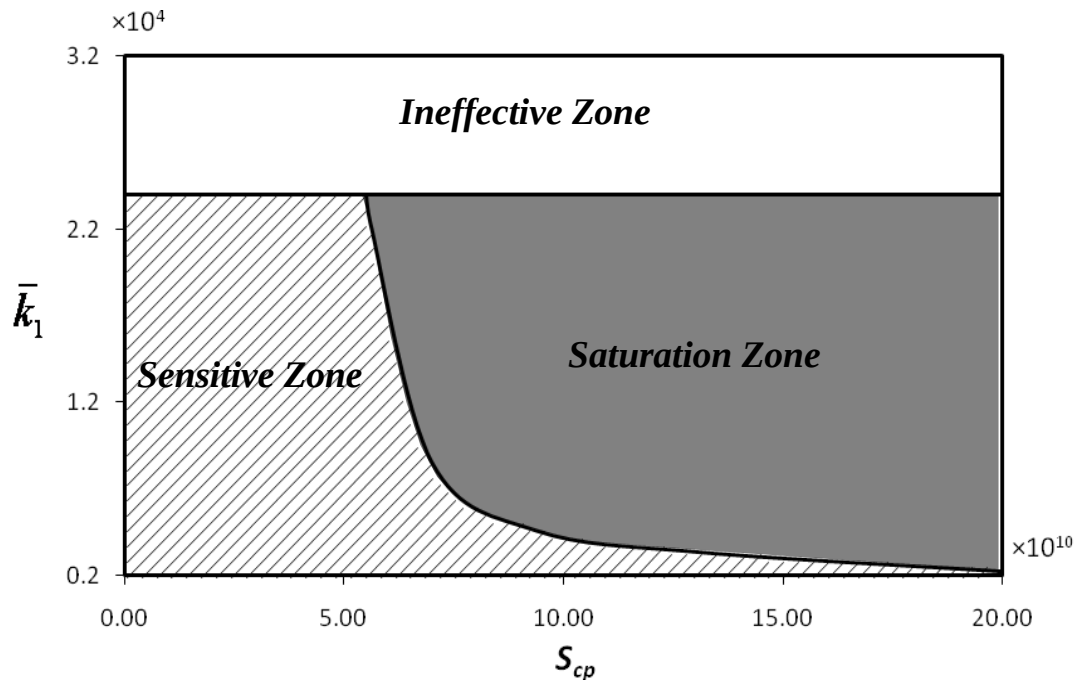


Fig.6-6 Effectiveness map of incorporating tricalcium phosphates to reduce the degradation rate of polyesters. The horizontal axis represents the strength of the calcium phosphate dissolution and the vertical axis represents the strength of the uncatalytic hydrolysis. Ineffective zone: incorporating tricalcium phosphate is ineffective. Sensitive zone: degradation rate can be altered by changing S_{cp} (through changing volume fraction or particle size of calcium phosphate for examples). Saturation zone: changing S_{cp} has little effect on the degradation rate of the polyester.

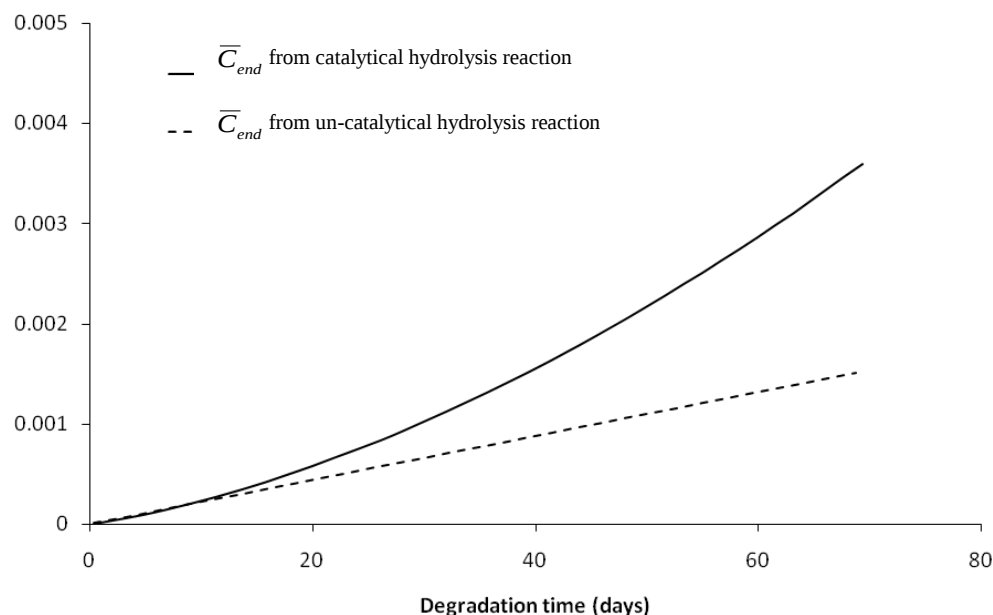


Fig. 6-7 Number of chain scissions of the polyester versus time due to the uncatalytic and autocatalytic hydrolysis respectively for the value of $\bar{k}_1$ at the lower boundary of the ineffective region as shown in Fig 6.6.

6.4. COMPARISON WITH EXPERIMENTAL DATA

Using the mathematical model, it is now possible to provide an understanding in the behaviour of PDLLA/TCP composites observed by previous researchers. Heidemann *et al.* (2001) provided *in vivo* data of average molecular weight as a function of time for their PDLLA/TCP composite and pure PDLLA respectively. Fig. 6-8 shows the fitting between the mathematical model and the experimental data. It was unclear whether α - or β -TCP particles were used in the experiment. Here the solubility data for α -TCP is used because all the other experimental cases discussed in this section are for α -TCP. The model parameters used in the fitting are given in Tables 6-1 and 6-2. The parameters contained in Table 6-1 are common to all the cases in this section. The parameters in Table 6-2 are unique to this specific case. The parameters on the third row of Table 6-2, i.e. A_d , k_1 and k_2 , are the only parameters that were adjusted for the fitting. Fig. 6-8 shows that the model can capture the molecular weight change for both pure PDLLA and PDLLA/TCP composite very well during the early stage of the degradation.

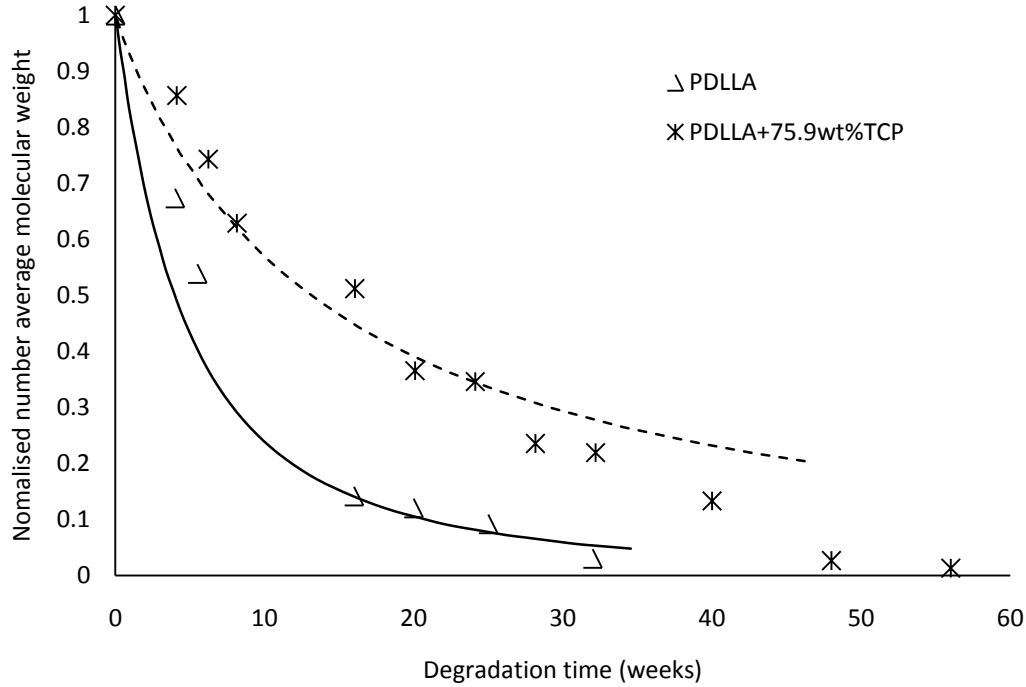


Fig. 6-8 Average molecular weight as a function of time for PDLLA/TCP composite and pure PDLLA. The lines are results predicted by the mathematical model while the discrete symbols are experimental data due to Heidemann *et al.* (2001).

We also used the solubility data for β -TCP and obtained similar good fitting by adjusting parameters in Table 6-2. Next we consider the experiment by Ehrenfried *et al.* (2008) who studied the degradation behaviour of poly(D,L-lactide-co-glycolide) with a D,L-lactide to glycolide ratio of 50:50 (PLGA50:50) containing α -TCP particles. The particle radius is $r_0 = 30\mu m$. The weight percentage of the α -TCP particles was varied from 5% to 40%. The composites were degraded in PBS without changing the solution during the entire degradation process. The pH values of the PBS were recorded at various times of the degradation which reproduced in Fig. 6-9.

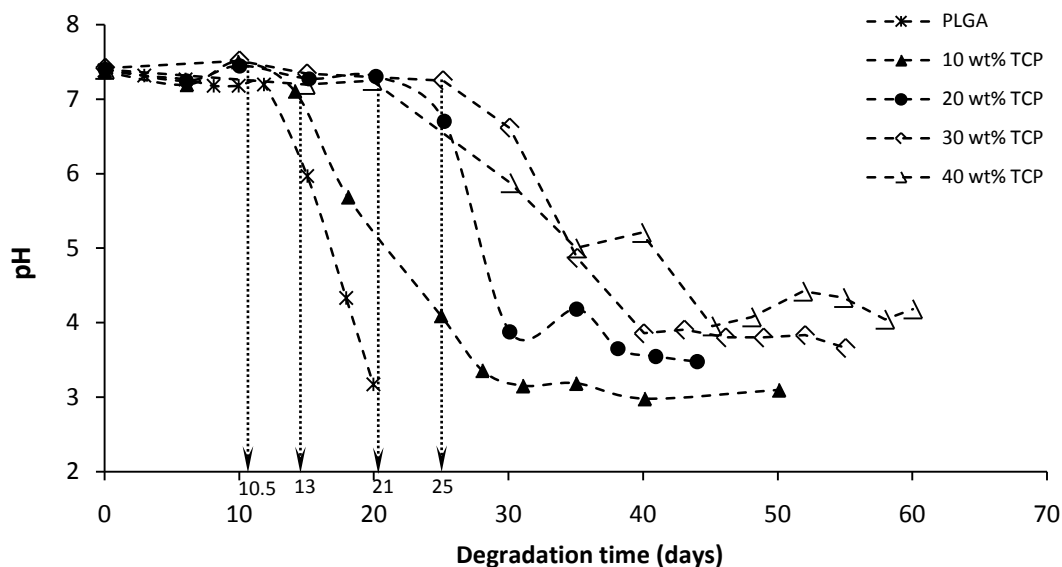


Fig.6-9. The pH value in the PBS versus degradation time for composites between PLGA50:50 and α -TCP of different weight percentages. Reproduced from Ehrenfried *et al.* (2008).

