Impact on controlled drug delivery

(lactic-co-glycolic) acid: and physicochemical properties of pol

Mechanisms for modifying the physicochemical
DECLARATION

This 16th day of July 2007

........................................

[Signature]

For any degree or examination at this or any other university, the University of the Witwatersrand, Johannesburg, it has not been submitted before submitted for the degree of Master of Pharmacy in the Faculty of Health Sciences in Sibongile Ruth Shibamba declare this dissertation as my own work. It is being...
To God be the glory, for His mercy and loving-kindness forever.

Foundation (NYF), Department of Leukemia (D.L.), South Africa

This research was made possible through the financial assistance of the National Research

In dedicating this family, without whom a degree would have been just a dream.

my brothers and sisters in the Egyptian Medical, Emile, Soliman and Phumzile Shabangu; my niece and

Elizabeth Shabangu; my brothers, Shakir and Siyabisi; my sister, Ziyadah and her children;

and a nieces model in our family. Lastly, my deepest gratitude belongs to my mother, Mrs. Hlakazi,

over the years, in particular, my uncle, Mr. Phatho, who continues to be an inspiration

I would like to express my gratitude to my whole family, staff, and everyone for their support.

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I would like to express my gratitude to Prof. Vyas Pillay for his course, motivation and

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SUMMARY
In memory of my father Ezekiel Macbain's, Sibembo, I(under this dedication to all the


PREPARATIONS:
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Applicant: University of the Western Cape.

Inventors: Siombo, R. Sibanda, V., Pilly, Y., Yehya E., Choonara and Michael P. Dancwerts.


INTRODUCTION AND MOTIVATION FOR THIS STUDY

CHAPTER ONE

TABLE OF CONTENT

List of Figures
List of Tables
Table of Contents
Patent
Patents
Publications
Dedication
Summary
Acknowledgements
Declaration
CHAPTER TWO

DEVELOPMENT OF A SALTED-OUT AND CROSS-LINKED PLA SCAFFOLD
CHAPTER 3

QUANTUM ENERGY TRANSITIONS OF THE PLGA SCAFFOLD

EUCATION OF THE IN VITRO PHYSICOMECHANICAL AND AB INITIO
Morphology

Scanning Electron Microscopic Image Analyses of the PLA Scaffold

Proposed Interactions Between PLA Chirns and Cross-Linking Lons

Results and Discussion

Thermal Transition Analysis of the PLA Scaffolds

Evaluation of the Molecular Structural Transformations within PLA Scaffolds

Determination of the Physicochemical Properties of the PLA

Characterization of the PLA Scaffolds

Preparation of PLA Scaffolds

Building the Experimental Design

Materials

Materials and Methods

Polymer Modification with Silk and Ions

Introduction

PHYSICOCHEMICAL PROPERTIES OF THE PLA SCAFFOLD

THE EFFECTS OF SALTS ON THE PHYSICOCHEMICAL AND

CHAPTER FOUR

Concluding Remarks

Molecular Interaction Level

Identification of the Quantum Mechanical Energy Transitions at a

Properties

Values for Matrix Resilience, Energy Absorbed, and Mass Depletion

Comparison of the Experimental Vs. (Predicted) Fitted Response
Concluding Remarks

5.4

5.8.6

5.8.5

5.8.4

5.8.3

5.8.2

5.8.1

5.8

5.7.8

5.7.7

5.7.6

5.7.5

5.7.4

5.7.3

5.7.2

5.7.1

5.7

5.6

5.5

5.4

4.8

4.7

4.6

4.5

4.4

4.3

4.2

4.1

4.0

3.9

3.8

3.7

3.6

3.5

3.4

3.3

3.2

3.1

3.0

2.9

2.8

2.7

2.6

2.5

2.4

2.3

2.2

2.1

2.0

1.9

1.8

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1.4

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Materials

Preparation of the scaffolds

Building the experimental design

Preparation of a calibration curve for the spectroscopic

Determination of Melatonin Release from the PLGA scaffold

Drug Enhancement Efficiency of the scaffolds

In Vivo Drug Release from the PLGA scaffold

Statistical Optimization

Kinetic Models Employed to Evaluate the Drug Release Mechanism

Results and Discussion

Response Surface Plots Indicating the Effects of Variables on the

Response

Characterization of the In Vivo Drug Release from the PLGA scaffold

Drug Enhancement Efficiency of the PLGA scaffolds

Statistical Analysis for Optimization of the Drug Enhancement Efficiency

Mean Dissolution Time and Drug Release Kinetics of the PLGA scaffold

In Vitro Drug Release Studies from the Optimized PLGA scaffold

Kinetic Analysis of the Drug Release Mechanisms from the PLGA scaffold

Concluding Remarks
CHAPTER 6

MONOLITHIC MATRIX SYSTEM
IN VITRO AMITRIPTYLINE HCl RELEASE FROM A PLA COMPRRESSSED
MODEL DRUG: AMITRIPTYLINE HCl (WATER SOLUBLE)
CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

7.1

7.2

Recommendations

7.3

Conclusions

REFERENCES

8

189

191

194
| Table 1.1 | General Physicochemical and the Physicochemical Properties of soluble PLA Grades |
| Table 2.2 | PLA: The physicochemical properties of soluble PLA Grades |
| Table 2.3 | Semis illustrating the ability of ions to cause water salting-out |
| Table 2.4 | Classification of ions, used in terms of their aqueous ionic salting-out power |
| Table 2.5 | The reaction of random input variables on the salting-out of various PLA grades (RG 502, RG 503 and RG 604) |
| Table 2.6 | Scald yield after salting-out and cross-linking with various B-coefficients of polymer, viscosity and the viscosity Jones-Doek |
| Table 3.1 | Normalized factor levels of the independent variables for the FDCD |
| Table 3.2 | Textural parameters and settings Randomeized experimental runs generated from the FDCD |
| Table 3.3 | Textural parameter settings |
| Table 3.4 | Factor levels of the independent variables for the Box- |
| Table 4.1 | Behren Design Box-Behnken template with randomly generated PLA |
| Table 4.2 | Behavioral Design |
| Table 4.3 | Textural parameters and settings |
| Table 4.4 | Physicochemical properties of the salts employed during cross-linking of PLA |
| Table 4.5 | Thermal parameters of naive and selfed-out PLA employing DSC |

**LIST OF TABLES**
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>EH2N values obtained from the four independent samples of 180</td>
</tr>
<tr>
<td>6.3</td>
<td>Textural settings employed for EH2N value calculations</td>
</tr>
<tr>
<td>6.2</td>
<td>Normalized factor levels of the independent variables</td>
</tr>
<tr>
<td></td>
<td>of the TGA Amplitude</td>
</tr>
<tr>
<td>6.1</td>
<td>The Physicalchemical and Physico-mechanical Properties</td>
</tr>
<tr>
<td>6.0</td>
<td>Swelling studies of the PLGA scaffolds loaded with melatonin</td>
</tr>
<tr>
<td>5.7</td>
<td>Mechanical predictors for melatonin release from the PLGA</td>
</tr>
<tr>
<td>5.6</td>
<td>Drug release kinetics obtained from the various diffusion,</td>
</tr>
<tr>
<td>5.5</td>
<td>Desired and Experimental responses for the optimized PLGA</td>
</tr>
<tr>
<td>5.4</td>
<td>Settmg for Response Optimization</td>
</tr>
<tr>
<td>5.3</td>
<td>The Drug release at 30 days (%); Mean Dissolution Time</td>
</tr>
<tr>
<td>5.2</td>
<td>Factor levels of the Independent Formulation Variables</td>
</tr>
<tr>
<td>5.1</td>
<td>The Physicalchemical and Physico-mechanical Properties</td>
</tr>
<tr>
<td>4.4</td>
<td>(MDT 30) and the release constant (C) of the PLGA scaffolds</td>
</tr>
<tr>
<td>4.3</td>
<td>Table 5.5</td>
</tr>
<tr>
<td>4.2</td>
<td>Table 5.4</td>
</tr>
<tr>
<td>4.1</td>
<td>Table 5.3</td>
</tr>
<tr>
<td>4.0</td>
<td>Table 5.2</td>
</tr>
<tr>
<td>3.9</td>
<td>Table 5.1</td>
</tr>
<tr>
<td>3.8</td>
<td>Table 5.0</td>
</tr>
<tr>
<td>3.7</td>
<td>Table 4.9</td>
</tr>
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<td>3.6</td>
<td>Table 4.8</td>
</tr>
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<td>Table 4.7</td>
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<tr>
<td>3.4</td>
<td>Table 4.6</td>
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<td>3.3</td>
<td>Table 4.5</td>
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<td>3.2</td>
<td>Table 4.4</td>
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<td>3.1</td>
<td>Table 4.3</td>
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<td>Table 1.2</td>
</tr>
<tr>
<td></td>
<td>Table 1.1</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 1.  Typical force-distance and force-time profiles of PLA.

Figure 2.  Scanning electron micrograph of a freeze-dried, freeze-polymerized enzyme.

Figure 3.  Schematic diagram of the mechanism of degradation of PLA.

Figure 4.  Mass detection.

Figure 5.  Molecular weight and polydispersity of PLA.

Figure 6.  Molecular weight and polydispersity of PLA.

Figure 7.  Molecular weight and polydispersity of PLA.

Figure 8.  Molecular weight and polydispersity of PLA.

Figure 9.  Molecular weight and polydispersity of PLA.

Figure 10.  Molecular weight and polydispersity of PLA.

Figure 11.  Molecular weight and polydispersity of PLA.

Figure 12.  Molecular weight and polydispersity of PLA.

Figure 13.  Molecular weight and polydispersity of PLA.

Figure 14.  Molecular weight and polydispersity of PLA.

Figure 15.  Molecular weight and polydispersity of PLA.

Figure 16.  Molecular weight and polydispersity of PLA.

Figure 17.  Molecular weight and polydispersity of PLA.

Figure 18.  Molecular weight and polydispersity of PLA.

Figure 19.  Molecular weight and polydispersity of PLA.

Figure 20.  Molecular weight and polydispersity of PLA.

Figure 21.  Molecular weight and polydispersity of PLA.

Figure 22.  Molecular weight and polydispersity of PLA.

Figure 23.  Molecular weight and polydispersity of PLA.

Figure 24.  Molecular weight and polydispersity of PLA.

Figure 25.  Molecular weight and polydispersity of PLA.

Figure 26.  Molecular weight and polydispersity of PLA.

Figure 27.  Molecular weight and polydispersity of PLA.

Figure 28.  Molecular weight and polydispersity of PLA.

Figure 29.  Molecular weight and polydispersity of PLA.

Figure 30.  Molecular weight and polydispersity of PLA.

Figure 31.  Molecular weight and polydispersity of PLA.

Figure 32.  Molecular weight and polydispersity of PLA.

Figure 33.  Molecular weight and polydispersity of PLA.

Figure 34.  Molecular weight and polydispersity of PLA.

Figure 35.  Molecular weight and polydispersity of PLA.

Figure 36.  Molecular weight and polydispersity of PLA.

Figure 37.  Molecular weight and polydispersity of PLA.

Figure 38.  Molecular weight and polydispersity of PLA.

Figure 39.  Molecular weight and polydispersity of PLA.

Figure 40.  Molecular weight and polydispersity of PLA.

Figure 41.  Molecular weight and polydispersity of PLA.

Figure 42.  Molecular weight and polydispersity of PLA.

Figure 43.  Molecular weight and polydispersity of PLA.

Figure 44.  Molecular weight and polydispersity of PLA.

Figure 45.  Molecular weight and polydispersity of PLA.

Figure 46.  Molecular weight and polydispersity of PLA.

Figure 47.  Molecular weight and polydispersity of PLA.

Figure 48.  Molecular weight and polydispersity of PLA.

Figure 49.  Molecular weight and polydispersity of PLA.

Figure 50.  Molecular weight and polydispersity of PLA.
development and modification of these materials in order to address the wide range
match their specific applications. The challenge is to accelerate research in the
to novel bioerodable polymers with unique properties to

et al., 2007; Kumar et al., 2007; Yang et al., 2007; Cheng
and Panagkura, 2004; Kumar et al., 2006; Liu et al., 2006; Vito et al., 2006; Chiang
approach to their modification for drug delivery and tissue engineering (Dhamkhar,
ene drug efficacy. Recently, there has been a significant advance in the science
enhanced need for subsequent surgery for the removal of the device, and also
completely eliminated from the body. Thus, bioerodable polymers not only
period of time, and subsequently degrade biologically or enzymatically and be
by virtue of its bioerodable property, such a device is able to function for a predetermined

et al., 2006; Liu et al., 2006; Potrovic and Stochel, 2006; Xue et al., 2006).
dervice, such as drugs, vaccines, hormones and cells for tissue engineering (Kumar et
local delivery systems, and the controlled release of bioactive transplanted by the
controlled release of bioactive transplanted by the
dormous and cells for tissue engineering (Kumar et
Kushnirski and Tepel, 2004; Chowdhury and Akele, 2005). The use of these
bioerodable polymers have presented new approaches to clinical medicine by

1.7 Background

INTRODUCTION AND MOTIVATION FOR THIS STUDY

CHAPTER ONE
By altering the chemical backbone or side chain of the existing polymer (Krantz et al., 2006),
mainly tailored by altering the molecule mass during polymerization or synthetically,
PLA, PGA, and PLGA. Their physicochemical and physicomechanical properties are
The majority of synthetic biodegradable polymers are linear thermoplastics such as
be produced with modifiable properties (Gomez et al., 2006).
Alternatively, synthetic biodegradable polymers are more levorable, since most can
intermediate processing mechanisms have made them unpopular in biomedicine.
Indeed, however, the viability of polymer delivery, the lack of stability and the
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1.2 Medication of Biodegradable Polymers for Drug Delivery

(Sander et al., 2004; Carini and Peschuk, 2005).