It can be observed from the figure that the pH of PBS remains constant until a critical time and incorporating TCP particles extends this critical time. Ehrenfried *et al.* (2008) did not monitor the change in molecular weight of the PLGA during their experiment. A direct comparison between the model prediction and the experimental data is therefore not possible. However an indirect comparison is possible by arguing that the critical times of the different composites observed by Ehrenfried *et al.* (2008) correspond to a single critical average molecular weight of the PLGA. Hurrell and Cameron (2001^a, 2001^b) suggested that oligomers produced by the polymer chain scission are only released into the degradation media when the average molecular weight of the polymer is reduced to a critical value. Fig. 6-10 shows the predicted average molecular weight as a function of time for the PLGA containing α -TCP particles of different weight percentages. The data used in the calculation are provided in Table 6-1 and 6-3. Again, only the parameters in the last row of Table 6-3, i.e. A_d , k_1 and k_2 , were adjusted to fit with the experimental data. If we assume that the samples start to release oligomers when the average molecular weight of the PLGA is reduced to 48% of its initial value, then a fairly good agreement between the model

prediction (Fig 6-10) and the experimental data (Fig 6-9) can be observed for the critical degradation times at which the samples start to release oligomers.

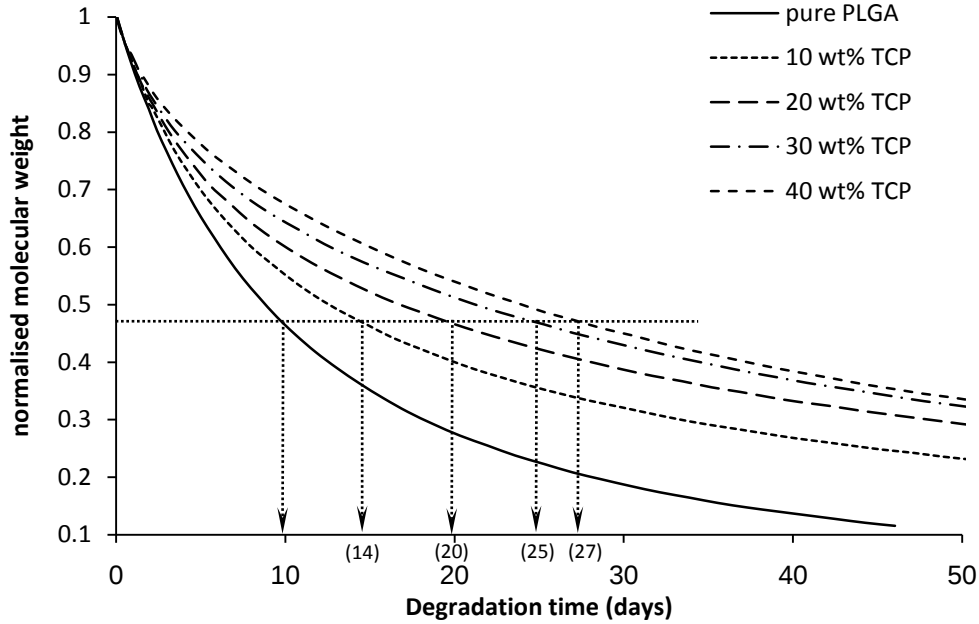


Fig. 6-10 Predicted average molecular weight as a function of time for PLGA containing α -TCP particles of different weight percentages.

Finally we consider the experiment by Yang *et al.* (2009) who studied the degradation behaviour of the PLGA50:50 containing α -TCP particles of very different sizes. Fig. 6-11 shows their data of pH value in PBS as a function of time for the pure PLGA and composites containing 30 weight percentage of α -TCP particles of $0.05 \mu\text{m}$ and $4 \mu\text{m}$ in radius respectively.

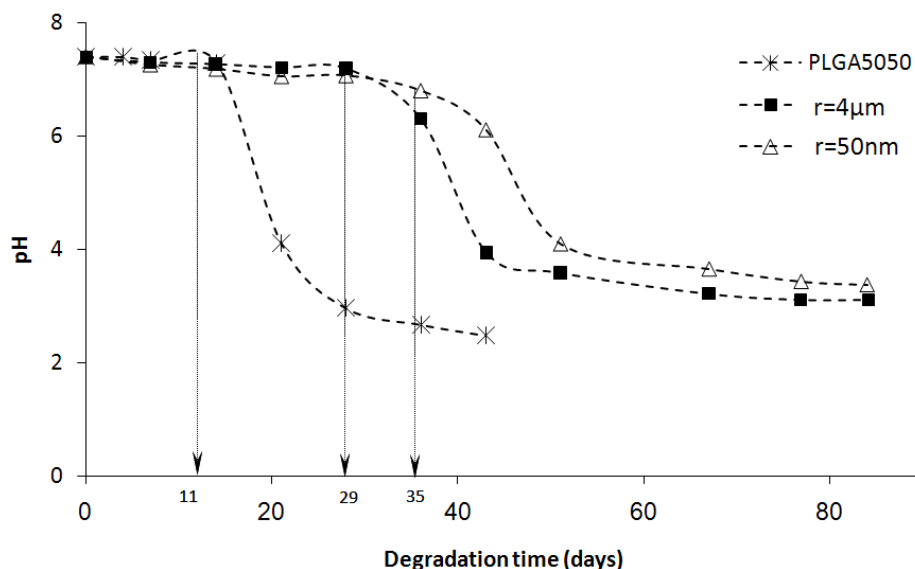


Fig. 6-11. The pH value in PBS as a function of time for the pure PLGA50:50 and composites containing 30 weight percentage of α -TCP particles of $0.05\mu\text{m}$ and $4\mu\text{m}$ in radius respectively., reproduced from Yang *et al.* (2009)

It can be observed that incorporating α -TCP particles delayed the change in pH of the PBS but reducing the particle size by nearly two orders of magnitude had a relatively minor impact on the PLGA degradation rate. Fig. 6-12 shows the predicted average molecular weight as a function of time for the pure PLGA and composites containing α -TCP particles of different sizes.

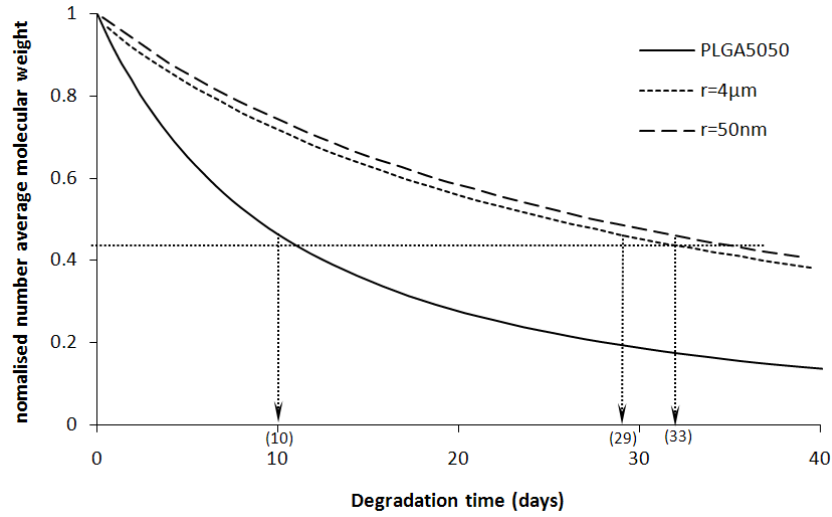


Fig. 6-12 Predicted average molecular weight as a function of time for pure PLGA and PLGA containing 30 weight percentage of α -TCP particles of $0.05 \mu m$ and $4 \mu m$ in radius respectively.

The data used in the calculation are provided in Tables 6-1 and 6-3 (except for the particle size). Again if we assume that the samples start to release oligomers when the average molecular weight of PLGA is reduced to 48% of its initial value, then a fairly good agreement between the model prediction (Fig. 6-12) and the experimental data (Fig. 6-11) can be observed for the critical degradation times at which the samples start to release oligomers.

Table 6-3. Parameters in the model for cases by Ehrenfried *et al.* (2008) and Yang *et al.* (2009)

$(M_{n0})_{PLGA} = 260300 g / mol$	$M_{unit} = 65 g / mol$	$\rho_{poly} = 1.125 g / cm^3$
$A_d = 4.9 \times 10^{-4} mol / m^2 week$	$k_1 = 7 \times 10^{-5} / week$	$k_2 = 1.61 \times 10^{-4} \sqrt{\frac{m^3}{mol}} / week$

The experimental data shown in Figs. 6-9 and 6-11 shows a saturation behaviour. In the case of Fig. 6-9, the degradation rate of the polymer cannot be further reduced significantly by increasing the weight percentage of the TCP particles from 30% to 40%. In the case of Fig. 6-11, the degradation rate is not reduced drastically as the particle size of the TCP particles is changed from about $4\ \mu\text{m}$ to about $0.05\ \mu\text{m}$. Fig. 6-13 shows the calculated half degradation time as a function of the TCP dissolution strength S_{cp} using the data in Tables 6-1 and 6-3 for all the cases shown in Figs. 6-9 and 6-11. The case at the origin represents pure PLGA. Cases A-D represent PLGA50:50 containing 10%, 20%, 30% and 40% weight percentages of α -TCP particles of $30\ \mu\text{m}$ in radius respectively.