Engineering devices has been instrumental in their use for medical applications
as well as their potential to be designed into various drug delivery and tissue-
Furthermore, the ability of PLGA to dissolve in both organic and nongradient solvents
administration (FDA) as generally regarded as safe (GRAS) materials.
supplied mechanical strength and hence has approval by the US Food and Drug
desirable properties, namely, biocompatibility, biodegradability, non-immunogenicity,
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desirable properties, namely, biocompatibility, biodegradability, non-immunogenicity,
care. In such cases a localized controlled drug release implant may be beneficial.

patients autonomy and to reduce the psychological and social burdens of nursing
that traditionally demand high care, it is vital to reduce nursing care, establish
A future concept namely, patient independence is extremely important in diseases

(Thornton et al., 2005; Emery et al., 2006).

owing to the regulated pharmacokinetics and pharmacodynamics of drug effects.

Consequently, there is selectivity of the pharmacologic activity at receptor site,
administration and optimal use of central nervous system (CNS) drugs, include maintenance of drug levels within the desired therapeutic range. Lower drug
therapy, cannot be sufficiently accentuated. The advantages of such a system
drug release, especially in illnesses that require chronic suppressive maintenance
The significance of modified biodegradable polymers in controlled and sustained

parameters.

mechanisms of engineering and transmutation of the polymer in terms of such

The performance of drug delivery devices in vivo and in vivo depends on the
dependent on hydrolytic degradation, and the influence of pH on disintegration
polymers in physiological media. The dynamics of these processes are primarily
properties of drug delivery devices is key to the functioning of biodegradable
The correlation between the physicochemical physicochemical and release

Jayakumar et al., 2007).

Factor-a (TNF-a) with free radicals that are detrimental to neurons (Gao et al., 2002).

Produced inflammatory and neurotrophic factors such as cytokines and tumor necrosis factor investigations have highlighted researchers on the microglia-
el. (2004: LaThompson, 2004: Ahmed et al., 2005: Velmekh et el., 2005: Velmekh et al., personify intellectual, social and occupational functions in the patient (Groom et al., 2001: Groom et al., cognitive deficits such as aphasia, apraxia and agnosia, consequently disrupting the

Each of these disorders affects a distinct sections of the brain, causing motor and/or

Lateral Scarcities and Huntington's Disease

The major disorders include Alzheimer's Disease, Parkinson's Disease, Amyotrophic

Lateral Scarcities. For a diverse group of diseases that have several commonalities


Problems (Marino, 1994: Lee et al., 2001: Shih and Brandt, 2002: Flassman et al.,

the are those characterized by neuronal or neurological-mediated accumulation of neu-
nurological disorders lead to dementia and/or abnormal motor symptomology. Among

The term neurodegenerative disorders encompasses a variety of underlying

4

Current Trends and Challenges of Neurodegenerative Disorders

(Jamshed and Fassini, 2006).

This in turn will eliminate the need for monitored and nurse-regulated drug therapy
These disorders usually begin after the age of 60 and risk goes up with age. For

The burden of neurodegenerative disorders on individuals, families and our health care

The world prevalence of Parkinson's disease is 150 per 100,000 and increasing.

The age of 60 (Patonick, 2005).

Prevalence of 9 million people by the year 2070 and 34% of that population to be over

Years (Patonick, 2005). Statistics by a United Nations (UN) report predicts a

approximately 13% for age group 60-69 years and 35% for age group above 80

grown from 60.7% in the year 2000 to 90.6% in 2025. The prevalence is

example, the number of South Africans suffering from Alzheimer's disease has
effects at higher doses due to dose accumulation. Daily, depending on the therapeutic goal. This results in greater frequency of side cholesterol-sequestering inhibitors (CHE-1) such as donepezil (Aricept), that is administered current limitations in Alzheimer's Disease include oral administration of CNS) to provide localized drug delivery that improves drug efficacy. For example, in addition, the formulation could be implanted into the central nervous system by daily dose.

absence of nursing care, eradicate the need for patients to remember to take their long-term controlled drug delivery which would reduce nursing care, and in the deleterious side effects and incompliance. An ideal form of therapy could provide require frequent dosing and hence leading to continuous nursing. numerous they are either formulated as orally administered tablets, capsules or liquids which The major limitations of current therapies for neurodegenerative disorders is that Neurodegenerative Disorders
1.4.1 Limitations in the Current Therapeutic Approaches for

A Statement of the Problem

2007.

targets by synchronized therapeutic strategies (Huang, 2006; Lim, et al., may share a common or overlapping pathogenic mechanisms which could be molecular pathogenic mechanisms could instigate the neurodegenerative disorders Research findings that implicate the commonalities in protein aggregation and
could be reduced by controlled drug delivery. Side effects are due to peak-trough changes of the drug plasma concentration and to dose-related toxicity. Few of these psychiatric improvements, however, these formulations also lead to side effects such as dizziness, extrapyramidal, anticholinergic, and motor effects due to peripheral toxicity. 

Alteratively, olanzapine 5 mg per day is given with L-3,4-dihydroxyphenylalanine (L-DOPA) or selegiline (Selegil) per day. 

2004. 

Selegiline or a monoamine oxidase type B inhibitor is an adjunct to L-DOPA, 

delivery. For Huntington's Disease, quinidine 250 mg daily, a dopamine re-uptake inhibitor, caused dyskinesia, rigidity, and tremor because of the uncontrolled release of dopa. These effects, however, lead to increased peripheral levodopa and the toxicity dosage forms. However, lead to increased peripheral levodopa and the toxicity of levodopa to dopamine in an effort to reduce peripheral side effects. These are of 

Parkinson's Disease, levodopa is combined with an aromatic amino acid such as tyrosine, or and a dopamine agonist or a levodopa decarboxylase inhibitor, carbidopa (Carnitriple) to reduce peripheral conversion of levodopa into dopamine. The same short-comings are experienced with other neurodegenerative disorders. 

2004. 

Symptoms similar to other CHFs, with higher doses, Clinical trials demonstrated no treatment effects at doses of bromocriptine and produced adverse gastrointestinal effects. It was reported that galantamine consistently failed to display statistically significant daily administration (Grenier et al., 2004). In their study, Olum and Schneider (2001) reported that galantamine (Reminyl®) is also available in the form of tablets and requires twice daily administration.
in view of these facts, local delivery of drugs to the brain may produce a solution to

methods of drug delivery.

not be due to a lack of drug potency, but rather attributed to the limitations in the
bioadhesive agents in the diagnosis and therapy of neurodegenerative disorders may
significantly impede the delivery of drugs to the brain. Therapeutically, failure of some
systems has lagged behind due to the poor CNS penetration along with the
consequently, the development of biocompatible, bioadhesive and mimetic central
occuliption.

When 500 Da and therefore cannot cross the BBB.

Da. Of all known central nervous system drugs, 98% have a molecular mass larger
the brain, permitting only molecules that have a molecular mass smaller than 500
kinetics that cause side effects. The BBB controls the passage of substances into
constituent of the BBB on the passage of drugs to the brain, and the drug release
another sobering fact in the treatment of neurodegenerative disorders is the
1.4.2 The Constituent of the Blood Brain Barrier (BBB)

2007.
 delivers in the treatment of these disorders (Martín-Carvajal et al, 2007; Volles et al.
successful conventional delivery has the ability for localized and controlled drug
therapeutically effective, drug toxicity and high nursing care. To date, there has been no
been found to have numerous side effects, such as higher doses required. Lower
employed in the delivery of bioactives to the CNS. Few have serious limitations. Table 1.1 displays some of the current strategies employed in the delivery of drugs to the CNS, such as, prodrug. While these options are available for drug delivery to the brain, considerable efforts have gone into developing novel delivery techniques to the liquid solubility, molecular mass and the extent of ionization (Rapoport et al 1979). Physicochemical and the physicochemical properties of the compound, such as, passage of compounds across the endothelial cells of the BBB depends on the BBB has major repercussions for the passage of bioactives into the brain. The therapeutic strategies that will deliver drugs to the CNS in a safe and effective manner (Kilian et al, 2000; Bartczak, 2004).
<table>
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<th>Benefits</th>
<th>Limitations</th>
</tr>
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<tr>
<td>Easy to move</td>
<td>High at site in brain</td>
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<tr>
<td>Fluid soluble</td>
<td>Contraindication of lipid soluble drugs</td>
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<td>No need for energy</td>
<td>Contraindication of functional groups of certain</td>
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<td>Can recognize and select</td>
<td>Drug utilization via</td>
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<tr>
<td>Can recognize and select</td>
<td>Contraindication of functional groups of certain</td>
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Table 1.1. The Benefits and Limitations of the Current and Explored Strategies of Drug Delivery to the Brain
drugs for the localized treatment of neurodegenerative disorders.

upgraded into a CNS implant, incorporated with anti-oxidants and anti-inflammatories a period of more than three months. This subcutaneous implant could be further Alzheimer's Disease. It was demonstrated that drug delivery could be achieved over a subcutaneous implant for the delivery of diclofenac sodium in the treatment of the use of a PLGA-alginate polyphosphate drug delivery device as a potential.

Most recently, Sweet (2009) conducted both in vivo and in vitro studies to investigate the formulation of drug delivery devices (Jain, 2000).

(Katz, 2001; Vozzi et al., 2003), surgical injuries (Benenson, 1991), and the used in various applications, some of which include the fabrication of tissue scaffolds include in particular the thermoplastic polymer, PLGA. These polymers have been neuromuscular disorders such delivery devices based on polymer matrices growing need for controlled drug therapy (Etter et al., 2004; Fung et al., 2004; Jackson et al., 2004; Li and Liu, 2004; Parri et al., 2004; Yoo et al., 2004). In addition, kinetically recycled attention to address the Novel biodegradable materials are increasingly receiving attention to address the

1.5 Proposed Solution to the Problem

deveases is an option that this research is proposing. Controlled drug release in the brain through implantable biodegradable polymers The need for improvement of drug delivery systems to the brain cannot be disputed.
encapsulation efficiency (average 5-35%), as well as inadequate and non-

versatile dependent on the microparticle size, variability of drug loading and

microparticulate PLGA formulations include the uptake by macrophages, which is

key to controlling the release of the biocytotoxic agent. Other shortcoming of existing
diffusion and egression, the processes of polymer relaxation and disorganization are

the release rate of the biocytotoxic agent may be significantly regulated. In addition to

considering the independence of polymorphic degradation and polymeric properties.

In a smaller allosterephatic effect (Caperton and Lange; 1996: Fu et al., 2000),
dilomers can escape from the polymeric surface before local degradation, resulting

the rates of degradation at the surface and the interior of the matrix, in general,

chemical reaction(s) and dissolution principles, results in a differentiation between

dissolution degradation simultaneously sufficient. This process continues diffusion

polymer, with soluble compounds moving slowly towards the diffusion front as

enough to slow dissolution in the aqueous medium, diffusion begins within the bulk

as soon as the molecular mass of the partially degraded macromolecules is low

degradation proceeds homogeneously.

macromolecules remain insoluble in the surrounding medium and segmental

the hydrolytic reaction of other ether bonds, transiently, partially degraded

bond cleavage generates a new carboxyl and group that in principle, can catalyze

penetrates into the interstitial and hydrolytic cleavage of ester bonds begin. Each ester

When a native PLGA device is in contact with an aqueous environment, water

through bulk hydrolysis of the ester bonds (Pramanick and Robinson, 1977).

Despite the overall attractiveness of most thermoplastic polymers, they degrade
Furthermore, polymers can be rendered sterre by introducing chemical bonds and cross-linking through the use of cross-linking, thermal, curing, or phase separation, causing phase separation (Kato et al., 2003). Mutual partion miscibility of the two liquids, therefore, causes an increase in the distribution of the two particular solvent, reduces the swelling of biodegradable polymers. The addition of salts to an aqueous phase (1999) described the use of insoluble electrolytes to minimize swelling and release and salting-out and salting-in have been used in polymer modification. Zhong et al. (2004) modified the use of insoluble electrolytes to minimize swelling and release.

Polymers

Stress-strain curves may provide information on the stiffness and ductility of the polymer, which can also control characteristics such as rigidity and permeability. Overall chain flexibility of the polymer, changing the molecular mass and functionality temperature reduces Young's modulus as well as tensile strength and hence the properties are also profoundly affected by the increase in temperature. In general, mechanical, electric, and thermal properties of the polymer are affected by the chemical nature, processing variables, and morphologic characteristics (Ailhaud et al., 1999). Support for polymer-cell interactions and restricted swelling (Ailhaud et al., 2002) suggests that neurodegenerative disorders, the polymers should display enhanced adhesion (Kang et al., 2005). Additionally, the polymers are particularly important in the formulation process, especially when expensive materials such as proteins, vaccines, and genes are encapsulated (Combes-Carree et al., 2007; Haddad et al., 2006; Lee et al., 2007).
materials with desirable properties for controlled drug delivery.

physicochemical and physicochemical properties with the design of novel polymers. Exploring the processes for the modification of the physical and physicochemical properties of polymers is a significant aspect of research directed towards the mechanisms associated with the manipulation of the actual methods for modifying polymer physicochemical and the development of novel biodegradable materials with controlled drug delivery.

Materials with desirable properties for controlled drug delivery.