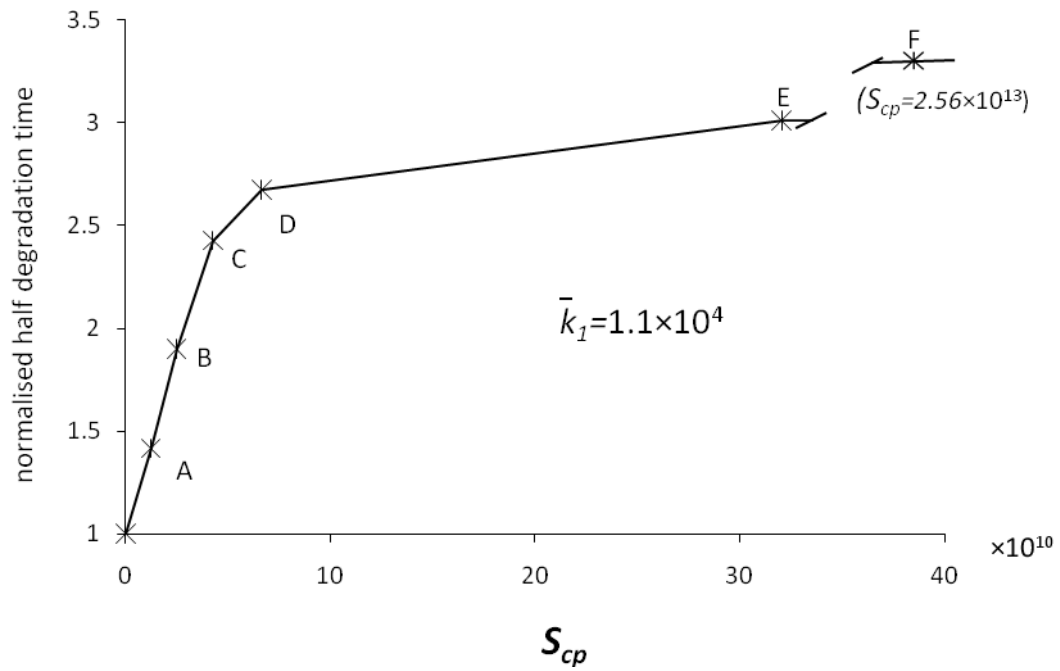


Fig.6-13. Calculated half degradation time as a function of TCP dissolution strength S_{cp} for cases shown in Figs.6-9 and 6-11. Cases A-D represent PLGA50:50 containing α -TCP particles of $30\ \mu\text{m}$ in radius of 10%, 20%, 30% and 40% weight percentages respectively. Cases E and F represent PLGA50:50 containing 30% weight percentage of α -TCP particles of $4\ \mu\text{m}$ and $0.05\ \mu\text{m}$ in radius respectively. Case F is outside the range of the figure.

It can be observed that cases A, B and C are all in the sensitive zone where an increase in S_{cp} leads to a large increase in the half degradation time, while case D almost reaches the saturation zone. Cases E and F represent PLGA50:50 containing 30% of α -TCP particles of $4\ \mu m$ and $0.05\ \mu m$ in radius respectively. It can be observed that these two cases are in the saturation zone. In particular, case F is outside the range of the figure by an order of magnitude meaning a huge increase in S_{cp} only led to a small increase in the half degradation time. Fig. 6-14 shows the calculated concentrations of H^+ in the polymer matrix as a function of time for the cases shown in Fig 6-13.

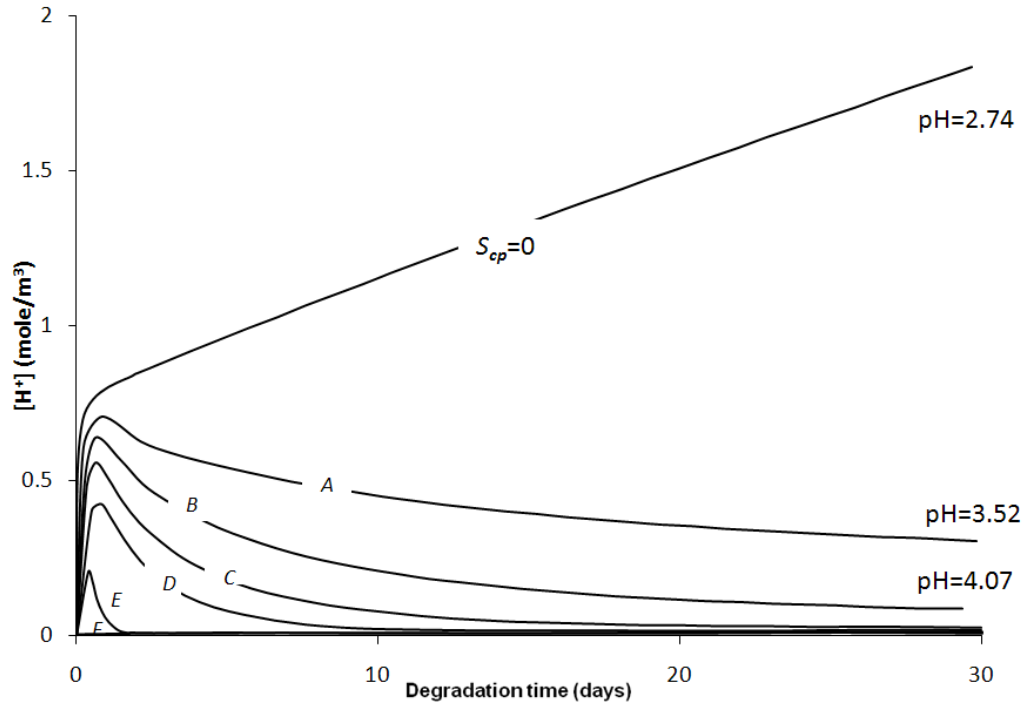


Fig. 6-14 Calculated concentrations of H^+ in the polymer matrix as a function of time for the cases shown in Fig.6-13. The pH values shown on the right are for pure PLGA, cases A and B (PLGA50:50 containing α -TCP particles of $30\ \mu m$ in radius of 10% and 20%) respectively at 30 days, which can be compared to the corresponding pH values measured in the PBS as shown in Fig. 6-9.

The pH values shown on the right are for pure PLGA, cases A and B respectively at 30 days, which can be compared with the corresponding pH values measured in the PBS as shown in Fig.6-9. The model has clearly captured both the saturation behaviour and the buffering effect of incorporating TCP in the various polyesters.

6.5. CONCLUSIONS

The mathematical model presented in this chapter can capture the observed degradation behaviour of polyester/TCP composites. In particular, the numerical study offers an in-depth understanding in the observed saturation behaviour when incorporating a TCP phase into various polyesters. The TCP effectiveness map can be used to guide the design of these composite materials. The map highlighted an issue which has not been paid enough attention – for a specific polyester it is important to know separately the non-catalytic and autocatalytic contributions to the hydrolysis reaction in order to understand the effectiveness of incorporating TCP in the polymer. Incorporating TCP would not be much usefully in altering the degradation rate for a polyester which mainly degrades by non-catalytic hydrolysis. A note of caution is that the model ignores the diffusion of the various reaction products out of the composite into the degradation media. The model presented in this chapter is therefore only valid for the early stage of degradation before a critical molecular weight is reached.

CHAPTER SEVEN – A PHASE FIELD MODEL FOR THE SWELLING AND DRUG RELEASE FROM POLYMERIC MATRIX MADE OF HYDROXYPROPYL METHYLCELLULOSE (HPMC)

This chapter presents a preliminary study on an important issue that naturally follows the main body of work in this thesis – polymer swelling and drug release. The focus of this thesis so far has been on polymer degradation. However the polymers also swell as they take up water. Drugs, such as growth factors, are often embedded in the polymer matrix and released to encourage cell differentiation in tissue engineering or to cure diseases in controlled drug delivery. Drug release is very sensitive to free volume of the polymer matrix. Even a small swelling can significantly accelerate the drug release. A full study of these issues is beyond the time limit of this project. Here a preliminary study is presented which opens the door for further research. To highlight the issue of swelling HPMC, a polymer widely used for controlled release tablets, is selected which has a much larger swelling ratio than the PLA/PGA copolymers.

7.1. INTRODUCTION

Oral controlled drug delivery has been intensively researched for decades. Systems for sustained control drug delivery are mainly based on polymers that do not change their chemical structure, and whose mechanism is demonstrated by swelling. To be successfully used in controlled drug delivery formulations, a polymer must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure and be readily processable. Swelling polymers and hydrogels, also known as glassy hydrogels or hydrophilic gums, are popular for sustained drug release. In swelling-controlled release system, once the tablets are swallowed, water/solvent penetrate the polymer, swelling occurs and a thin layer of polymer in rubbery state is formed. During the swelling process, three distinct fronts are observed (Kiil and Dam-Johansen, 2003): swelling front, diffusion front and erosion front. The swelling interface is between glassy and rubbery polymer. Diffusion interface consists of the boundary between solid and dissolved drug and the last interface is the boundary between the matrix surface and the solvent. As swelling proceeds,

the swelling front moves inwards whereas diffusion front and eroding front move outwards due to swelling. Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic polymer used for the preparation of oral controlled drug release systems because it is non-toxic, easy to handle, relatively cheap and easy to compact (Siepmann and Peppas, 2001; Heng *et al.*, 2001). Basically HPMC is a cellulose derivative, consisting of a backbone of cellulose with methoxylic and hydroxypropoxylic moieties substituted onto the glucose units. The advantage of HPMC is its high swellability, which has a significant effect on the drug release kinetics. Various studies have been carried out to understand the mechanism of HPMC systems (Siepmann and Peppas, 2001; Heng *et al.*, 2001; Viridén *et al.*, 2009^a; Larsson *et al.*, 2010; Miranda *et al.*, 2006; Laaksonen *et al.*, 2009; Conti *et al.*, 2007^a; Conti *et al.*, 2007^b; Viridén *et al.*, 2009^b; Viridén *et al.*, 2009^c).

A number of experiments and computational studies have been carried out recently to elucidate swelling process and drug release. Swelling will affect water diffusivity into polymer, incorporated drug release through rubbery polymer matrix and polymer chain dissolution. Narasimhan and Peppas (1997) used molecular theories in a continuum framework. Moving boundary theory, free volume theory, Flory-Rehner equation and disentanglement rate of polymer were all applied to their models. They concluded that the predictions agreed with experiment data well. However, they also provided information that it is necessary to relate the molecular properties, chemistry properties for example, to continuous model. Then it is indispensable to learn the intrinsically relationships among different components. In their study all the parameters were obtained from experiments directly or indirectly. Laaksonen *et al.* (2009) presented a cellular automata model for modelling swelling-controlled drug release. They divided a release device into square cells. Each cell represents one of six states in that domain including water, solid drug, mobile drug, polymer, wet polymer and wet polymer with drug. Cells were allowed to change their states according to certain statistic rules. In their model, diffusion and swelling were simulated using random walk of mobile cells and the kinetics of chemical and physical process by probabilities of conversion from one state to another. Then they studied how different parameters affect release profile. The model parameters could be obtained from control experiment directly. They also compared their prediction with experiment data

obtained by Narasimhan and Peppas (1997) for validation. Although their cellular automata model provides a new way to understand controlled drug release, the model parameters should be acquired from experiments for specific polymers which limited the model from predicting different controlled release systems with different chemical structures.

Kiil and Dam-Johansen (2003) developed a comprehensive mathematical model describing transient drug delivery from HPMC matrices. Water-induced swelling, drug dissolution, and external and internal mass transport resistances of dissolved drug, has been simulated by mathematical models. Their model was established by using kinetic laws for drug/water diffusion, moving boundary theories and mass balance rules for dissolved drug/water. The equations were then solved by the method of orthogonal collocation (Kiil and Dam-Johansen, 2003). They compared their model predictions of drug release and radial front movements in a 1D axisymmetric cylinder with the experiment data obtained from (Bettini *et al.*, 2001) for three drugs and good agreements were indicated for positions of swelling front and erosion front.