(Septo et al., 2000; Deng, 2002; Mc Cullogue et al., 2004; Trepanier et al., 2004).

Physicochemical properties of polymers generally focus on biocompatibility, biodegradability, and controlled drug delivery.

Studies conducted on biodegradable polymers generally focus on biocompatibility, biodegradability, and controlled drug delivery. Numerous controlled drug-delivery systems are of great demand for new biomedical applications. Numerous controlled drug-delivery systems are of great demand for new biomedical applications. Numerous controlled drug-delivery systems are of great demand for new biomedical applications.

1.6 Reasons and Motivation for this Study

of neurodegenerative disorders (Cadee et al., 2001; Liu et al., 2004; Polenz et al., 2006).

Moreover, soluble oligomeric forms of α-synuclein and subsequent cross-linking of α-synuclein with toxic salsolinol in the presence of organic and inorganic solvents is of great interest in terms of potential therapeutic approaches for diagnostically severe physicochemical and physicochemical properties. This study's objective is to establish the mechanisms associated with the salsolinol-induced cross-linking of polymers are extremely large, multi-dimensional molecules with relative concentrations of the polymer as well as the functional molecule. Such the rigidity of the material. The extent of cross-linking achieved depends on the

2.0
drug-loaded modified PLGA scaffold is envisaged to serve as an alternative device between a water-miscible organic solvent and an aqueous-solvent environment. The
out and subsequent cross-linking of the hydrophobic polymer using the interaction
of PLGA. In this study, modification of PLGA was based on the principle of salting-
systems may be used as salting-out and cross-linking agents to alter the properties
of PLGA through salting-out. In this regard, the application of salts and other solvents
of PLGA to deplete no research has fully explored the mechanisms of modifying the properties

Kinetics during application as a drug delivery scaffold.
PLGA can be precisely altered to achieve superior degradation and drug release
backbone. This specific physicochemical and physiomechanical properties of
with this application. In this study, we are recommending the modification of the PLGA
polymers with physicochemical and physiomechanical properties that are consistent
biodegradable materials. This approach would allow for the design of tailor-made
The latter approach poses a challenge to most polymer scientists. If attainable for all
modifications to the existing backbone of the polymer
and costly. Therefore, an alternative approach could be to apply a series of chemical
functionalities from its initial steps. This process can be exhaustive, time-consuming, and
may be enhanced. However, for each application, the polymer needs to be re-
application. In order to achieve this, the flexibility in the synthesis of native polymers
of biomaterial applications. An ideal biodegradable polymer should possess
various polymeric materials need to be synthesized to appropriately match a number
1. The overall aim of this study is therefore to establish the mechanisms associated with the synthesis and subsequent cross-linking of PLGA in the presence of organic solvents, based on the foundation of these physicochemical and biochemical transitions.

2. The following objectives are outlined:

- To synthesize various PLGA using silver-out and subsequent cross-linking technologies and a combination of chemical inducers such as N,N-dimethylformamide (DMF) and acetone based on statistical Design of Experiments, namely, Face-Centered Central Composite Design (FCCD) and Response Surface Methodology (RSM).
- To elucidate the physicochemical and adiabatic quantum energy transitions of the novel cross-linked PLGA scaffold during in vivo degradation.
- To elucidate the physicochemical and physical properties of the novel scaffold, particularly the fiber morphology and stress-strain behavior of PLGA through textural profiling and the correlation between the reactivity of the chemical inducers and the extent of polymer cross-linking.

3. In order to accomplish this aim, the following objectives are outlined:

- Depression, which may be useful in the treatment of common neurodegenerative disorders and controlled delivery of biorheologic agents, such as melatonin, and milifluidine HCL viscoelasticity and biocompatibility will be designed as a potential scaffold for the physicochemical transitions, a polymer blend with a balance between physicochemical transitions and inorganic solvents. Based on the foundation of these physicochemical and the characteristics of the scaffold, and subsequent cross-linking of PLGA in the presence of organic solvents, this strategy is expected to provide prolonged drug release.

1.7 Aim and Objectives of this Study
Chapter Two of this dissertation describes the development of the PLAGA scaffold.

is provided for the reader not to lose focus of the fundamental issues of this study. A flow diagram
then outlines the solution to these challenges using novel biodegradable polymers.
neurodegenerative disorders, the consistency of the BBB are specified. This section
challenges of neurodegenerative disorders, and the delivery of drugs to the brain. The limitations of the prevalent therapeutic approaches for
current trends and challenges of neurodegenerative disorders and the delivery of
aspects of modulating biodegradable polymers for drug delivery. It also outlines the
Chapter One of this dissertation introduces the study by presenting the fundamental

1.8 OVERVIEW OF DISSERTATION

Methodology (RS3M) and kinetic modeling of drug release data using
kinetics based on design of experiments (DOE) such as response surface
To predict and simulate responses such as polymer swelling and erosion
PLGA scaffold and compressed monolithic matrix systems; and
To assess the in vitro dissolution and drug release characteristics of the novel
and antimicrobial HCl

To formulate novel drug delivery systems such as a scaffold and a

4. To formulate novel drug delivery systems such as a scaffold and a

Aim of neurodegenerative disorders, the model drugs being melatonin
compressed monolithic matrix system incorporating biodegradable for the

In Chapter One of this dissertation, we explore the mechanisms associated with self-assembly and the subsequent cross-linking process of self-assembly and subsequent cross-linking. It attempts to explain the presence of organic solvents and ionic salts. In this chapter,

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In Chapter One of this dissertation, we explore the mechanisms associated with self-assembly and the subsequent cross-linking process of self-assembly and subsequent cross-linking. It attempts to explain the presence of organic solvents and ionic salts. In this chapter,
Transitions are established.

The correlation between the types of salts employed and the extent of PLA chain reactivity on the degree of swelling-and cross-linking of PLA is this regard. The Three. The Fourth, Chapter of this dissertation demonstrates the effect of various subsequent to establishing the stability of the novel modified PLA in Chapter

Scrofolds.

correlate to the stabilization of the physicochemical properties of the PLA intercalating molecules are used to indicate the ability of the composite system to construct energy transitions in the conformed energy state of the scaffold and the application as a device to be implanted into the subarachnoid space in the brain. In addition these transitions are used to establish if can be tailored to suit the

Scaffold degradation dynamics.

phosphoethanolamine (PBE) are used as assessment tools for elucidating the absorbed and mass detection during degradation of the novel PLA scaffolds in optimization. The physicochemical transitions in matrix resiliency, energy FCCD. In order to select the optimal number of experiments needed for process cross-linking technology in accordance with a statistical screening design, namely. Under degradation, variants of PLA scaffolds were synthesized using salting-out and

intra-molecular energy transitions of the novel cross-linked PLA scaffold during in Chapter Three, the study elucidates the physicochemical transitions and the eg

Independent formulation variables.

the author also discusses the selection process of the materials used and the
Drug and the modified PLGA Amphot严厉打击HCl was used as the model drug. The
linked in the absence of the drug which was followed by direct compression of the
systems. In the second approach, PLGA was selected and subjected to cross-
followed by direct compression of the samples into compressed monolithic matrix
forming of PLGA at various salt concentrations in the presence of the drug, which was
adapted. The first approach incorporates the salt- and subsequent cross-
compressed monolithic matrix system. In this section of study, two approaches were
Chapter Six of this dissertation focuses on adapting the PLGA scaffold into a
achieving an ideal zero-order melatonin release.
and analyzed by UV-spectroscopy (278 nm) to establish if the scaffold is capable of
PBS: pH 7.4; 37°C, and the release media is sampled at pre-determined intervals
This chapter, in vivo release studies are performed in phosphate buffered saline
optimize the formulation for application in the delivery of melatonin to the brain. In
Five, in vitro dissolution and drug release studies were conducted, in order to
The applicability of the scaffold for controlled drug delivery is determined in Chapter
linked in this chapter
physicochemical and the physicochemical textual characterizations. The principles by which the
Calorimetry (DSC) and textural profiling analyses. The principles by which the
Microscopy (SEM). Fourier Transform Infrared (FTIR). Differential Scanning
physicochemical and thermal characterizations were then analyzed by Scanning Electron
number of experiments for optimization. Geometric, physicochemical,
technology in accordance with a box-Behnken statistical design to select the optimal
various of PLGA scaffolds were prepared using salt- and cross-linking.
The objectives of the study and also delimit the practical work that is to be undertaken in fulfillment of each objective.

The work plan is designed in a form of a flow diagram that guided the study in a step-by-step manner through the entire project. The following flow diagram verifies that the purpose of this study.

Supplementary to that are the recommendations for future research in this area.

Finally, in Chapter Seven, the author outlines the concluding summary of the study.

categorized. This section of the study also considered the compressibility of PLGA. drug release characteristics of the compressed monolithic matrix systems were
Mechanisms for Modifying the Physicochemical and Physicomechanical Properties of Poly (Lactic-Co-Glycolic) Acid: Impact on Controlled Drug Delivery

AIM: The overall aim was to focus on the dynamic mechanisms of polymer modification with emphasis on salting-out and cross-linking in both organic and inorganic solvents as an in vitro approach to design a superior drug delivery system that may be potentially useful in the model condition, Alzheimer's Disease (AD).

Objective 1: Synthesize variants of PLGA, Salting-out end, subsequent cross-linking.
- Preliminary studies for the development of a novel biodegradable PLGA scaffold.
- Statistical Design: Formulate salting-out PLGA scaffolds using a four factor, two centerpoint quadratic FAST-Formatted ODD.

Objective 2: Elucidate the physicomechanical and ad initio quantum energy transitions of the novel PLGA in vitro degradation.
- Textural Profiling to assess stress-strain behavior of PLGA and matrix tolerance in tension.

Objective 3: Elucidate physicochemical (PC) & physicomechanical (PM) properties of the novel PLGA scaffold.

Objective 4: Designing drug delivery systems using novel PLGA matrices.
- Scaffolds and monolithic matrices for the PLGA implant.

Objective 5: Assess the in vitro dissolution and drug release characteristics of the PLGA implant.
- Scanning Electron Microscope to view microscopic structure.
- Differential Scanning Calorimetry for thermal analysis of PLGA.
- X-Ray Diffraction to establish the crystallinity of PLGA.
- Mean dissolution time and in vitro release studies analyzed by Hoppensberg Model to analyze erosion of PLGA.
- Reynolds - Number to analyze flow of molten polymer.

Objective 6: Predict and simulate responses such as polymer swelling and erosion based on Win Nonlin.
- Power Law, and variable to describe drug release kinetics.

Develop a controlled-release implant to be used in the treatment of Neurodegenerative Disorder.
Due to the hydrophilicity of PLGA, its instantaneously coagulates upon contact with organic solvents and an azeotropic environment at a particular pH and ionic strength. Our and subsequent cross-linked, where the polymer interacts with a water-miscible

In this study, the modification of PLGA was based on the principles of rapidly setting-

must be readily processible (Shi et al., 2005; Saweljan and Haris, 2006).

In addition, the device should have minimal undesired hemolytic degradation, and
its application as a scaffold for implantation into the subarachnoid cavity in the brain
with specifically designed physicochemical and physiomechanical features to suit
modifying the polymer, PLGA, in order to develop a novel biodegradable scaffold.

This section of this study focused on the establishment of the mechanisms for

2000).

non-immunogenic and capable of controlling the rate of drug release (Mokry et al.,
modulated in accordance with their specific applications, to develop materials that are
biocompatible. In addition, biocompatible and biodegradable polymers need to be
nontoxic. It is imperative to select materials that exhibit good
unresolved immunological response nor demonstrate extreme immunogenicity or
2003; Laschke, 2004). This means that the material must neither elicit an
because of cell immunity responses or unresolved drug delivery (Lellemann et al.,
a device for drug delivery must not fail or be rejected by the body after implantation

2.1 Introduction

DEVELOPMENT OF A SALTED-OUT AND CROSS-LINKED PLGA SCAFFOLD

CHAPTER TWO
parameters of the implant that include size of the scaffold. Implementation of the device was also considered, as it would determine the solubility, density, and the ability to stabilize water. For the final product, the size of polycaprolactone (PLGA) ion exchange ability, ionic strength, ionic volume, pH in aqueous solutions, and salts were examined for features such as the ability to dissolve PLGA, adsorption purposes of salting-out and cross-linking. The chemical inducers, namely, solvents and conditions such as the temperature and the pressure were also considered for the processing networks through hydrogen and ionic bonding was selected. The processing of the polymer with desirable functional groups that can form complexation, thereby, the factors may impact the formulation process of a support scaffold.

According to Okamoto et al. (2004), as well as Okamoto and Fukumura molecular mass distribution and morphology of the polymer were determined. Molecular volume, molecular mass, polar groups such as -OH and -COOH, configuration of structure, molecular mass, chemical composition, distribution of repeating units in multimers, the presence of formulation variables to be employed in the process, in addition, factors such as the formation of a network structure to establish the lower and upper limits for the dependent and independent variables. Furthermore, this phenomenon is able to moderate the swelling and erosion kinetics of polymers as well as physical and chemical properties of the polymer. Salts in polymer matrices that lead to the transformation of the physicalchemical and salting-out and cross-linking encompass a large variety of phenomena induced by an aqueous phase, thus resulting in a solid ceramic-like material.
The manufacturing costs and the feasibility
of the polymer and the chemical initiators used to transform the polymer and the
mechanisms of modification were selected in accordance with the above-mentioned
properties. Thus, the polymer used, the mechanism used for polymer modification, chemical initiators,
and the consistencies of a device's performance strongly depend on the properties of the
vivo (microchip and tissue) used. Klibanski et al. (2003; Georges et al., 2003) rely on the physiological and physical/mechanical properties during its use in
order to possess an optimum level of resilience, modulus, and endurance. In order to

\[ \text{yield} \]

\[ \text{be free from toxic degradation products and neuro-comparable} \]

\[ \text{be readily reproducible, cost-effective with a stable shelf-life} \]

\[ \text{stabilize the drug in the pharmacological and environmental agents, rapid degradation} \]

\[ \text{provide a depot effect of the drug and prolong its release over time} \]

implantable.

Biodegradable, thus eliminating the need for a second surgery to remove the
An ideal device for implantation into the subarachnoid cavity of the brain should
 affects the functioning of the polymer in drug delivery. Thus, during the selection of PLA:PGA tend to affect the degree of crystallinity of the co-polymer, which in turn affects the rate of degradation. The ratios of 

PLA to PGA in vivo and in vitro (Thern et al., 1992; Li, 1999) in addition, the release of the degradative rate which implies that during the polymerization process of PLA, the release amounts of the two enantiomeric forms of PLA differ considerably.

The degradation rates of the two enantiomeric forms of PLA differ considerably.

Poly(D-1-lactide) (PDL) and Poly(L-lactide) (PLL) (Middleton and Tipton, 2000) are amorphous or semi-crystalline. It is a highly crystalline polymer as compared to the amorphous counterpart. PEGA is one of the simplest linear di-lactide polymers with no chirality. In the presence of a pendant OH group on the carbon of PLA, the chirality (L- and D- lactide) is preserved. The presence of a substituted C=O atom is found in two enantiomeric forms, namely L(+)-lactide and D(+)-lactide. PGA is a poly-0-H acid that possesses an asymmetrical polyglycolic acid (PGA) and PLGA is a copolymer of two di-lactide polymers, poly-0-H acid (PLA) and polyglycolic acid (PGA), PEGA is a poly-0-H acid (PGA) and PLGA is a copolymer of two di-lactide polymers, poly-0-H acid (PLA) and polyglycolic acid (PGA).

Concern for this study (Basu et al., 2007) remove the implant. The selection of a suitable polymer was therefore a major application. This includes creating degradable polymers that allow room for degradation. This involves creating products and its properties readily tailored for specific and the success of the device functioning in vivo. Thus, the material selected ought to be easily bio-reducible and its properties readily tailored for specific degradation type, degradation products and susceptibility, the rate of drug release. The type of polymer employed will have an influence on the degradation rate.

2.2 The Properties of Native PLGA
with higher molecular masses tend to have higher inherent viscosities (Table 2.1). As a result, PLA grades esterification reactions in the process of polymerization. Viscosity is, in such a case, catalyzed, temperature, as well as the position of equilibrium involving water during the difference in molecular mass is attributed to various stoichiometric quantities of ester functional groups (Ranucci et al., 2006; Neaden et al., 2005).

polyesters, such as PLA. Molecular mass increases in direct proportion with the solubility decreases (Ravel et al., 2005; Basu et al., 2006; Neuzillet et al., 2005). In such cases, molecular mass are increased, its viscosity tends to increase. However, its range of molecular mass and inherent viscosities as the polymers dimensions, the majority of synthetic biodegradable polymers, including PLA have a wide.

et al., 2006).

To achieve the required degree of crystallinity of the native PLA (Park, 1994; Ching process of various PLA grades, the ratios of PLA:PGA need to be verified in order.
The choice of PLGA as a polymer for the formulation of the scaffold originated from et al., 2000; Fahnay et al., 2005).

Non-toxic degradation products and modifiable degradation rate (Massy et al., 2006).

and the modifiable intrinsic structure (Dong et al., 2006; Jeong et al., 2006).

Hydrophobicity, chemical stability, excellent thermo-reversible properties (Johnson et al., 1997; Johnson et al., 2000).


Biocompatibility, non-thermosensitive, and non-toxic (Langer and.

for biomedical uses as follows:

Some of the properties of PLGA that has made this polymer a favorable candidate

<table>
<thead>
<tr>
<th>Property</th>
<th>PLGA Grade</th>
<th>PLGA 504</th>
<th>PLGA 603</th>
<th>PLGA 602</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Mass</td>
<td>15,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>(C5H9O2)6-C5H9O2-C5H9O2-C5H9O2-C5H9O2-C5H9O2</td>
<td>(C5H9O2)6-C5H9O2-C5H9O2-C5H9O2-C5H9O2-C5H9O2</td>
<td>(C5H9O2)6-C5H9O2-C5H9O2-C5H9O2-C5H9O2-C5H9O2</td>
<td>(C5H9O2)6-C5H9O2-C5H9O2-C5H9O2-C5H9O2-C5H9O2</td>
</tr>
<tr>
<td>Type of Polymer</td>
<td>A-OH polymer</td>
<td>A-OH polymer</td>
<td>A-OH polymer</td>
<td>A-OH polymer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>40-55</td>
<td>40-55</td>
<td>40-55</td>
<td>40-55</td>
</tr>
<tr>
<td>Glass Transition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscosity (dl/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inherent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthomorphic</td>
<td></td>
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<td>Orthomorphic</td>
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</tr>
</tbody>
</table>
Figure 2.1: Schematic diagram of the metabolic degradation of PGA (Source: adapted from Bosmann et al., 1977; Grazin and Reschke, 2005).

Body as illustrated in Figure 2.1 (Nem et al., 2000; Hsu et al., 2006).

Further more, the non-toxic elimination contrasts cost-effectiveness to the system, as setbacks such as the decrease in pH and affecting the surrounding tissues.

The PLLA device is intended for use in vivo and feel degradation would create

---

There will be no local inflammation in the area (Hsu et al., 2006).
readouts and the polymer

Processing and curing of the polymer, such as fast-setting colloids between the solvent plays a key role in the chemical reactions that take place during the polymer modification and drug incorporation are performed in solution. Thus, the both the polymer and the solvent employed (especially 2006), most procedures of The solubility of polymers depends on the chemical and the physical properties of

2.3.7 Solvent Selection for Separating-out and Cross-linking

Polymeric properties that are tailor-made to match its intended application.

that would still-polymers into a polymeric scaffold with balanced viscoelastic and Bemer, 2006). During preliminary studies we set out to establish chemical influences and antagonistetic effect such as decrease in reactivity, stability or solubility (Zanini and antagonistic interactions between the chemical inducers may result in an polymer. In contrast, the interaction between the chemical inducers may result in an that produces enhanced stability, improved viscoelasticity and strength of the There can be a synergistic interaction between the solvent, the salt and the polymer.

solubility and stability of the scaffold.

In addition, these reagents are incorporated to create and maintain the desired physicochemical and physicochemical properties of the polymeric matrix into the polymer in order to induce self-assembly and cross-linking as well as enhance locally bounded. The reagents, namely, the solvents and ionic salts are incorporated against phase with subsequent cross-linking, where molecules are covalently or during self-assembly in organic phase (containing the polymer) is separated from the

2.3 Establishing Suitable Independent Formulation Variables
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Chemical Formula</th>
<th>Density (g/cm³)</th>
<th>Tg (°C)</th>
<th>Dc (DC)</th>
<th>Bp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>H₂O</td>
<td>0.997</td>
<td>100</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Dimethyl acetate</td>
<td>CH₃COOCH₃</td>
<td>0.882</td>
<td>97</td>
<td>1.075</td>
<td></td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>C₇H₇Cl</td>
<td>1.50</td>
<td>131</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>C₃H₆O</td>
<td>0.790</td>
<td>17.2</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>CH₃CN</td>
<td>0.790</td>
<td>17.2</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>CHCl₃</td>
<td>1.430</td>
<td>40.1</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Formamide (DMF)</td>
<td>HCON(CH₂)₂</td>
<td>0.940</td>
<td>39.3</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>N,N-Dimethylformamide (DMF)</td>
<td>HCON(CH₂)₂</td>
<td>0.940</td>
<td>39.3</td>
<td>63</td>
<td></td>
</tr>
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<td>0.940</td>
<td>39.3</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3 The physical and chemical properties of solvents used in salting-out PLA.
denitrification tends to increase the propensity of polymers to aggregate and settle.

The effect of salts on the interaction between polymeric particles in aqueous solution
Salts were selected in terms of their capability to salt-out and cross-link polymers.

2.3.2 Salt Selection for Salting-Out and Cross-Linking


I linking are greatly influenced by the type of salt in the aqueous solution (Gu et al.,

philosophy separation process. Solvent-induced interactions during salting-out and cross-

solution during the salting-out and cross-linking processes. In general, enhancing the

-OH bond and because they are prolific, they will accept a proton from the aqueous

Dicarboxylic solvents such as acetic acid, DME, and DMSO contain a CO bond without a

reaction (Gunasekaran, 1996; Chundara, A, and Balaghi, 2000; Bagchi, 2001).

Wet forces, dipole-dipole and electrostatic forces are the key to the chemical
distribution, leading to different charges at each end. Thus, in polar solvation, van der

non-polar solvation, because the dielectric constant of polar solvents is much lower

correspond, since they only have a C=O group. Polar solvation will differ from

cross-linking interaction, where the polymeric solvents such as acetic acid, DME cannot

water, a typical polar solvent can donate an H+ from its -OH group to form H-bonds

electron acceptor such as O2 or N2. and can exchange protons as a result.

catalyst in the reaction. Protons have a hydrogen atom attached to an

reaction, the solvents offer an ion or free radical to the system, which acts as a

understanding of the solvents effect on electron transfer reactions. During a chemical

The advances in the studies of solvation dynamics have allowed better
Strongly hydrated anions

\[ \text{N}^3 \left(\text{CH}_3\right)_4 < \text{NH}_4^- < \text{R}^3 < \text{Cs}^- < \text{K}^- < \text{Na}^- < \text{Li}^- < \text{H}^- < \text{H}_2\text{O}^- \]

Most destabilizing

\[ \text{Cl}^- < \text{SO}_4^{2-} < \text{PO}_4^{3-} < \text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^- < \text{NO}_3^- < \text{ClO}_4^- \]

\[ \text{Most destabilizing} \quad \text{Most destabilizing} \]

\[ \text{Table 2.3. Series illustrating the ability of ions to cause water destabilization} \]

Maccagnini et al., 2007; Rennoucourt et al., 2007.

In aqueous solution, the stability of the polymer is the result of balance between the hydration of the polymer and the solvation of the ions. A polymer will have a higher solubility or stability the more ions there are to interact with, which is why it is so important to choose the right ions to achieve the desired solubility or stability. The stability of the polymer can be measured by the change in surface tension of water when it is added to the solution.

Zang and Bem, 2006, work done by Melander & Horvath (1977) deduced that in
Viscosity Jones-Dole-g coefficient

of hydration and the

arrows, which include molal aqueous boiling-point elevation of hydration and the

2004). Table 2.4 presents various properties of the typical salting-out conditions and
describes how such aggregates are formed to solubilize (salting-in) Wtachy et al.
souple particles (salting-out), while chaotropic salts such as K+ C2H5 and T acetate
kysmoforic salts such as Li+, Na+, and F promote the aggregation of hydrophobic
particless leads to stabilization of polymers aggregates during salting-out
preferential exclusion of both salts from the solution shell and from the polymer
Moreover, salts may have preferential action on polymers. The subsequent

polymer in order to salt-out (Sobol et al., 1999).
cell employed (Sobol et al., 1999) during dissolution and drug release in physiological media is attributed to the type of
terature of the newly synthesized polymer. In addition, the hydration of the polymer
physicochemical and the physicochemical properties as well as the conformational
out and cross-linking the above-mentioned properties of the sella will influence the
differentiate the shed's, thus, decreasing the local density of water. When used for selling-
hydration and may reside comfortably within the dehydrogelation structure of water
creates a higher local density of water, while larger ions have positive entropies of
small ions are strongly hydrated, leading to negative entropies of hydration. This

\begin{table}[h]
\centering
\begin{tabular}{cccccccc}
\hline
\textbf{Cations} & \textbf{Volume} & \textbf{Ionic Volume} & \textbf{Ionic
Anions} & \textbf{Dole} & \textbf{Jones-} & \textbf{Jones-
Dole} & \textbf{Dole} \\
\hline
\textbf{Na} & \textbf{0.270} & \textbf{0.327} & \textbf{Cl} & \textbf{0.026} & \textbf{0.019} & \textbf{0.026} & \textbf{0.019} \\
\textbf{Ca} & \textbf{0.072} & \textbf{0.074} & \textbf{Mg} & \textbf{0.011} & \textbf{0.013} & \textbf{0.011} & \textbf{0.013} \\
\textbf{K} & \textbf{0.033} & \textbf{0.033} & \textbf{BR} & \textbf{0.040} & \textbf{0.040} & \textbf{0.040} & \textbf{0.040} \\
\textbf{NH}_3 & \textbf{0.000} & \textbf{0.000} & \textbf{Cl} & \textbf{0.000} & \textbf{0.000} & \textbf{0.000} & \textbf{0.000} \\
\textbf{Fe} & \textbf{0.043} & \textbf{0.043} & \textbf{P} & \textbf{0.009} & \textbf{0.009} & \textbf{0.009} & \textbf{0.009} \\
\textbf{N} & \textbf{0.009} & \textbf{0.009} & \textbf{N} & \textbf{0.009} & \textbf{0.009} & \textbf{0.009} & \textbf{0.009} \\
\hline
\end{tabular}
\caption{Classification of ions used in terms of their aqueous ionic volumes.}
\end{table}
\[ \text{Equation 2.1} \]

as described in Equation (2.1) (Friedman, 1972).