Dealing with the moving boundaries is a major challenge when modelling the polymer swelling. The method used by Kiil and Dam-Johansen (2003) cannot be extended to full three dimensional problems. In this chapter a phase field method is proposed using the model developed by Kiil and Dam-Johansen (2003) as an demonstration example. Although the study presented here is limited to axisymmetric problems, this method can be readily extended to three dimensional problems. The phase field method has been widely used for solving interfacial problems, especially for modelling microstructure evolution of engineering materials (Steunbach and Shchyglo, 2011).

7.2. A PHASE FIELD MODEL FOR THE SWELLING AND DRUG RELEASE FROM HPMC TABLET

Once a tablet is in contact with a solvent, the solvent molecules (water for example) penetrate the polymer which increases the free volume of the crystalline HPMC. A thin layer of gel phase is formed when the water concentration exceeds a critical value. Fig. 7-1 shows a cylindrical tablet which is placed between two glasses.

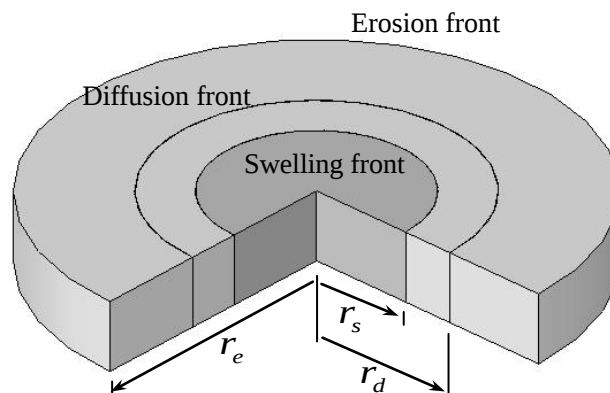


Fig.7-1 A schematic diagram of the three fronts during polymer swelling and drug diffusion

The swelling and drug diffusion only occur in the radial direction. Three fronts: a swelling front, a diffusion front and an erosion front, are observed during the swelling process. The dark grey colour indicates the crystalline core while the light grey indicates the gel phase (swelling HPMC). The swelling front migrates inwards and the erosion front migrates outwards representing the phase change from crystalline HPMC to gel HPMC and water induced swelling respectively. The diffusion front separates the dissolved and undissolved drug particles in the matrix.

A phase field model is presented here to describe the drug release from highly swellable HPMC tablets. This model is a phase field version of the model developed by Kiil and Dam-Johansen (2003). The main assumptions of this model include:

- Drug release and water diffusion in the radial direction only are considered
- The matrix swells when the threshold water concentration for swelling, c_w^* , is exceeded.
- Upon water exposure equilibrium is established instantaneously between water and the swollen matrix at the erosion front.
- Polymer erosion is negligible.
- Kinetic drug dissolution is substituted by using water solubility of the drug.

- f) The pores formed in the polymer gel by dissolving drug particles are filled up with water instantaneously.

The swelling, diffusion and erosion fronts separate a drug release system into four zones:

- zone1: crystalline core including crystalline drug and HPMC molecules;
- zone2: gel phase with undissolved drug molecules;
- zone3: gel phase with dissolved drug molecules;
- zone4: the solvent.

Three phase field variables: η_w , η_d and η_t are introduced to describe the different zones and the position of the three fronts can be determined from the values of the three phase field variables. These variables replace the definition of the sharp fronts such that two distinct values, 0 and 1, are assigned to each variable on either side of a front with a smooth change across a front. Table 7-1 indicates the values of the phase field variables and the drug and water concentrations in the different zones:

- η_w separates the whole system into two phases by the existence of water molecule. 0 is assigned to zone 1 and 1 is assigned to zones 2, 3 and 4.
- η_d divides system into two phases according to whether the drug is dissolved or not. 0 is assigned to zones 1 and 2 while 1 is assigned to zones 3 and 4. Although zone 2 is the gel phase, drugs are not able to diffuse as they are undissolved in this zone.
- η_t separates the polymer phase and solvent phase. 0 is assigned to zones 1, 2 and 3 which belong to the tablet domain while 1 is assigned to zone 4.

Table 7-1. Values of the phase field variables and concentrations in different zones

	1.Crystalline core	2.Swelling gel+ undissolved drug	3.Swelling gel+ dissolved drug	4.Solvent
η_w	0	1	1	1
η_d	0	0	1	1
η_t	0	0	0	1
c_w	0	c_w	c_w	$c_{w,eq}$
c_d	$c_{d,eq}$	$c_{d,eq}$	c_d	Undefined

The main mechanisms considered by Kiil and Dam-Johansen in their model are swelling induced water diffusion and drug release. Nothing happens in zone 1 because there is no water in this zone. Drug diffusion only takes place in zone 3. Following Kiil and Dam-Johansen (2003), the migration velocities of the swelling and erosion fronts are given by

$$v_s = \begin{cases} 0, & c_w < c_w^* \\ k_s(c_w - c_w^*)^n, & c_w \geq c_w^* \end{cases} \quad (7-1)$$

$$v_e = (f_s - 1) \frac{r_s}{r_e} v_s \quad (7-2)$$

in which v_s and v_e are rates of swelling front movement and erosion front movement, respectively, k_s n are kinetic parameters, f_s is the equilibrium swelling ratio of the polymer, r_s and r_e are the radius of swelling front and erosion front, c_w and c_w^* are water concentration and threshold of water concentration for swelling. In the phase field model the fronts are “diffused” with a small width. Their exact positions can be determined by setting $\eta_w = 0.5$ for the swelling front and $\eta_t = 0.5$ for the erosion front. Following Kiil and Dam-Johansen (2003), the migration velocity of the diffusion front is given by

$$v_d = \frac{M_D D_{GD} f_s}{V_D \rho_D (1 - \varepsilon_0)} \frac{\partial c_d}{\partial r} \Big|_{r_d} - (f_s - 1) \frac{r_s}{r_d} v_s \quad (7-3)$$

In which M_D is molar mass of drug, D_{GD} is diffusion coefficient of drug, V_D is the volume fraction of drug, ρ_D is the density of drug and ε_0 is the initial porosity of complete matrix system and c_d is drug concentration. r_d is the radius of diffusion front which is determined by setting $\eta_d = 0.5$.

The central idea of the phase field method is that the field variables follow the following kinetic equations:

$$\frac{d\eta_w}{dt} = v_s \frac{d\eta_w}{dr} + D_{\eta_w} \frac{\partial^2 \eta_w}{\partial r^2} \quad (7-4)$$

$$\frac{d\eta_t}{dt} = -v_e \frac{d\eta_t}{dr} + D_{\eta_t} \frac{\partial^2 \eta_t}{\partial r^2} \quad (7-5)$$

$$\frac{d\eta_d}{dt} = v_d \frac{d\eta_d}{dr} + D_{\eta_d} \frac{\partial^2 \eta_d}{\partial r^2} \quad (7-6)$$

The first terms on the right hand side of these equations represent the front migration with the corresponding velocities. The second terms ensure numerical stability and give the fronts finite and small widths. The values of D_{η_w} , D_{η_d} and D_{η_t} are empirical and much smaller compared to the diffusion coefficients of water and drug. In eqn. (7-4) we have taken v_s as a field variable (different points of the diffused front has a different velocity according to its water concentration) which is calculated using eqn. (7-1). On the other hand v_d and v_e have been taken as single values for the entire diffused fronts. v_d and v_e are calculated using eqns. (7-2) and (7-3) from v_s at $\eta_w = 0.5$.

Water balance can be expressed in gel zone as:

$$\frac{dc_w}{dt} = -\frac{1}{r} \left[\frac{\partial}{\partial r} (r j_{w,r}) \right] - v_e \frac{dc_w}{dr} - c_w (1 - \eta_t) \eta_w \dot{\epsilon}_v \quad (7-7)$$

in which c_w is water concentration, $j_{w,r}$ is the flux of water diffusion given by

$$j_{w,r} = -(\eta_w D_w) \frac{dc_w}{dr} \quad (7-8)$$

D_w is diffusion coefficient of water, $\dot{\epsilon}_v$ is the strain rate of swelling gel given by:

$$\dot{\epsilon}_v = \frac{\Delta V_{total}}{V_{gel}} = \frac{2\pi r_e L \frac{dr_e}{dt}}{\pi r_e^2 L - \pi r_s^2 L} = \frac{2r_e}{r_e^2 - r_s^2} \frac{dr_e}{dt} \quad (7-9)$$

From eqn. (7-7), it is apparently that the rate of water concentration is resulted from three terms on the right hand side: water diffusion (the first term), gel domain shift due to swelling (the second term) and water induced swelling (the third term). $j_{w,r}$ is multiplied by the phase field parameter η_w to represent the moving swelling front. In the domain of crystalline phase, $j_{w,r}$ is reduced to zero while $j_{w,r} = -D_w \frac{dc_w}{dr}$ in the gel phase. The value of the water flux then changes from zero to $-D_w \frac{dc_w}{dr}$ smoothly across the swelling

boundary. The boundary condition on the erosion front is given by

$$\text{If } \eta_t > 0.5 \text{ then } c_w = c_{w,eq} \quad (7-10)$$

in which $c_{w,eq}$ is the equilibrium water concentration. Note that there is no boundary condition for the water diffusion at the swelling front in the phase field model.

The mass balance of dissolved drug is given by:

$$\frac{V_{HPMC} \rho_{HPMC} (1 - \varepsilon_0)}{\rho_w f_s} \frac{\partial(c_d c_w)}{\partial t} = -\frac{1}{r} \left[\frac{\partial}{\partial r} (r j_{d,r}) \right] - v_e \frac{dc_d}{dr} \quad (7-11)$$

in which $j_{d,r}$ is the flux of drug diffusion

$$j_{d,r} = -(\eta_d D_{DG}) \frac{dc_d}{dr} \quad (7-12)$$

with the boundary conditions at the diffusion front

$$\text{If } \eta_d < 0.5 \text{ then } c_d = c_{d,eq} \quad (7-13)$$

$$j_{d,r} \Big|_{r_e} = k_{L,D} c_d \Big|_{r_e} \quad (7-14)$$

where D_{DG} is diffusion coefficient of the drug, c_d is drug concentration and $c_{d,eq}$ is equilibrium drug concentration. V_{HPMC} , ρ_{HPMC} , ρ_w , $j_{d,r}$ are volume fraction of HPMC, density of HPMC, water density and drug diffusion flux, respectively. $j_{d,r} = 0$ in zones 1 and 2 and $j_{d,r} = -D_{DG} \frac{dc_d}{dr}$ in zone 3. It changes from zero to $-D_{DG} \frac{dc_d}{dr}$ across the diffusion front. The second term on the right hand side of eqn. (7-11) indicates the domain shifting of the gel phase due to swelling.