The concentration of the ionic or salt species is illustrated in the following equation known
been posulated that the hydrophobic effect is directly proportional to the
dimensional effect. This phenomenon is termed the hydrophobic effect; it has
water permeating the polymer to aggregate, subsequently cross-link and form a 3-
in water-salt-polymer solutions, the salts lend to transform the molecular structure of
polymeric hydrophobic effect, which is attributed to the reactivity of the salts (lo et
ions that produce stoichiometric fluctuations. This can be explained as a transition of the
physicochemical and the physicochemical properties of a polymer by incorporating
phase. Salting-out, a colloidal phenomenon, also has the capacity to modulate the
polymer network is then removed from the solution, leaving a polymer-depleted
polymer-poor phase within a water-salt-polymer solution. The 3-dimensional
(salting-in). Salting-out employs thermodynamic principles to create polymer-rich and
agglomerated solutions and cause them to disassociate, as opposed to salting-out
Salting-out occurs when solvated ions precipitate polymers in the presence of

Linking

2.4 Mechanisms of PLGA Modification: Salting-Out and Subsequent Cross-

\[ \text{Equation 2.1} \]
salt and water molecules in a similar manner. If possessive polar groups such as OH- and COOH and therefore interacts with the (Rehmann et al., 1978). Although PEO used in this study is a hydrophobic polymer, -NH2 groups are the specific sites of adsorption for water molecules, which are also an area of larger for water to adsorb, such as in Nylon-6, where the polymer is not hydrogenated in aqueous media (Rehmann, 1976). Hydrophilic sites of a swelling gellation in aqueous media (Rehmann, 1976). Hydrophilic sites of a the lower, thus the ion-pairs present in charged polymers are responsible for their molecules around a polar group also depends on the physicalchemical properties of Benardac and co-workers (1996) revealed that the quantity of adsorbed water

Zainudin et al., 2007).

properties of the polar group (Stephenson et al., 2007; Tarse et al., 2007) tend to adsorb water molecules in a configuration that depends on the COOH leads to adsorb water molecules in a configuration that depends on the -carboxylic acid effect (Polymers with polar groups such as -OH and - free from hydrogen, increases in concentration, decrease and self-associates higher is excluded from the free hydration shell of the solution. The polymer is thus possessive higher change densities tend to bind covalently to water, such that the phases and increase pore size and interconnection of the salt which can direct the interfacial tension between polymer in water and in salt solution, the salt concentration, and the seaweeds physicalchemical and physicalchemical properties. Include material solidusities of the

The range of parameters that influence the swelling-out system, and thus the resulting

K is the Severance swelling-out coefficient of the salt and

c is the molal concentration of the salt and
(Rockville Chemicals, South Africa) were used as salts. An analytical mass balance
C6H12O6, CaCO3, Na2SO4, Al2(SO4)3, Ca(OH)2, ZnO, CuO, MgO, and NH4OH
metathetical urea, limed, refined, Hopkiny's ZK were used as solvents. HCl, KCl, NaCl,
distilled water, acetic acid, acetonitrile, chloroform, chloroform, DMF, DMSO, and
molecular mass and inherent viscosities of these grades are listed in Table 2.1.

These resins, R500, R5050 and R5060, with 5:5:0 PLA:PGA ratios (The Vahrens
PLGA was purchased from Bocchinger Ingelheim Pharma (Ingelheim, Germany)

2.5 Materials and Methods
PLGA Grades.

determine the ability of the independent formulation variables to self-consolidate
the independent formulation variables. Symptoms of the PLGA scaffold at various
The following experiments were conducted to establish the lower and upper limits for

2.6 Materials and Methods
Groups of the polymer.

the side-chain of the polymer, due to ion interactions between the side- and side
and the side- as well as the inter-cross-linking among PLGA strands is subsequent to
sells. In this study, the inter-cross-linking between the monomers of PLGA strands
beyond the level of, or eta-functional organic cations such as alkylation
multiplier cations such as copper, calcium, aluminum, magnesium, strontium,
polymerizable cations such as sodium, monovalent cation, as well as divalent, tervalent and
polymerizable structural integrity. Cations that have been utilized in cross-linking of
cross-linking ions are employed to generate flexible polymers and to augment

Cross-linking can bond the polymer and the salts both covalently and ionically.
and precipitation of the polymer as well as obliterating a desirable yield. Indicators of success in salting-out were the ability of the salt to cause precipitation of the polymer as well as facilitating salting-out of PLLA. With regards to the solvents, the solvents were evaluated with respect to the ability and time taken to dissolve quantitatively in terms of their ability to induce salting-out of PLLA. The efficiencies of the solvents used were evaluated quantitatively in terms of the scaffold yield and various PLLA grades.

2.3.3 The Effect of the Independent Formulation Variables on the Salting-Out of Solvent or salt and allowed to dry over a period of 48 hours. From the cross-linking solution, washed with deionized water to remove any excess solution to induce salting-out of the polymer. The resulting scaffolds were removed were prepared as 5% w/v salt aqueous solutions and added to the polymer-solvent decrease the pH to a pH range of 1.5-3.5. Salting-out and cross-linking solutions using HCL, a 100ml of hydrochloric acid (0.1M) was added to the solution to PLLA grade was dissolved in 15ml of solvent in separate glass vials. To scaffold of solvents and salts to form scaffolds. Approximately 0.2g and 0.4g of each native PLLA grades were selected and subjected to cross-linked with various quantities of substances and the scaffolds.

(Deerfield Instruments Co., USA, 0.5 mg) was used to determine the mass of each
PLA were mainly the public solvents, including methanol. The choice and subsequently successful in dissolving PLA with other solvents. Solvents that could not self-polymer when a salt solution was added. Even though the salt solution was dissolved PLA, but were not able to self-polymer and subsequently cross-link the solvents, namely, acetonitrile, chloroformene, chloroform and methanol succeeded to dissolve PLA.

$$\text{RG 502} > 0.32 \pm 0.44 \text{ d/l} > \text{RG 504} = 0.45 \pm 0.60 \text{ d/l}$$

The time taken to dissolve PLA given that the inherent viscosity of RG 502 = 0.16 ± 0.24 d/l > RG 504 = 0.45 ± 0.60 d/l > RG 503 > RG 502 > RG 603. This occurs could be explained in any solvent that dissolved PLA, the time taken to dissolve the respective grade in Table 2.5.

Dissolve the polymer as outlined in Table 2.5. unable to dissolve PLA; however, there was a variation in the amount of time taken to dissolve various grades of this polymer. Numerous solvents, namely, acetonitrile, DME and DMSO were acceptable quantitatively (yield). PLA is insoluble in water due to the hydrophobic nature of the polymer. PLA can be successfully in self-polymer and subsequently cross-linking of PLA in pharmaceutically experiments approach.

This section will, however, focus on elucidating the solvents and salts that were considered and has to be monitored individually as well as collectively. This will be

2.6 Results and Discussion
The polymer was used between 0% to 2% by weight in each solvent. The concentration of solvents suitable for polymer application was 1 to 1.5%.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>NACCO,</th>
<th>Zinc Chloride</th>
<th>Ethylene glycol</th>
<th>AlAc</th>
<th>NIBS</th>
<th>OME</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-V 10</td>
<td>1.2 min</td>
<td>S/O = 1</td>
<td>Acetone + DMF</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMF</td>
<td>Acetone</td>
</tr>
<tr>
<td>D-V 12</td>
<td>1.5 min</td>
<td>S/O = 1</td>
<td>Acetone + DMF</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMF</td>
<td>Acetone</td>
</tr>
<tr>
<td>D-V 15</td>
<td>1.5 min</td>
<td>S/O = 1</td>
<td>Acetone + DMF</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMF</td>
<td>Acetone</td>
</tr>
<tr>
<td>D-V 16</td>
<td>1.0 min</td>
<td>S/O = 1</td>
<td>Acetone + DMF</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMSO</td>
<td>Acetone + DMF</td>
<td>Acetone</td>
</tr>
</tbody>
</table>

Table 2.5: The reaction of random initial variables on the tailing-out of various PLA.
measured was the cohesive ceramic-like structure. Measured with respect to the scaffold yield as listed in Table 2.6. The scaffold from the solution. The effectiveness of the scaff to salt-out PLA was further and DMSF molecules, and subsequently causes coagulation and salt-out of PLA where DMSF and protocan sal water undergo transient charge transfer between water.

Further illustrations on this phenomenon are found in Figure 3.3 (Chapter Three).

be the reason most proof solvents failed to salt-out PLA.

chemical reaction, a proof solvent such as methanol donates a proton. This could solution may not be able to salt-out PLA. This study earlier mentioned that in a solvent, whereby a proton may be momentarily transferred from the salt solution to the polymer solvent. A solvent that is unable to accept the proton from the salt solution to during salt-out reactions, there is an interaction between the salt solution and the
Two distinct stages were observed. Solvent and the viscosity of the polymer in dissolving PLGA in the various solvents revealed that the time taken by PLGA to dissolve depends on both the type of employing PLGA in the formulation of devices for in vivo application. This study has the rapid solvation of PLGA in any biocompatible organic solvent is fundamental for the coalescence of the PLGA strands. It be involved in salting-out by enhancing the formation of bonds, thus agglomerating the supramolecular salts with the exception of Al(OH)₃. This implies that chloride ions could chloride salts produced higher quantities of scaffold yields in comparison with the salt and the polymer grade employed in salting-out the PLGA. In general, the results displayed in Table 2.5 reveal that the scaffold yield was influenced by the

<table>
<thead>
<tr>
<th>(F2)</th>
<th>(F2)</th>
<th>(F2)</th>
<th>(F2)</th>
<th>(F2)</th>
<th>(F2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.472</td>
<td>0.342</td>
<td>0.242</td>
<td>0.154</td>
<td>0.053</td>
<td>0.032</td>
</tr>
<tr>
<td>0.297</td>
<td>0.098</td>
<td>0.032</td>
<td>0.014</td>
<td>0.073</td>
<td>0.029</td>
</tr>
<tr>
<td>0.452</td>
<td>0.199</td>
<td>0.102</td>
<td>0.037</td>
<td>0.022</td>
<td>0.024</td>
</tr>
<tr>
<td>0.404</td>
<td>0.199</td>
<td>0.102</td>
<td>0.037</td>
<td>0.022</td>
<td>0.024</td>
</tr>
<tr>
<td>0.374</td>
<td>0.183</td>
<td>0.119</td>
<td>0.022</td>
<td>0.025</td>
<td>0.024</td>
</tr>
<tr>
<td>0.448</td>
<td>0.183</td>
<td>0.119</td>
<td>0.022</td>
<td>0.025</td>
<td>0.024</td>
</tr>
<tr>
<td>0.424</td>
<td>0.183</td>
<td>0.119</td>
<td>0.022</td>
<td>0.025</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Table 2.5: Scaffold yield after salting-out and cross-linking with various salts.
\[ X \text{ is the Flory-Huggins interaction parameter.} \]

\[ N' \text{ is the number of solvent molecules.} \]

\[ N_1 \text{ is the number of polymer molecules.} \]

\[ X_1 \text{ is the volume fraction of the solvent.} \]

\[ N \text{ is the number of solvent molecules.} \]

\[ T \text{ is the temperature.} \]

\[ k \text{ is the Boltzmann constant (1.38 x 10^{-23} Joules per Kelvin). Relates energy to} \]

\[ \Delta G \text{ is the Gibbs free energy change of mixing.} \]

\[ \text{Where,} \]

\[ \Delta G^\text{mix} = kT \left( N' X_1 N_1 + N N_1 N_1 X' N' X' \right) \]

As presented in Equation 2.2,

explained thermodynamically using Sperringer's solution thermodynamic nonideality.

explained thermodynamic using Sperringer's solution thermodynamic nonideality.

The concentration of the polymer and a solvent depends on the temperature.

The solution was influenced by the solvent and PLAGA grade used. The Gibbs free energy

The time taken to change the viscosity of the solution from a gel to a less viscous

dispersed into a less viscous yellow solution.

The solution turned into a yellowish sticky gel, which then slowly

PLAGA absorbed the solvent to form a gel and:
Including scales, are multi-functional and have sizes that can react with several adjacent molecules. Upon developing a solution, subsequent cross-linking of the monomeric units of PLGA into dimensional structure. Thus, the polymer is activated by the solvent to interact with scales inherent within the polymer chains causing them to self-assemble around a C-C bond-angle fixed at 109°, and the C-C molecular distance at 1.54 Å. However, polymers that have their chemical backbone based on C-C such as PLA have the segments, resulting in an initial configuration. Rotation about the bonds between segments, with no interaction between the effect of these forces leads the polymer to assume a configuration that permits a free monomers as well as solvent molecules are exactly counter-balanced. The coupled attractive and repulsive forces on each polymer segment (owing to other attractive and repulsive forces on each polymer segment) and the polymer chains adopt a configuration such that the self-agglomeration and cross-linking on addition of a salt solution, pressure and temperature of the reaction. This in turn will affect the rate of polymer reveal that the quantities of solvent and polymer molecules will influence the interaction between the polymer and solvent. The factors delineated in the above Equation rely on the temperature and pressure of the system, are influenced by the interaction.
novel PLA scaffolds produced.

physicochemical and the ad initio quantum mechanical energy transitions of the
scaffolds. Chapter Three and Four then follow evaluating the physicochemical
independent formulation variables that may be used in synthesizing the PLA
Chapter Two of this study focused on establishing the type and the quantities of
molecular mass of the polymer
congelate into a thick gel appeared to be influenced by both the salt and the
when compared to other salts. Thus, the ability of the polymer and the salt to
of PLA. The chloride salts such as NaCl and AlCl3 demonstrated a higher yield
and cross-linking species as well as the viscosity, molecular mass and concentration
The yields were found to vary, depending on the various factors such as salting-out

2.7 Concluding Remarks
PLGA is an immune and anti-inflammatory response. In addition, the accumulation of degradation products in vivo leads to cause and subsequent decrease in the concentration, which leads to toxicity and a peak-trough causing a sharp rise of the drug plasma concentration. This is often followed by an uncontrolled release of the drug from the polymer, due to lack of toughness and viscoelasticity (Elgersma, 2006). In physiological conditions, with uncontrolled release kinetics of the delivered drug, due to lack of control of drug delivery systems are characterized by vigorous polymers.

In an attempt to predict this suitability for use in rate-modulated drug delivery, characteristics and the stability of the potential scaffold from a molecular viewpoint in molecular level. These studies were conducted to understand the degradation requirements of the scaffold and subsequently crosslinked PLGA scaffold. In this section, the study elucidated the in vitro physicochemical transitions of the

3.1 Introduction

Quantum Energy Transitions of the PLGA Scaffold

Chapter Three
Degraded macromolecules is sufficiently low, diffusion begins within the matrix. Once the molecular mass of the partially surrounding medium and sequential erosion proceeds homogeneously (Vill et al., 2012), erosion of the other ester bonds. Partially degraded macromolecules remain insoluble in the collagen generated a new chemical and group that catalyzes the hydrolytic reaction simultaneous loss of mass (Spain et al., 1996; Yoon and Park, 2001). Flud initiation into further hydrolysis cleavage of the other bonds. Each ester bond erosion occurs when exposed to physiological media. Devices made of polyurethane-PLGA blend are used in delivering drug delivery devices. (Oliphant et al., 2000; Carg and Kokkoli, 2002).

Microenvironment of the tissue region is pertinent to the performance of the device (Vill et al., 2004). The influence of these factors on application and adhesion to the degradation still require further exploration (Li and Vet, 1995; Shi, and Anderson, 1997). Structural stability studies on PLGA regarding solvency addition, physicochemical and mechanical dynamics during in vitro bio.

Seeding in tissue engineering infections by being utilized for embedding drug delivery devices and scaffolds for cell
OH-polymers. Thus, tendency to physical and chemical degradation during storage
PLGA degrades has also been found to considerably affect the degradation rate of the
proteolysis, namely, DMSO and acetic, curing and sterilization of the
accelerated by polar protic solvents, such as Z-pyridine as compared to polar
In addition, Dong and co-workers (2006) revealed that degradation of PLGA may be

temperature and water content in the biocompatible solvents used.
PLGA in in-situ forming systems was found to increase with the increase in storage
de long et el., 2005), in a study by Dong and co-workers (2006) the degradation of
of degradation of the device (Bhargava and Alonso, 1998; Banerji and Redwan, 2005).
solvents and ions that are present in the system will determine the type and the rate
into the device, the pH of the system, the environmental temperature, as well as the
Thus the morphology of the device, the amount of biodegradable molecules incorporated

amine-based drugs (Siegel et el., 2006).
In incorporated bioceramic, such as, acidic drugs, salt-based drugs and tertiary
el, 2006) and
particle size, presence of plasmin or catalase (Stihl et el., 2005; Dong et
Formulation properties, such as, shape, size, presence of salts in the device;
Strength, pH, solvent, presence of bioceramics (Romola et el., 2005);
Physiological fluid or release medium properties such as, temperature, Ionic
et al., 2006),
release of lactose:pyridine acid in PLGA, crystallinity, and molecular weight (Shin et
Some of the factors that influence PLGA degradation include:
In section one, degradation mechanism. This is one of the challenges of this polymer, as mentioned revealed that n-aliphatic PLA, being an α-0 polymer, undergoes the type I mechanism in a combination of the three mechanisms. Zhang and co-workers (1993) cause the degradation of the polymer degradation. Type I involves the cleavage of unstable linkages of a cross-linked network that is used and hydrolyzed, leading to the solubilization of the entire structure. Type II involves the cleavage of unstable linkages of a cross-linked network that is used and hydrolyzed, leading to the solubilization of the entire structure. Type III is where the hydrophobic side groups of a polymer are eliminated from the body by normal metabolic pathways. Lactic acid and glycolic acid. These non-toxic products are biodegradable, and are predominantly via chemical hydrolysis of the hydrophobic unstable ester bonds into products that undergo solubilization. Cooper et al. (1996) detailed that PLA degrades the labile bond in the polymer backbone resulting in lower molecular weight degradation chemical degradation have been reported, which include Type I, where cleavage of chemical degradation of the labile bond. This is termed chemical degradation. Polymers can be biodegradable polymers. Devices can degrade either by enzymatic or non-enzymatic

3.2 Chemical Degradation of PLA

(Siepmann, 2006).
resilience and work performed are compromised. The second stage is the hydrolysis of the ester bond occurs during this stage the physicochemical properties, such as water diffuses into the amorphous regions quickly and then clearance of the end type of degradation of the polymer. PLA undergoes two degradation stages, and type of degradation of the polymer. PLA needs to reverse the factors that influence the rate.

In order to solve this problem, one can use to reverse the factors that influence the rate of degradation still exists. Health care devices, the challenge of uncontrollable degradation still exists. Products, namely, lactide and glycolic acids. Although PCL has been used in many of the surrounding issues caused by the increase in the degradation concurrently at an unpredictable rate. In terms of PCL, there is a decrease in the degradation of this type of degradation is that the end polymer device degrades polymer particles start to solubilize (Vollma and Larkosz, 2004).

Polymeric devices, such that drug release may be easily controlled. When water into the bulk polymer, the device undergoes surface erosion that is predictable such that drug release may be easily controlled. When water into the bulk polymer, the device undergoes surface erosion that is predictable such that drug release may be easily controlled. When water into the bulk polymer, the device undergoes surface erosion that is predictable such that drug release may be easily controlled. The rate of degradation of these polymeric devices synthesized from poly(lactides and poly(oxy)esters usually
and impede dissociation of the polymer network. Links between the polymer chains obstruct the free movement of water molecules within the polymer matrix (Grassl and Grassl, 2009). The presence of cross- and intermolecular reactions, salt-out, and cross-linking techniques can be used to modify the physicochemical properties of the device to restrict the transport of cross-linking ions, due to the presence of electrolyte species within the medium, these voids are a result of interactions between short and long distance media. These voids are a result of interactions between short and long distance media to constrain and clusters of fluid molecules in the presence of physiological solutions. Cross-linking interactions have a synergistic role in the ability to restrict the biocompatibility and increased viscosity of the polymer's structure. Polymeric voids resulting from cross-linked interactions have a synergistic role in the ability to restrict the biocompatibility and increased viscosity of the polymer's structure. Polymeric voids resulting from cross-linked interactions have a synergistic role in the ability to restrict the biocompatibility and increased viscosity of the polymer's structure. Polymeric voids within the polymer matrix can affect the degradation process of the polymer and subsequent cross-linking technique to form a cross-linked polymer. In Chapter Two of this dissertation, we investigated the biological development of the device.
Changes of the cross-links resulting in PCL scaffold displacement and enzyme sensitivity may decrease during incubation in PBS that is attributable to backbone scission with solvation ions. However, the degree of these physicalchemical properties of native PLLA, through the formation of a scaffold intact links like the PLLA structure, are proposed to be augmented by self-lining and subsequent cross-linking of the physicalchemical properties such as the energy absorbed and matrix stiffness.

Dependence of polymer hydrogen free energy on the solute size and shape (spherelike, cylindrical, and others) have yielded evidence on the hydrogen bonding of the micro-environmental structure with a decrease in quantum swelling of the micro-environmental structure with a decrease in quantum swelling of the polymer backbone (Warmack and others 2002). These studies have resulted in further stabilization to the polymer matrix. When hydrogenated and unhydrogenated ions are bound extremely to voids it may result in unpredictable yields of voids and subsequently fewer hydrogen bonding clusters within the matrix will result in further stabilization to the polymer. A polymer scaffold whereby the stereodimensional configuration provides a void area and performance of the intermediate sol-gel matrix as well as its energy stability. Otherwise, the polymer chain dimensional nature, the nature, stability bonding is restricted, the contours of the scaffold may be attributed to hydrogen bonding extremely and thus will elucidate the overall design of the scaffold. If logic or correlation matrix that could be either cross-linked within the polymer matrix or sol-gel-like within the scaffold, will depend on the extent of cross-linking ions located within the overall textural properties and energy transitions occurring across molecular level.
Various biological molecules of lower and higher molecular weights, conditions, as well as to predict the polymer-membrane interactions between PCL scaffolds and biological and the aqueous environment. The transition in energy is used to significant system, that result from molecular interactions between the polymer, incorporated physiological fluids, is the transition in the quantum mechanical energy of the biological system. In addition, the aspect of equal importance when a polymer-based device is incorporated into the system can aid in elucidating these energy transitions.

The emerging field of molecular modeling with ad into quantum energy stabilizes the electronic field of molecular modeling within the quantum mechanical energy of the system. During self-assembly may further elucidate the scaffolds' final energy. The energy flux of the newly formed scaffold at a molecular level, the energy flux of molecular configuration of molecules may also lead to prominent energy transfer with the resultant molecular dynamics of a scaffold or PCL scaffold and stereocomplexation.

2002; Malinovská et al., 2005; and Cox, 1992; Alvarez-Lorenzo et al., 2002; Fries V. and Schaller, 2002. Scaffolds with degradation, with degradation timescales ranging from 48 hours to 1 year (cochran degradation). Biodegradable cross-linking may result in a coordinable surface erosion degree of PLLA can be enhanced by hydrophobic combination with hydrophobically depending on the stereocomplexation configuration of the polymer groups. In general, the PLLA scaffolds may result slower than hydrogels.
determine the stability of molecules (Chiu et al., 2007). Energy stored in their physical arrangement. These parameters can be employed to
and the forces that act upon them, as well as the kinetic energy of the potential
study of quantum mechanical energy became concerned with the motion of such particles
system, which is smaller than it would be if either of the particles was on its own. The
particles interact with one another; they both contribute to the net energies of the
The theory and the methodologies of interference posulate that if two processes or

(Pedersen et al., 1983).
fulfillment of the enduring promise of quantum mechanics has held for biochemistry
chemistry and numerical analysis in the last few decades has made possible the
surface near local minima or transition states. The advancement in computational
very geometries and force constants for regions of a molecule's potential energy
The primary objective of quantum chemical and mechanistic studies is to be able to

al., 2002; Garg and Korkali, 2005).
the performance of the device during clinical delivery of tissue engineering (Oltham et
application and adaption to the micromenvironment of the tissue/organ is pertinent to
Shive and Anderson, 1997; Wu, 2004). The influence of these properties on
physicochemical and physicochemical advancements, and the molecular dynamics
studies on PLGA regarding solvency addition, incorporation of biological factors, and
stability of PLGA scaffolds have not been reported. Moreover, the structural stability
substances, such as DMF, water, hydrochloric acid and phosphoric buffer ions on the
To our knowledge, the effects of molecular interactions between PLGA and various
revealed that potential energy change during the proton transfer is tightly regulated and quantum chemical calculations, in their study, Yoshitani and co-workers (2006) polymers, molecule is placed in a solvent of a buffer system by molecular dynamics, This method is able to determine the proton-transfer processes that occur when a calculation following molecular dynamics (MD) simulations (Nichols et al., 2007). water and polymer molecules within the potential energy change through quantitatively the interactions between the solvency ions, utilizing the parabola continuum model (PCM) to mimic these effects. The changes polymers can be studied by ab initio calculations up to MP2/cc-PVTZ/MP2/6-31G+. geometries plus frequencies, the effects of solvation on the conformation energies of molecular orbitals. In addition to energies, equilibrium and transition-state functions. A, for an n-electron system, is the single determinant of the occupied secondly, to assume the Hartree-Fock theory wherein the simplest useful wave function, by Schaeffer (1972), firstly to formulate the Born-Oppenheimer approximation and the most common ways to predict the energy for a molecular system were defined. mechanical contributions derived from the energy state of the electron shells. electromagnetic considerations such as van der Waals forces and the quantum model further energy transfer of bonded atoms may be negligible is secondary results from the vibrational motions, angular motions and electric charge on the most within the bonds of that molecule, in bonded atoms, the energy components contribute to the temperature of the molecules, and the potential energy is the change in the average kinetic energy of the particles is neglected in the
The interactions between the molecules and the transitions that result from laboratory experiments. These programs are able to predict a realistic description of the transitions, which are difficult and even impossible to render evident through experiments. They are able to impact on the overall physicochemical transitions of the system involving reaction mechanisms that may provide information about molecules or reactions and establish a reaction mechanism since computational chemistry can be used to model reactions and compounds experimentally. This is of prime interest if we want to understand phenomena by running calculations on computer rather than by examining physical properties of the novel self-assembled PLGA scaffolds produced. Understanding the effect of self-assembling and cross-linking reagents on the trans-dimensional PLGA scaffold. Understanding the chemistry at a molecular level is crucial in revealing the physicochemical transitions occurring on formation of the novel scaffolds. The scaffolds obtained by self-assembling and subsequent cross-linking of the PLGA scaffolds can be analyzed using textural analysis. In the work we set to use both the textural analysis and the initial computational results and the incorporated ions from the buffer and the solvent by the composition and the geometry of the surrounding molecules of the polymer.
Characteristics of the response of interest relationships between the physical and mechanical properties of the scaffold and its degradation and understanding of the physical and chemical processes involved in the degradation process. Several factors and optimization were conducted in order to optimize certain processes, such as the in vitro models and chemical optimization. Almost all the tests conducted on the scaffold involved several factors and optimization of the experimental work. The goal is shifted from screening to scaffold optimization of the study. Two, accordingly, enable us to single out the best materials and equipment for the study variables on a pair-wise interaction effects. The preliminary studies in Chapter information, however, only provide information on the directed additive effects of the and upper levels of the combinations of the variables studied ranges. This type ofwere screened designs that compromise the ideal and error runs at the extreme lower in the preliminary studies of the scaffold development, the experiments employed

3.5 Statistical Design of Experiments

PLGA scaffolds through physical and chemical transitions occurring during salting-out of native PLGA to form which allows us to obtain additional information such as the chemistry related to the use to confirm experimental results, and a crucial adjunct to experimental studies the power of molecular mechanisms and quantum chemical calculations which allows Computational chemistry is therefore both an independent research tool that uses
Response function in order to predict the system optimum more accurately.