Fig. 7-2 provides the initial conditions for all the variables and system sizes of the model.

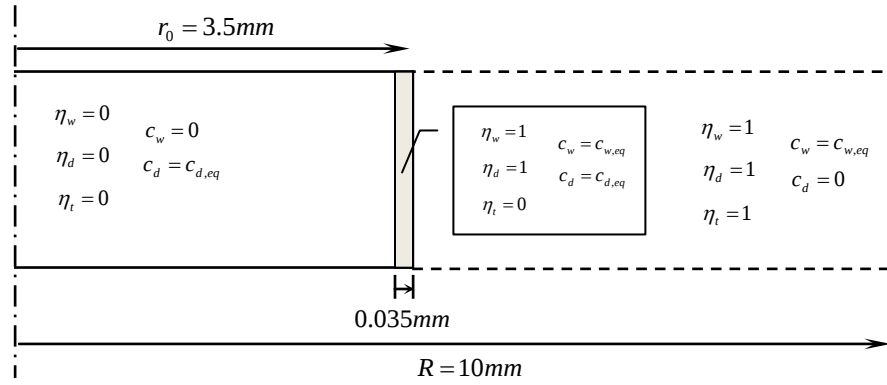


Fig.7-2 Initial conditions

The initial radius of the tablet is $r_0 = 3.5\text{mm}$ while the whole system size is $R = 10\text{mm}$. The tablet domain is indicated by solid boundaries while the solvent domain is indicated by dashed boundaries. Note the light grey area is a very thin gel band with width 0.035mm for the numerical calculation to start. The initial radii of three fronts therefore are $r_s(t = 0) = 3.465\text{mm}$, $r_d(t = 0) = 3.5\text{mm}$ and $r_t(t = 0) = 3.5\text{mm}$. Values of all the variables in the tablet domain, the thin gel band and the solvent are shown in Fig. 7-2. Fig. 7-3 provides the boundary conditions for all the variables of the model.

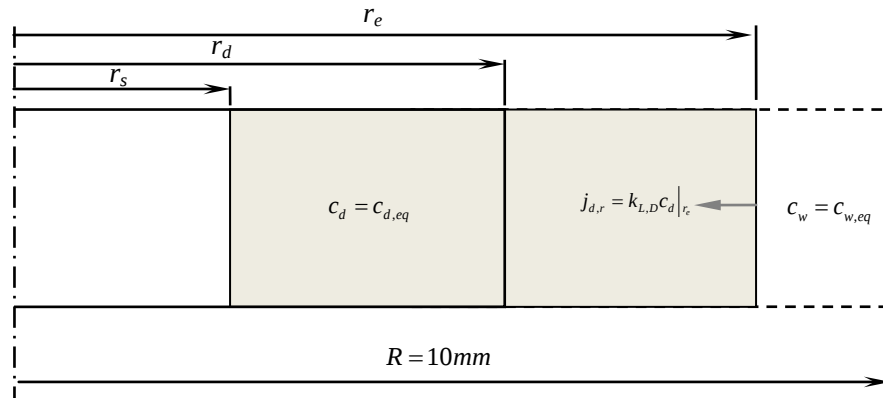


Fig.7-3 Boundary conditions

The partial differential equations are solved using central finite difference method and Euler time integration scheme. A computer program is written in FORTRAN 90. The grid size for the finite difference scheme was found to be $\Delta r = 0.02\text{mm}$ and the time step length was found to be $\Delta \text{time} = 0.05\text{s}$ to ensure convergence for all the cases in the following sections.

The computational time for one complete simulation takes less than one minute on a laptop PC.

7.3. RESULTS

This section provide comparison between the model prediction with the experimental data reported by Bettini *et al.* (2001, 1994) for a tablet loaded with BPP with 60% mass fraction while the mass fraction for HPMC is 33%.

7.3.1 Experiment descriptions

Only a brief description is provided for the experiment here while the details of the can be found in the references. Tablet was clamped between two transparent Plexiglas discs with diameter 30mm and thickness 5mm and then mounted into a dissolution apparatus with 1L water. Their set up allowed the water diffusion only taking place at the r direction (radial direction). The temperature of this experiment was maintained at the body temperature of 37°C. Experimental data such as the positions of three fronts were recorded by video through the transparent Plexiglas discs and then image software was applied to analyze the photographs. The experimental data required in next section are: positions of three fronts and the fraction drug release.

7.3.2 Parameter estimation

A set of parameters are required in the model. They can be divided into two groups: one can be obtained directly from experiments and drug/water/HPMC physical properties; another group then is estimated or adjusted from the final experimental data. Most values of parameters and their estimations are available in ref (Kiil and Dam-Johansen, 2003) which are reproduced here in Table 7-2 (drug parameters are for BPP). The additional parameters or changes of the adjusted parameters used in this phase field -model are provided in Table 7-3.

Table 7-2. Model parameters provided by ref (Kiil and Dam-Johansen, 2003)

$c_{d,eq}$	$0.65g/cm^3$
M_D	$553.6g/mol$
f_s	4.23
$k_{L,D}$	$2.4 \times 10^{-6}m/s$
ρ_D	$1.394g/cm^3$
ρ_{HPMC}	$1326kg/m^3$
ρ_w	$993kg/m^3$
M_w	$18g/mol$
$c_{w,eq}$	$5.1g\ water/ g\ HPMC$
k_s	$1.5 \times 10^{-6}m/s \cdot (g\ HPMC/g\ water)^n$
n	2.5
c_w^*	$0.259g\ water/ g\ HPMC$
ε_0	0.092
D_w	$1.9 \times 10^{-4}mm^2 / s$

Table 7-3. Additional parameters and adjusted parameters in the phase field model

D_{η_w}	$5 \times 10^{-6}mm^2 / s$
D_{η_d}	$1 \times 10^{-6}mm^2 / s$
D_{η_t}	$1 \times 10^{-6}mm^2 / s$
D_{GD}	$1.7 \times 10^{-4}mm^2 / s$
Δt	$0.05s$
Δx	$0.02mm$

Table 7-3 lists the additional parameter needed in the phase field model. D_{η_s} , D_{η_d} and D_{η_t}

are the three coefficients for the second terms in three kinetic equations for η_s , η_d and η_t , respectively. As aforementioned the second term in each kinetic equation of is used to stabilize the equation. The estimations of the coefficient are therefore mainly depended on the rates of the three front migration velocities: v_s , v_d and v_e . The criterions for selecting the values of these three coefficients are

- converging the results from kinetic equations, and
- letting the phase field kinetic equations to perform sharp interfaces (i.e. when the interface width is approaching zero).

According to the criterions, values of these coefficients are found to be $D_{\eta_w} = 5 \times 10^{-6} \text{ mm}^2 / \text{s}$, $D_{\eta_d} = 1 \times 10^{-6} \text{ mm}^2 / \text{s}$ and $D_{\eta_t} = 1 \times 10^{-6} \text{ mm}^2 / \text{s}$. From the literature, the diffusion coefficient of water diffusion is $D_w = 1.9 \times 10^{-4} \text{ mm}^2 / \text{s}$. The values of D_{η_s} , D_{η_d} and D_{η_t} are relatively small (less than 1%) when compared with the water diffusion coefficient.

7.3.3 Comparison between model predictions and experimental data

We compared two positions from model prediction and experimental data and the results are shown in Fig.7-4.

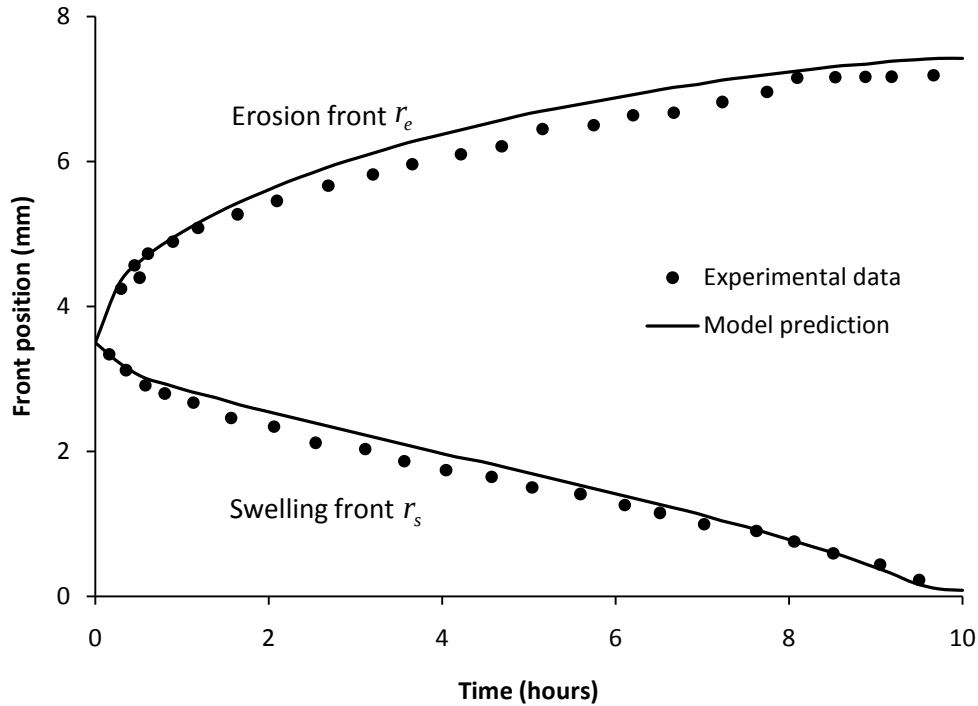


Fig.7-4 Comparisons between model predictions (solid lines) and experimental data (dots). Experimental data are obtained from Bettini *et al.* (2001, 1994): the initial radiuses of erosion front and swelling front are 3.5 mm.

Dots indicate results from experiment while solid lines are from model prediction. Because position of swelling front is approaching zero at hour 10, the maximum swelling time of all the predictions is limited to 10 hours. This model is not valid for swelling after 10 hours in this case. As we discussed previously, rate of movement for the erosion front is a function of the swelling front moving rate and this relation cannot be achieved after 10 hours. We therefore set both rates to zero when $r_s < 0.1$ mm. Radius of the swelling front decreased with time due to water penetrating into the tablet by diffusion. Simultaneously radius of the erosion front increased because of water induced swelling. As water penetrated into crystalline core, solid drug became dispersed in water molecules in the gel phase. They were undissolved in zone 2 while in zone 3 drug molecules became dissolved and diffusible. Fig. 7-5 illustrates the fraction drug release as function of time for both model prediction (solid line) and experimental data (dots).

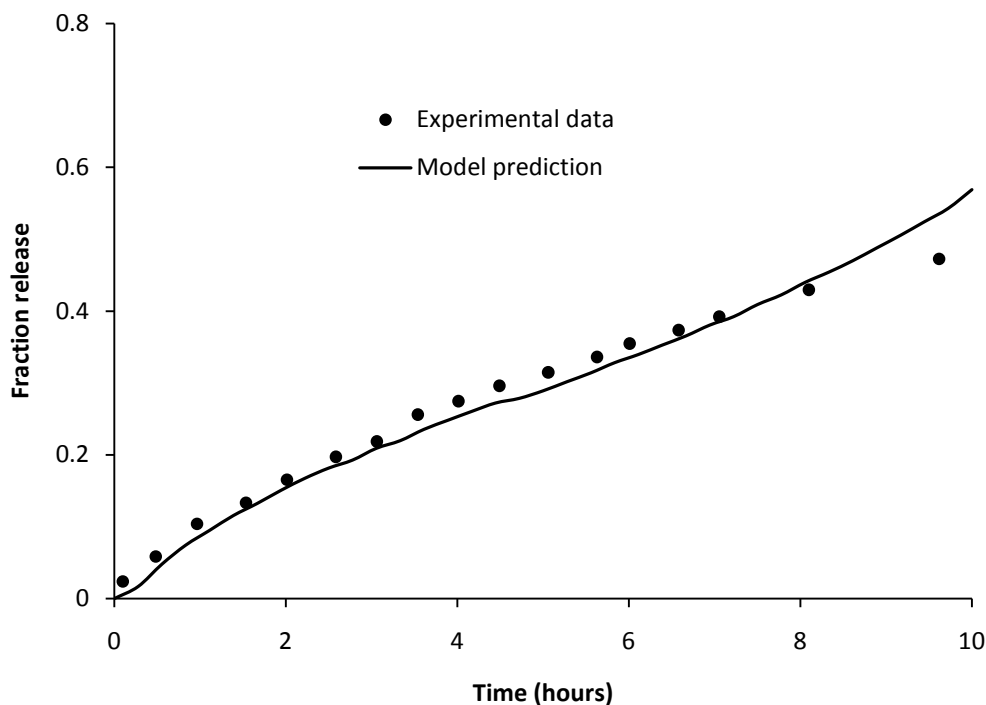


Fig.7-5 Comparison between model prediction and experimental data: normalised drug release as function of time.

At hour 10, the whole tablet was fully swelled and the fraction drug release had reached 50% (experimental data). The rest of fraction release cannot be simulated because of the model limitations. Fig. 7-5 indicates the release rate decreased a little bit at the beginning (gradient of the solid line) and then after about 5 hours the rate increased. This should be elucidated as below: In the first 5 hours, diffusion front remained unchanged. The total amount of dissolved drug did not increase with time until diffusion front moved towards the swelling front. Erosion front moved outward simultaneously which enlarged the domain of dissolved drug but decreased the concentration of drug which resulted in drug release rate reducing. On the contrary after 5 hours, diffusion front moved inward to enlarge the total amount of dissolved drug which resulted in drug release rate increasing. Both figs give good agreements between experiments and model prediction except data for diffusion front. Søren Kiil and Kim Dam-Johansen didn't get a good agreement for diffusion front and they thought the uncertainty of the key parameters put into the model can provide some explanations.

Figs. 7-6 and 7-7 illustrate order parameters (η_d and η_t) with drug concentrations at two different times (time=2.5 hours and time=7.5 hours) respectively.

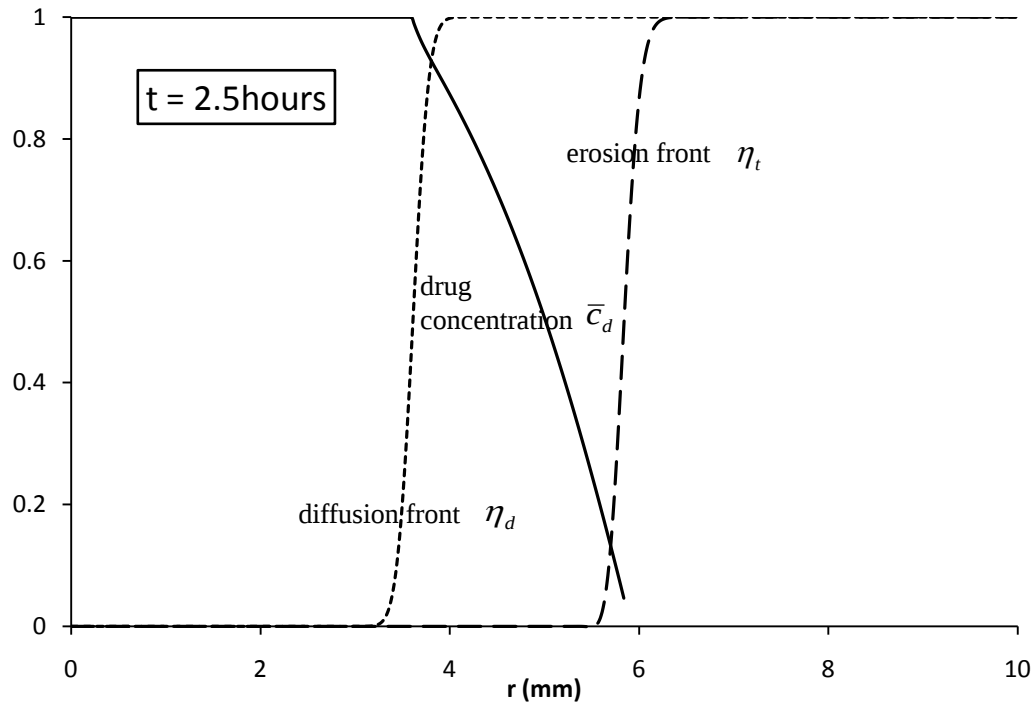


Fig. 7-6 Normalised drug concentration (solid line), η_d and η_t (dashed lines) as functions of r at time=2.5 hours. The initial radius of tablet is 3.5mm and the total size of the system is 10mm.

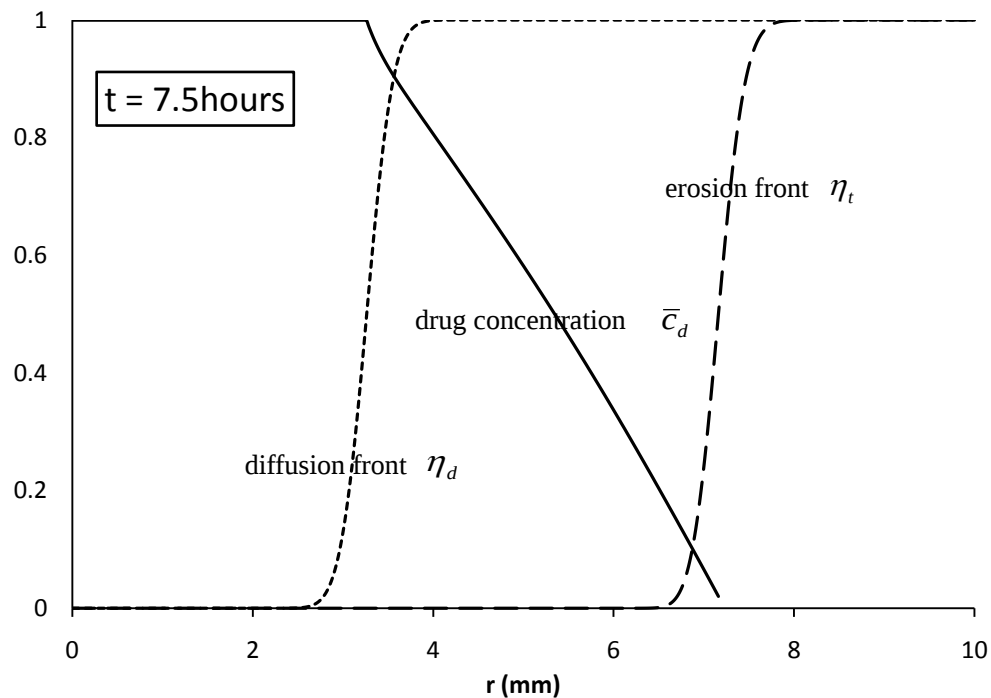


Fig. 7-7 normalised drug concentration (solid line), η_d and η_t (dashed lines) as functions of r coordinate at time=7.5 hours. The initial radius of tablet is 3.5mm and the total size of the system is 10mm.

Similarly Figs. 7-8 and 7-9 illustrate η_s and η_t with water concentrations at two different times (time=2.5 hours and time=7.5 hours) respectively.

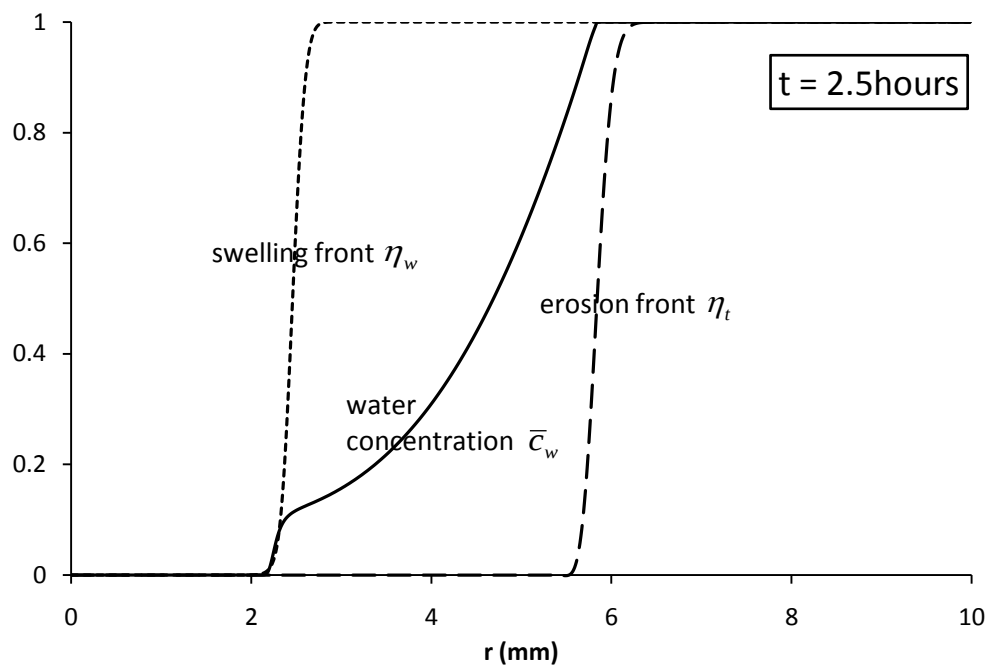


Fig. 7-8 Normalised water concentration (solid line), η_w and η_t (dashed lines) as functions of r coordinate at time=7.5 hours. The initial radius of tablet is 3.5mm and the total size of the system is 10mm.