Response. Second-order experimental designs are then employed to fit a quadratic experimental designs are applied when locating the region containing the optimal experimental region (Myers and Montgomery, 1999). In general, the first-order illustrative precisely how responses behave at all values of the variables in the RSM allows one to define empirical models, such as quadratic polynomials, that et al., 1990).

and a similar response within restricted regions of the operability space (Donohue approach the relationship between a set of controllable random input variables fundamental hypotheses that low-order polynomial models can be used to known as the response surface methods (RSMs). RSMs are based on the widely used statistical experimental designs for the optimization of experiments are valuable and experimental conditions for achieving the optimized process. The most objectives of the study, and it may be successfully employed in order to find the best The experimental design strategy is selected in accordance with the particular variables and their interactions on response variations can be established.

a planned sequence of tests, called a design, to study the influence of the random input applied to yield applicable and objective conclusions. DOE can be used to perform procedure for setting up experiments with the intention that the data obtained can be formulation. Design of Experiments (DOE) is therefore an efficient statistical necessary that we can identify factors that are influential to the properties of the process, and to achieve the desired characteristics of a drug delivery device. It is in order to design experiments efficiently and be able to monitor each formulation.
Equation 3.1

\[ q = \frac{1}{N_{\text{tr}}} \]

From the design center, star points and \( \pm 0.75 \) center points. The axial points are located at distances of poles at the origin. A CCD for \( k \) factors consists of \( 2k \) factorial points, 2 axial or the intervals \([-1, 1])

Each CCD consists of cube points at the corners of a unit cube that is the product of or outside the cube, and center.

The CCD is often used to provide estimation of a second-order equation.

Each design variable has to be studied at three distinct levels at least, and therefore, the estimation of curvature. To determine quadratic regression model coefficients, a factorial design with center points, augmented with a group of star points that permit Wendon CCD, commonly known as CCD contains an embedded factorial or factorial (CCD). CCD is one of the RSM designs that can fit a full quadratic model. A Box-CEPT composite design is the central composite design.

One of the most preferred RSM is the central composite design.

Design points will best reveal aspects of the process of interest (Box et al., 1978).

The basic dilemma of experimental design is deciding what pattern of effects, pairwise interaction effects, and/or linear effects may be represented. Moreover, the RSM is able to provide information on the direct effects or the midpoints of the study range, while the other levels in the interior of the range may also be represented. Furthermore, the RSM includes fields in which one or more of the independent variables are set at

The RSM includes fields in which one or more of the independent variables are set at
employing Design of Experiments. Furthermore, the ad infinitum quantum mechanical
transformations of novel sodiumpent and subsequently crosstalked PLGA scaffold
This study therefore, proposes to explore the in vivo physicalmechanical property
study, with a = 1 (Przysiezniak et al., 1996),
which have two levels per factor. A face-centered CCD (Faced) was chosen for this
CCD designs. CCDS have three levels per factor in contrast with the other types.
Types of CCDS, namely, Circumscribed (CCS), Inscribed (CCI) and Face-centered
includes the region of interest as defined by the variable bounds. There are three
Furthermore, a face-centered CCD can be used when the region of applicability
Experimental regions of interest and applicability due to their variability.
"The CCDS are extremely flexible and can be used under different
significant curvature effects.
analysis of the data from the first subset points indicates the absence of
subset estimates curvature effects. The second subset need not be run when
subset estimates linear and two-factor interaction effects while the second
"A CCD can be conducted sequentially, that is, it can be partitioned into two
Experimental error in the least number of required runs (Donat et al., 2006).
able to provide much information on experiment variable effects and overall
CCD's are very efficient with respect to the number of runs required, and are

To their following advantages:
than three levels (-1: 0: +1) (Leves et al., 1999). The CCDS have gained popularity.
M represents the number of rectangular runs used to study the variables at not more
their physicochemical properties. After 0, 7, 10, 15, 25 and 30 days post-incubation the scaffolds were assessed for
and collected at 10 rpm in a shakerbath (Labert, Stuart SBS-400, Gdanting, South
The detached scaffold samples were then immersed in 100 ml PBS (pH 7.4, 37°C) for
induced shrinking onto scaffolds that were vacuum dried to remove excess solvent.
of protonated water (pH 1.5) (HCl) was added to the polymeric solution and
weighed, dissolved in DMF, and placed in 200 ml glass beakers. Varying quantities
PLGA of various molecular masses designated as 1, 2 and 3 in Table 1 were

3.6.2 Formulation of the PLGA scaffolds

All other reagents were of analytical grade and used as supplied.
prepare the phosphate buffered saline (PBS) (Sartorius (Py) Ltd., Braintree, South
orthophosphoric acid, sodium chloride and potassium hydrogen phosphate were used to
serien (Roche, Chemical, Germany; South Africa) and disodium hydrogen
in Lebensmittel, Germany; N. V. diamytofumarate (DMF) was used as a
content and inherent viscosities ranging from 0.6-8.2 Kld were utilized (Boehringer
Resomer® grades comprising polylactide-co-glycolide (PLGA) with 50% lactide

3.6 Materials and Methods

scrolled at a molecular interaction level
PBS (pH 7.4, 37°C) was explored to deduce the in vivo stability of the novel PLGA
energy transitions employing PLGA monomeric units and interacting molecules in
Factors simultaneously (Cook and Cox, 1992).

This not screening the main interactions and effects of all the involved parameters. Thus not screening the main interactions and effects of all the involved which involves varying one factor at a time, while keeping constant all other of a second order. This is more superior to conventional methods of optimization number of experiments. FCCD was employed in this study to determine coefficients variables influencing the desired responses, by altering the variables in a limited allows for simultaneously studying the effect of several independent formulation (FCCD) was selected for optimization of the PLA scaffolds. The statistical model for a four factor, two centerpoint quadratic face-centered central composite design:

<table>
<thead>
<tr>
<th>Hours</th>
<th>2</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% PLA concentration</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>PLGA molecular mass</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water volume</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Low</th>
<th>Middle</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Level</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1. Normalized factor levels of the independent variables for the FCCD

3.6.3 Construction of the Experimental Design
Microsystems, Surrey, England) which captured stress-strain profiles with a high
analyzed using a Textural Analyzer (TAXT plus Texture Analyzer, Stable
Physicochemical transitions of the salted-out PEGA scaffolds in PBS were

3.6.4. Physicochemical Profiling of the PEGA Scaffolds

<table>
<thead>
<tr>
<th>Concentration (g/L)</th>
<th>Reaction Time (h)</th>
<th>PLGA Mw (kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>2.5</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>22</td>
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<td>3.5</td>
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<tr>
<td>22</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>23</td>
<td>6.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3.2: Randomized experimental runs generated from the FCCD.
Matrix resilience and energy absorbed were the two physical/mechanical properties determined by force-distance and force-time profiles generated (Fig. 3.1).

<table>
<thead>
<tr>
<th>50 kN</th>
<th>50 kN</th>
<th>Load cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 N</td>
<td>0.5 N</td>
<td>Trigger force</td>
</tr>
<tr>
<td>10 N</td>
<td>10 N</td>
<td>Trigger type</td>
</tr>
<tr>
<td>50%</td>
<td>40 N</td>
<td>Compression force/strain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1 mm/sec</th>
<th>1 mm/sec</th>
<th>Post-impact speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mm/sec</td>
<td>0.5 mm/sec</td>
<td>Test speed</td>
</tr>
<tr>
<td>1 mm/sec</td>
<td>1 mm/sec</td>
<td>Pre-impact speed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Matrix Resilience</th>
<th>Energy absorbed</th>
<th>Parameters</th>
<th>Table 3.2. Textural parameters and settings</th>
</tr>
</thead>
</table>

Analysis is shown in Table 3. Degree of accuracy and reproducibility of textural parameters calculated for the...
Figure 3.1. Typical residual force-distance and force-time profiles of销售额 unit PLA

- (a) Time (ms)
- (b) Distance (mm)
- (c) Energy Absorbed

Note: The diagrams illustrate the force-distance and force-time relationships for different scenarios. The shaded areas represent the energy absorbed by the material over time and distance.
molecules, and ligands provided in the software.

molecules were built by the atomic fragments.

dimeric formamide (DFA) molecules, water (H2O), hydrochloric acid (HCl) and PEG

hydropthical template of PLA monomer interactions with various quantum of

Energy transitions were calculated using Spartan 04, M 001 (HF/3-21G

3.6.5 Ab Initio Quantum Mechanical Energy Comprisons

zero was completed and recorded.

masses that was pre-weighted at time zero. The mass deflection from time

the scaffolds recovered at 7, 10, 14, 26 and 30 days after incubation were compared

growth media generated utilizing a calibrated analytical balance. The mass of

AI 7, 10, 14, 26 and 30 days post-incubation scaffolds were removed, dried and

100pm in a microplate (Labsystems, SBS400, CUS400, South Africa) at 250rpm.

Scaffold samples were pre-weighted, immersed in 10cm PEG and oscillated at

3.6.4.2 Geometric Analysis of Scaffolding PLA Scaffolds

between anchors 2 and 3 and 1 and 2 (ALC=ALC).

for calculating matrix resilience, which is represented by the ratio of the AUC

change shape on application of stress. Figure 3.10 depicts a Force-Time profile used

computing the matrix tolerance to assess the tendency of the PLA scaffolds to

area under the curve (AUC) [Nin-Joulie]. Figure 3.10 depicts the authors used for

Figure 3.1a depicts the profile anchors used in calculating the energy absorbed i.e.
delivery upon application of the scaffold for intended purpose. 

environment, degree of cell and tissue regeneration as well as the rate of drug cross-linking. Such transitions may directly impact the percentage of drug 

of the physiological and mechanical transitions that occur during scaffolding and subsequent 
The external morphological features of the scaffolded PLA scaffolds are indicative 

3.7 Results and Discussion 

other physical variables like magnetic field, gravitation and electric current. 

for PLA at room temperature and pressure (excluding moisture, radiation, effects of 
temporal framework of singular and collective interactions. The values obtained were 

computations of the global minimum energy levels for interacting molecules in a 
The simulated minimization energy levels were obtained for the optimized stabled
resulted in the unexpected formation of the C-C bond and the stereospecific configuration, with a free rotation about the chiral center that coupled effect of these forces induced the PLGA chains to adopt a meticulous attractive and repulsive forces on each chain were precisely counter-balanced. The during the second stage PLGA chains assume a configuration such that the PLGA adsorbs DMF to form a gel-like stage that slowly dispersed into solution. During solubilization of PLGA in DMF, two distinct stages were observed. Initially, bonding of reactive molecules to form a 3-dimensional scaffold. cross-linking of reactive PLGA. Cross-linking of the matrix occurred mainly by covalent shrinking of the system resulted in increased partitioning of PLGA H2O and HCl are deposited in future compartment the solvation energy and the solvent effects a molecular interaction solvation was conducted the mixed guanidine/molecular mechanochemical. This allowed for shrinking-on and subsequent cross-linking into the PLGA scaffold.

3.2. Simuliation of PLGA Monomer Interactions during Solubilization

environment as well as cell-seeding in drug delivery and tissue engineering. These folds provide an increased surface area for further drug intermolecular folds may be associated to cross-linked fibers within the PLGA matrix to resembling the body's extra-cellular matrix were presented. The external toughness and one PLGA scaffold (thickness=1mm) obtained. Surface folds and inter connectivity.
PLGA to form the novel scaffold.

Ion-solvent (H2O-DMF) interactions on phase separation during salting-out of native allowed us to speculate the relative importance of polymer-solvent (PLGA-DMF) and C-C molecular distance of 1.54 Å, as depicted in Figure 3. Accordingly, this model
Figure 3.4: PLGA Interaction Figures 3.4-3.6 Illustrating PLGA in a OH polyester and a

showing temporary proton and charge transfer from water molecule to PLGA molecule.
Internal energy of the system, bond-angle deformation, as well as interactions between atoms augmented the PEGA resulted from bond formation, resonance, and steric strain bond stretching. The enthalpy changes during self-assembly and close-intruding of the total quantum energy of the newly formed PEGA scaffold, which in turn the summation of energies of the system during molecular interactions, determined.

sales. scads, which is caused by a gain of electron energy introduced by the ions in the scaffold, which may have resulted in an increase in steric strain and internal energy of the hydrophobic PEGA chains. In addition, the stacking and subsequent cross-linling phenomenon is proposed to have exerted a preferential partitioning of the H₂O. This phenomenon allows the immediate surface of the PEGA, which affected the configuration and salvation shells of PEGA into scads. Owing to the hydrophobic nature of PEGA, junction zones were formed around the PEGA, which affected the configuration and salvation shells of solvent was key during the reaction. selfing-out effect increased due to solvency of the system and thus the polar apptec from H₂O molecules to DMF allowed PEGA to self-organize and DME occluded. The charge transfer processes, ionic interactions involving H₂O and DMF occurred. The charge transfer surfaces, forming on an outer solution shell in Figure 3.2a, as the reaction water molecules to the periphery, thereby causing water clusters to from the PEGA respectively. In Figure 3.2b, the hydrophobicity of PEGA networks drives Figure 3.2a depicts the ionic bond interactions between the N-O atoms of DMF and
decreased degradation rate in PBS. Increasing density is reduced, the materials will have increased resilience and a more molecular mass. PlGA concentration, volume of water and salting-out reaction time. The physical-mechanical properties of the scaffolds were governed by the PlGA hydrophilic interactions and hydrogen bonding.