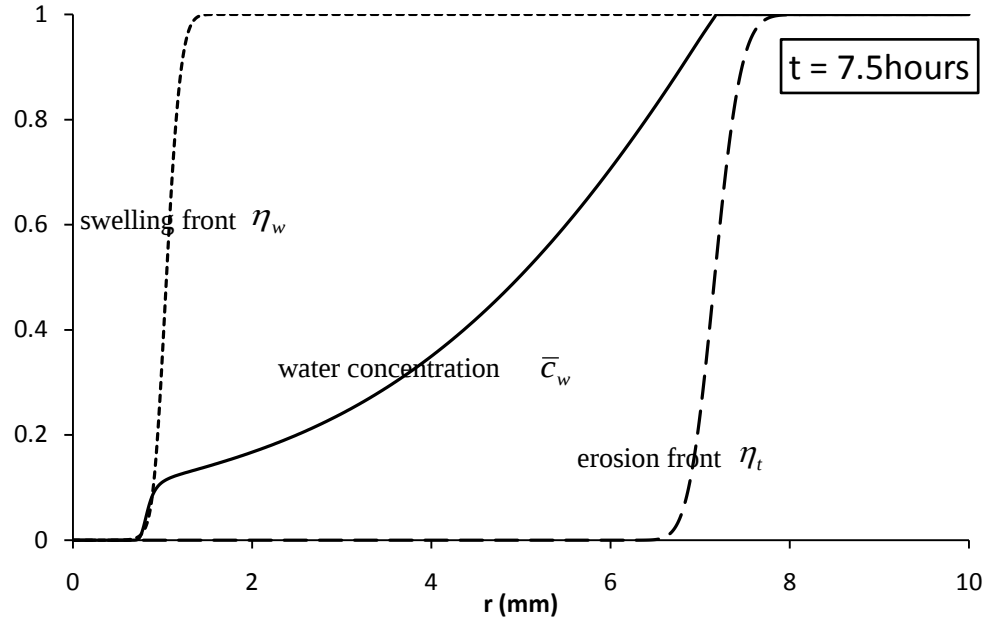


Fig. 7-9 Normalised water concentration (solid line), η_w and η_t (dashed lines) as functions of r coordinate at time=7.5 hours. The initial radius of tablet is 3.5mm and the total size of the system is 10mm.

The front positions in these figures can be considered as radiuses when η_s and η_t reached 0.5. At time=2.5hours, the radius of the tablet swelled from initial 3.5 mm to 5.5mm while swelling front moved 1.3 mm inward reaching 2.2mm. The water concentration decreased from the equilibrium value at the erosion front slightly and then suddenly reached zero at the swelling front. A sharp decreasing took place at swelling front due to eqn. (7-7). At the same time diffusion front remained unchanged while drug concentration decreased from diffusion front to erosion front due to equation 24. Only less than 20% drug released to the solvent. At time=7.5 hours, the total radius (radius of erosion front) reached 7mm while swelling front was approaching 1 mm. Diffusion front now moved inwards to the position of 3mm. In these five hours from time=2.5 to time=7.5, thickness of gel phase increased from around 3.3mm to 6mm while thickness of drug dissolved zone (zone 3) increased from 2mm to 4mm.

7.4. DISCUSSIONS

According to above results, the whole process of drug release from a swelling HPMC tablet are separated as three stages. Once a tablet is soaked in solvent, gel phase is then formed due to solvent molecule penetration. Firstly, the thicknesses of gel phase (zone2+zone3), drug dissolved phase (zone3) and drug dispersed phase (zone 2) increase. Although zone 3 is expanded due to movement of erosion front, diffusion front remains unchanged. The amount of dissolved drug is unchanged while the amount of undissolved drug is increasing due to the swelling front motion. More and more drug is waiting for dissolution. Secondly, as water continues to penetrate zone 3, zone2+zone3 expands while zone 1 shrinks. It is hard to see if zone 2 expands or shrinks because both boundaries (the swelling and diffusion fronts) of zone 2 move inward. In this stage, the amount of dissolved drug increases and the amount of undissolved drug depends on the thickness of zone2 which is uncertain. At last, when the swelling front approaches the axis all the drug molecules are either ready to dissolve in zone 2 or have dissolved in zone 3. Though the whole tablet reaches a fully gel phase, the thickness of the gel phase is still in expansion until the swelling ratio reaches f_s . In the last stage the thickness of zone 3 increases while that of zone 2 decreases until all drug molecules became dissolved. As aforementioned, the proposed model is only valid in the first two stages. A result from Fig. 7-5 indicates that after two stages the drug has released 50% with an approximate first order release profile. Modified phase field model can not only capture the main aspects of the drug release from a swelling HPMC tablet, but also opens a door for extending to 2D models.

7.5. CONCLUSIONS

This chapter presents a phase field model for drug release from highly swellable HPMC matrix. The main advantages of this phase field model are: the numerical solution strategy is very simple due to the elimination of the moving boundaries from the mathematical equations and the potential to be extended into 3 dimensional problems. Details of model set up and model predictions are also provided. Comparisons between the model predictions and experimental data show excellent agreement. Three distinguishing stages of the drug release from swellable matrix are discussed which can give some understanding to the behaviour of the tablet. In summary, this phase field model captures the most important release mechanisms and provides a means for tablet design based on computer modelling.

CHAPTER EIGHT - MAJOR CONCLUSION AND FUTURE WORK

8.1.CONCLUSION

In this thesis, a serial of mathematical models have been presented to predict the degradation behaviours of biodegradable polymers and their composites with TCP. Numerical methods, including the finite element method, finite difference method, kinetic Monte Carlo method, multi-scale modelling and phase field method, are all applies to this field of study in this thesis.

Chapter three presents a multi-scale model for the degradation of bioresorbable polyesters. Events that occur at the molecular scale, such as polymer chain scissions and oligomer production, are modelled at the molecular scale using the kinetic Monte Carlo scheme while events that occurs at the device scale, such as oligomer diffusion, is modelled using a macroscopic diffusion equation. The models at the two scales are connected at the finite difference nodes of the diffusion equation. This two-scale model was then used to predict the temporal evolution and spatial distribution of molecular weight distribution in a device as well as the oligomer diffusion which leads to the weight loss of the device. An expression for the macroscopic diffusion coefficient is used that takes into account of the porosity development in the polymer due to oligomers leaving the material. Detailed information about the polymer systems such as the initial molecular weight distribution, copolymer ratio and degree of crystallinity are part of the input of the model. It is shown that the model can accurately predict the effect of copolymer ratio on the degradation rate of copolymers and that the model predictions agree with existing experimental data in the literature. According to the multi-scale model, work which has been done previously is modified.

Chapter four provides a model for simultaneous crystallisation and biodegradation of biodegradable polymers. This is a phenomenological model which completed the degradation theory developed by Wang *et al.* (2008) to describe the interplay between crystallisation and hydrolysis reaction during the biodegradation of polyesters. A reaction diffusion equation was coupled with a set of partial differential equations for chain scission-induced crystallisation. These mathematical equations are solved numerically to compare with existing experimental data in the literature. A simple graphical means of quantifying

the effect of crystallisation on the biodegradation was presented. This model provides a tool to guide the design of bioresorbable devices.

The purpose of chapter five includes: (1) providing a summary of the mathematical models required to analyse accelerated degradation data and to indicate the pitfalls of using these models, (2) providing a simple version of the model in chapter four with an analytical solution that is convenient to use, and (3) demonstrating the application of the improved model in two different PLA systems. It is shown that the simple analytical relations between molecular weight and degradation time widely used in the literature can lead to inadequate conclusions. In more general situations, the rate equations are only part of a complete degradation model. Together with previous works in the literature, our study calls for care in using the accelerated testing technique. The modified accelerating degradation model is validated by comparing the model prediction results with the experiments carried out by Fraser Buchanan, Neill Weir and David Farrar (2004^a, 2004^b).

Chapter six presents a model for the biodegradation of composite materials made of polyesters and calcium phosphates. Composites of polyester and calcium phosphate are widely used in manufacturing internal fixation devices for bone repairing. This model presents an understanding in the hydrolysis reaction of the ester bonds, the acid dissociation of the carboxylic end groups, the dissolution of the calcium phosphates, and the buffering reactions by the dissolved phosphate. Partial differential equations are used to model these mechanisms and solved by numerical method. Comparisons are made between the model prediction and existing experimental data in the literature. Two non-dimensional groups of the physical and chemical parameters are identified which control the degradation behaviour of the composites. A calcium phosphate effectiveness map is established using the model to show the conditions under which incorporating calcium phosphates into polyesters is effective, saturated or ineffective.

Chapter seven presents a phase field model for the drug release from highly swellable HPMC matrix. This is a pilot research for modelling drug release from swelling polymers. The prototype of the phase field model is a mathematical model established by ref (Kiil and Dam-Johansen, 2003). The main advantages of the phase field model include: a) no

coordinate transformation is required and b) it is possible to extend the model into 3 dimensional problems. Comparison between model predictions and experimental data shows good agreements. Three distinguishing stages of drug release from swellable matrix are discussed which can provide explanations to the experimental results. The phase field model captures the most important release mechanisms and provides a means for design and formulation of new controlled release formulations.

8.2. FUTURE WORK

As discussed in the first chapter, the main concerns in tissue engineering are: 1) controlling the growth factor release in the scaffold for the purpose of stimulating cell differentiation; 2) controlling the nutrient transport in scaffold in order to achieve uniform tissue distribution; and 3) limiting the influence of acidic breakdown products on the bone healing response by introducing the ceramics which neutralise the acid release. In the future this PhD project should be extended to applying the mathematical models into bone tissue engineering to resolve those concerns. Here two models are outlined with some details as future work: 1) two-scale growth factor release model, and 2) multi-scale nutrient transport model.

1) A two-scale model to simulate the release of incorporating growth factors in the scaffold: The biggest problem in bone tissue engineering is the lacking of vascular which is being addressed by inducing certain growth factors to the scaffold to stimulate the differentiation of stem cells. If simply inject these proteins into scaffolds, they would release quickly within even one day, which will not meet the clinic requirements. Furthermore undesired side effects may arise when substances intended for local delivery to a specific tissue are not spatially contained. It is then necessary to control growth factors release rate using drug release systems. This model concentrates on particular GFs in bone tissue engineering: 1) bone morphogenetic proteins (BMPs), which induces cartilage and bone formation from non-skeletal cells; 2) transforming growth factor- β (TGF- β), which controls cell differentiation, stimulates cell proliferation and induces the formation of extracellular matrix; 3) basic fibroblast growth factors (bFGFs), which stimulates proliferation and differentiation of mesodermal tissues; and 4) vascular endothelial growth factors (VEGFs), which stimulates the growth of new blood vessels (Linkhart *et al.*, 1996; Mohan and Baylink, 1991). Additionally, various delivery systems are intensively used in the

applications (Narasimhan and Peppas, 1997; Freiberg and Zhu, 2004; Edlund and Albertsson, 2002; Sohler *et al.*, 2006; Hemin *et al.*, 2008; Langer, 1990) including dissolution of drugs, adsorption, emulsion techniques and suspension of the drug, and physical mixtures.

In the microscopic scale, polymer molecular distribution, copolymer ratio, chain scission rates and degree of crystallinity are the input data obtained from experiments directly. Chain scissions and crystallisation are simulated by using kinetic Monte Carlo method. Drug release, oligomer diffusion and water uptake are being applied globally in the macroscopic scale. Simultaneous degradation and crystallisation affect the release rate by increasing the effective diffusion coefficients. The diffusion coefficients, which mainly depend on porosity of the matrix, for soluble oligomer and growth factor change as degradation proceeds. On the contrary, drug release affects the oligomer diffusion. When drugs diffuse out into the media, the porosity of the matrix increases, resulting in a faster oligomer diffusion and a reduction of polymer degradation rate accordingly. Moreover, water uptake is a main mechanism in scaffold swelling which results in an increase of polymer chain mobility. Change of crystallinity is therefore being induced during degradation.

Different growth factor release systems shown in Fig.8-1 make the model more complicated: 1) Dissolution system: growth factors dissolved into matrix directly so that the distribution of GF acts as a simple global input. In this case, diffusion is the main mechanism of GF delivery. 2) Adsorption system: different from the dissolution system, adsorption system is a technique loading the GFs by simply adsorbing them on the material surface. Drug release in this system is controlled by desorption kinetics including material-GF interactions and drug diffusion. Drug diffusion is being simulated globally while the interactions between materials and GFs are being executed locally. 3) Emulsion systems: this system is more complicated than the previous two. Water in oil emulsions is prepared and fabricated into polymer scaffold. Technically hydrophilic growth factors are put into the water phase which is incorporated into lipophilic polymers. The emulsion system has the advantage of creating an even distribution of drugs inside the scaffold. Some mathematical models are also used to simulate the emulsion system. The mechanisms in

this system are governed by several partial differential equations (Fernando and Pedro, 2008). The computational models of the emulsion system are being incorporated into the two scale model presented in chapter three to simulate a complete GF delivery system. 4) Suspension of drug and physical mixture: physical materials mixed with GFs in solid state are processed into porous scaffolds. This system allows the delivery of GF lasting for over several weeks (Shea *et al.*, 1999). As different delivery systems can be simulated using the two scale model, a general framework is able to be established in order to guide optimising the design of scaffold.

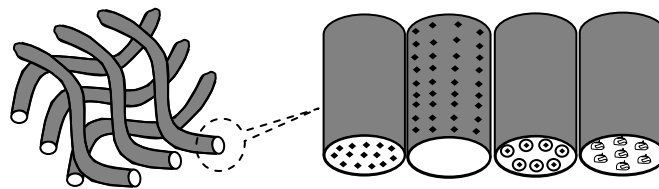


Fig.8-1 Schematic illustration of GF delivery

The biology process of tissue repair requires GFs with different doses and various release times to provide functions. Therefore to model more than two growth factors releasing from a scaffold would be a challenge. GF release mechanisms considered in the model above include molecular distribution of polymers, degree of crystallinity, copolymer ratio, growth factor types, and different release systems. A schematic illustration of this model is shown in Fig. 8-2. Aims of growth factor delivery are to stimulate the differentiation of stem cells, so that cell behaviours, which are ignored in the two scale model, have to be involved. In the following model, cell behaviours are being considered.

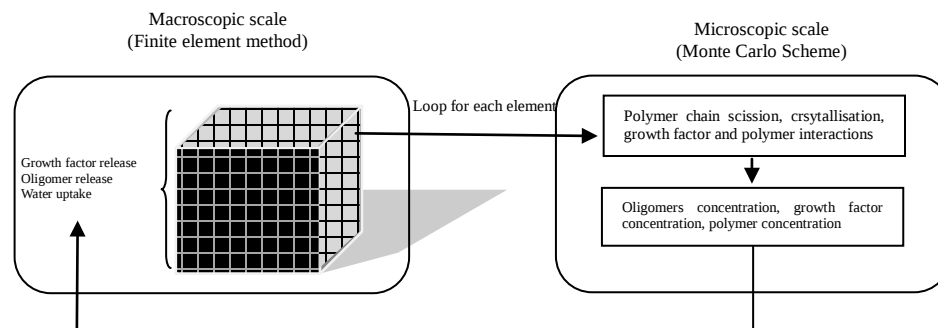


Fig.8-2 Schematic illustration of two scale GF release model

2) A multi-scale model to simulate nutrient transport in the scaffold:

The purpose of the multi-scale model is to model the nutrient transport in the scaffold. Cell

behaviours and tissue regeneration mainly depend on the nutrient supply. Cells without oxygen will become disordered and eventually die. Nutrient transport is demonstrated by a diffusion mechanism. The diffusion coefficients of nutrient transport depend on oligomer concentration, polymer concentration, growth factor diffusion and cell behaviours. A multi-scale model is being developed to describe these mechanisms. In the model, mechanisms happening over the scaffold are treated globally. Partial differential equations are used to describe these mechanisms such as oligomer diffusion, GF release and nutrient transport. Mechanisms occurring in microscopic scale, such as cell differentiation, cell growth, polymer chain scissions and local crystallisation, are simulated by the kinetic Monte Carlo scheme and cellular automaton method (Zaman *et al.*, 2005; Deasy *et al.*, 2003). A simple multi-scale model used to describe the polymer degradation in 1-D dense device has been established in chapter three. In this work, similar model is being developed based on the previous model. The existing model will be extended to a 3D problem including the effect of cell behaviours and effect of growth factor release.

On the micro-scale, polymer chain scissions and local crystallisation are simulated. The change of crystallinity affects the chain scission rates by decreasing the concentration of ester bonds for amorphous polymer chains. Local crystallisation occurs because the mobility of amorphous polymer chains increases during degradation. This mechanism is influenced by many factors: chain scission, growth factor release and water uptake. Cell growth and differentiation are simulated using cellular automaton method. Cellular automaton methods base on explicitly modelling a large number of individual cells, which are subject to certain rules of conduct. By using this method, the complexity of global behaviours can be represented by a set of simple rules. The effect of growth factor on cell behaviours is therefore being integrated to the cellular automaton under a certain rule. As the size of cell units in cellular automaton method is much larger than that of a polymer repeat unit and smaller than that of a scaffold, this micro-scale contends two sub-scales: polymer chain scale and cell unit scale.

On the global-scale, oligomer diffusion, growth factor delivery, nutrient transport and water uptake are taken into account by applying Fick's law. Nutrients are consumed by cells for cell growth and differentiation. If nutrient supply in the scaffold is insufficient for cell activities, cells will become disorder. On the contrary, cells would grow to occupy the pores

of the scaffold and change the diffusion condition for soluble oligomers and nutrient subsequently. In addition, growth factors released from the scaffold affect diffusion coefficients of oligomer and nutrient diffusions. The diffusion coefficients of the growth factor also depend on oligomers, nutrient diffusions, and cell activities. In the macroscopic scale, all mechanisms are executed by using modified diffusion equations. These equations are then solved by finite element method for 3D scaffolds in various sophisticated shapes.

A three-scale model is then completed: polymer scale, cell unit scale and scaffold scale. The interplays among different components in the system are the remarkable challenges in the model. All three scales are being coupled with each other on a finite element integrating node. Furthermore, the three-scale model is readily extended from pure polymeric matrix to a TCP/polyester scaffold. The composites have some advantages: 1) they have good bone-bonding properties due to their osteoconductivity of the calcium phosphates; 2) the dissolved phosphate ions buffer the acidity of the carboxylic end groups (produced by the polyester chain cleavage) while the polyesters provide appropriate mechanical properties; 3) composites degrade more slowly than pure polymeric matrix to maintain the shape of the scaffold; 4) the pH value of the surrounding media remains stable for a longer time of the composites (Heidemann *et al.*, 2001; Ehrenfried *et al.*, 2008; Zhijie *et al.*, 2009). This three scale model is shown schematically in Fig. 8-3.

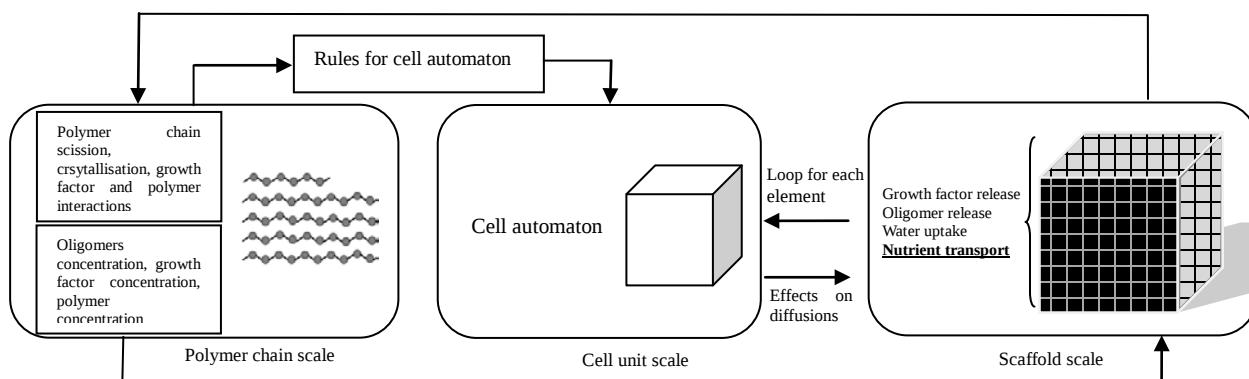


Fig.8-3 Schematic illustration of three scale nutrient transport model

The two scale growth factor release model will provide a framework for the model developer and hence they can develop more complex models based on this framework. It

also will help people designing the experiments to gain better functions of growth factors to avoid cell death and cell disorder. The second model will produce a better understanding of interplays in a scaffold among cells, growth factors, materials and the nutrient from which experimental researchers are able to control the experiment conditions such as cell seeding distribution, scaffold microstructures and the contents of the materials. Indeed, various animal experiments have shown the capacity of bone tissue engineering to produce bone. Surprisingly however, until recently, no convincing success has been achieved in human. Once lack of vascularisation, heterogeneous nutrient distribution and pH decreasing caused by degradable scaffold are all addressed, it is possible to pave the way for putting bone tissue engineering into clinical applications. Not only patients will benefit from bone tissue engineering but also NHS will be able to cut its budget in the future.

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