Hydrophilic interactions and hydrogen bonding immersed in PBS. Scaffolds may have interacted with the PBS by means of polar groups of each scaffold variant. The PlGA scaffolds degraded at varying rates when quantified in order to predict the dynamic transitions for flexibility and recyclability environment were analyzed. The extent of physical-mechanical modification was quantified in order to predict the dynamic transitions for flexibility and recyclability environment were analyzed. The extent of physical-mechanical modification was

Profile Analysis

3.7.3. Physical-mechanical Analysis of the PlGA Scaffolds Employing Textural

Scaffolds were assessed. PlGA scaffold during residence in PBS the physical-mechanical transitions of PlGA scaffolds reside in PBS over time, in order to assess the integrity of the scaffold and properties of native PlGA. However, these properties are influenced by transitions as salting-out brought about transitions in the physical-mechanical and physical-mechanical the system. Bond formation and conformational changes of the structure during resulted in resonance stabilization that also caused an increase in the enthalpy of formation of 3-dimensional PlGA scaffold decreased chain de-localization and
Figure 3.4. Profiles depicting the physiomechanical transitions of the salivary PLA.

and (c) Mass detection, over a 30-day period
scocholds immersed in PBS (pH 7.4, 37°C). Plots (a) matrix resilience, (b) energy absorbed.
transitions when immersed in PBS. The salted-out PLAGA scaffolds produced were concentration were less susceptible to degradation and physicochemical.

by the data was that the scaffolds with higher PLAGA molecular masses and significant reduction in PBS which significantly increased.

of scaffolds was also observed to decreased with an increase in scaffold residence in the peak energy absorbed by the scaffolds occurred at day 10. The mass variation was absorbed by the scaffolds when higher molecular masses of PLAGA were used.

increased resistance to external probe penetration. This indicated that excess energy absorbed by the scaffolds during external probe penetration (Figure 3.4c) time in PBS. Higher water volumes caused a decreased quantity of energy to be the ability of the scaffold to absorb energy was found to correlate with the residence

the matrix resilience transition in matrix resilience whereas higher salted-out water volumes decreased scaffolds that were salted-out utilizing higher PLAGA concentrations exhibited minimal transition in matrix resilience between 35-45% during the 30-day incubation. scaffold formulation numbers 1, 8, 10, 12, 14, 16, 22, and 23 indicated a dependence on the PLAGA scaffold formulation. For instance, the matrix resilience of resilience decreased with an increase in the incubation period (Figure 3.4a) and scaffold formulations immersed in PBS for 7, 10, 14, 26, and 30 days. Matrix Figure 3.4a depicts the transitions in matrix resilience of the twenty-six PLAGA
controlled drug delivery.

enhancement of the scaffold physicochemical properties making them suitable for
establishing the optimal combination of independent formulation variables for the
physicalmechanical properties were obtained. Surface plots were able to focus on
By utilizing the extruding techniques and subsequent cross-linking process scaffolds with novel

3.7.4 Response Surface Optimization of Scaffold Formulations

degradation and controlling further freedom to control drug release.
more hydrophilic and hence less prone to hydrolysis in PBS hence reducing
Increased further matrix resilience decreased linearly (Figure 3.5a, b, and e). Response surface plots indicated that the PLA molecular mass increased matrix resilience up to an optimal level of 100,000 Daltons. As the PLA molecular mass concentration increased (c), polymer molecular weight and settling time (d), polymer concentration (e), water volume and settling time (f), water volume and polymer molecular weight (g), and water volume and polymer volume (h). Figure 3.5. Response surface plots depicting resilience vs water volume and polymer volume.
Increasing concentration in increasing matrix resilience, the salting-out reaction time proved to be effective in augmenting the PLA increased matrix resilience only when the salting-out reaction time was longer. The observations also highlighted that higher PLA molecular mass resilience values, especially when the salting-out reaction time is decreased (Figure 4.5). An increased water volume generally led to decreased matrix concentration and molecular mass were significant in determining the matrix water volume or salting-out reaction time (Figure 3.5, c and d). Thus, the PLA increasing the PLA concentration increased matrix resilience in spite of changes in
Higher water volumes caused lower quantities of energy to be absorbed. The quantity of energy absorbed during textural probe penetration of the scroths demonstrated that water volume was found to influence the molecular weight and polymer concentration. Figure 2.6. Response surface plots depicting energy of absorption vs water volume and polymer molecular weight.
The absorption of energy started to decrease.

50% of the PLGA concentration reached a threshold level of 5% w/w, whereby the energy absorption of molecular mass resulted in an increased energy absorption (Figure 5). Therefore, decreasing the absorption of hydration-free energy, higher PLGA excess water molecules within the polymer film coupled with ion hydration, increased volume of water during setting-out and may have resulted in the entrapment of
Figure 3.7 Response surface plots depicting weight deflection vs. water volume and polymer concentration. (a) water volume and saltout time, (b) water volume and polymer weight, (c) polymer concentration and saltout time, (d) polymer molecular weight and polymer concentration, (e) polymer concentration and saltout time.
Properties of the novel PLGA scaffolds formed and 3.6 and concluded a fairly close correlation between all three physicochemical properties demonstrated similar trends for mass depletion as shown by Figures 3.5.
Figure 3.5. Profiles demonstrating the correlation between experimental and predicted values for Matrix Resilience, Energy Absorbed, and Mass. Detection: trained values for the response. RT: Matrix Resilience; E=Energy absorbed; W=Mass.
monomeric unit.

endothermic nature of the interaction comprising of 3 DME molecules and 1 PLA.

most stable conformation to co-exist at -4.9 Kcal/mol. This indicates an
followed by a third molecule of DME to confer a minimum energy consistent for the

The addition of a second DME molecule yielded an energy value of -19.2 Kcal/mol

analysis

addition of more than 1 DME molecule versus 1 PLA monomeric unit during
scope for further molecular interactions to occur. This observation prompted the
minimum. The lower energy level value of -6.3 Kcal/mol indicated the stability and
primary molecular interaction after repeated energy calculations for a global
produced an energy level of -5.2 Kcal/mol, with the H-bond of DME unperturbed in the

The addition of 1 DME molecule for collary interaction with 1 PLA monomeric unit

of 38.03 Kcal/mol utilizing Spartan 04 M001 software.

A single PLA monomeric unit was found to be stabilized at a minimum energy level

Interaction level

3.7.6. Elucidation of the Quantum Mechanical Energy Transitions at a Molecular

including a good fit to the model chosen.

differences were noted between the fitted and experimental values (p<0.05).

and fitted values for the dependent formulation variables. No statistically significant

Figure 3.6.a, b and c depicts the close correlation between the model experimental
of approximately 8.00 kcal/mol (1.89 - 2.74 kcal/mol) and 15 kcal/mol (4.95 -
requirements at this level of interaction indicate sizable positive energy contributions
presence of 1 PLGA monomeric unit for its energy dynamics. Significantly, all energy
and 2 H2O molecules at 28.52 kcal/mol and 27.14 kcal/mol respectively required the
stronger interaction between DMF and H2O molecule. The system consisting of 1
The composition system having an energy requirement of 4.46 kcal/mol indicated a

Importantly further stability to the system.

10.00 kcal/mol which indicated a superior endothermic energy domain capable of
between the H2O-borne energy requirements for a stable energy system was
of DMF, and the presence of 1 and 2 H2O molecules respectively. The difference
3.71 kcal/mol were obtained at this level with 1 PLGA monomeric unit, 2 molecules
raised the energy requirements. Energy values of 28.52 kcal/mol and
The addition of H2O to the composite system (1 PLGA unit, 3 DMF molecules)

uniform magnetic agitation with minimal disturbance of molecules.
hours and under the constant supply of external mechanical energy in the form of
The solution of PLGA in DMF was achieved mainly over longer periods of time (>12
interactions resulting in minimal interaction and slower solution of PLGA in DMF.
moieties versus the entire PLGA backbone. The energy levels were lower for the
molecules versus the entire PLGA backbone. The energy levels were lower for the
level which was a theoretical requirement for the primary solution shell of DMF
and 1 PLGA monomeric unit (formed a PLGA-DMF interaction template at a unit
energy requirement for this stable conformation at all molecules (3 DMF molecules
accounted for the lower solubility of PLGA when DMF was used as a solvent. The
The decreasing energy values revealed a trend of energy conservation that
The fact that the composite and the Z-HCl molecule systems had similar energy requirements and revealed the complexity of the systems energy profile.

The change in the energy profile with an energy value of 4.2326 kcal/mol at 4.5 kcal/mol and a Z-HCl molecule energy level of the composite system at 4.5 kcal/mol revealed the requirement and hence the ability to absorb more energy. The energy profile energy requirements to 4.2326 kcal/mol, thus indicating an endothermic energy process.

However, this reaction was measured and possessed a weak energy profile thus not instantly favored.

The strong molecular interaction between DMF and H2O molecules predisposed the shell formation between PLGA and DMF, which was important during solubilization. The phenomenon was short-lived but significantly contributed to the primary solvation exchange interaction phase between DMF and H2O molecules. This exothermic exchange interaction phase between DMF and H2O molecules.
almost pivotal change in energy to a value of -663.72 kcal/mol. This value was
further leap in energy occurred with the addition of 1 more PO₄ that resulted in an
the predominant endothermic energy trend which was relatively more stable. A
respectively (1 molecule of H₂O, effective change ~ -0.0 kcal/mol) thus contributed to
charged this energy requirement to -353.56 kcal/mol and -361.4 kcal/mol
requirements by 35.6 kcal/mol to -34.8 kcal/mol. Addition of 1 and 2 H₂O molecules
Further addition of 1 molecule of potassium chloride (KCl) decreased the energy

with the minimum energy level arising at -338.1 kcal/mol

chloride (NaCl) affected the system further to yield an energy value of -640 kcal/mol
until consolidating the computation domain. The addition of 1 molecule of sodium
phosphate ion (PO₄³⁻) in the presence of DMF, H₂O, HCl and I. Placing the
system, a difference of approximately -290 kcal/mol occurred with the addition of 1
upon addition of PO₄ to the template, a significant change the energy profile of the

molecules in the gel phase while others might tend to remain in a solution phase.
value at this level may lead to bifurcation phases with a few DMF, H₂O and HCl
an energy level of +43.5 kcal/mol. Hence significantly, an energy exchange of equal
effects of H₂O molecules and reduced the system to the primary solvation shells with
DMF molecules were added. The presence of HCl in the system neutralized the
molecules were added displayed an exothermic phenomenon in comparison to when
HCl stage of the composite system. The higher energy requirements when H₂O
affected transition stability from DMF solution to H₂O interactions and ultimately to the
tot. 00 kcal/mol. This indicated the overall stable energy required in the system to
backbone of PLGA.

work evaluates the pivotal role of small particles in the transformation of the chemical
out and cross-linking (Smith et al., 2007; Li et al., 2009 and Zago, 2004). Therefore, this
through ionic interactions between polymer-elas and polymer-polymer during swelling
which changes in morphology, resilience, and glass-transition temperature can be achieved
alteration of the 3-dimensional polymeric network that results from changes in bond
of block from PLGA delivery devices (Zhu and Schwiemer, 1999). The
Furthermore, evidence has shown the influence of salts on the stability and release
Hassan et al., 2001; Smith et al., 2001; Kuo and Leou, 2006).
manipulating of the chemical backbone using salts (Gao et al., 1998; Ju et al., 2000).
modification of aliphatic thermoplastic polyesters, such as PLGA, can be achieved by
physicochemical properties. Numerous laboratory findings have shown that the
attaining an optimized scaffold with modified physicochemical and
molecular mass of 55,000 Da. Diblock was selected for further investigation towards
concentration and how on the /m with degradation of PLGA, grade RG 504, with
Based on the findings of the proceeding chapter Three, on the effects of polymer

4.1 Introduction

PHYSICOCHEMICAL PROPERTIES OF THE PLGA SCAPFOLD

THE EFFECTS OF SALTS ON THE PHYSICOCHEMICAL AND

CHAPTER FOUR
In order to enhance the properties of the PLA scaffold, this study adopted the use of monomeric, dimeric, and tetrameric chloride polylethanes as suitable scaffolds for the use in the sintering and subsequent cross-linking in conjunction with the above-mentioned conditions. This study considered metal in accordance with the findings from the preliminary studies in Chapter Two and metal carboxylate. The cation also determines the solubility of the salt of the polymer. In addition, the cation should not form strong complexes with the salt. It would induce reduction-oxidation reactions and initiate the degradation process. The anion selected should not be an electron pair donor or a strong oxider. The modifying effect is a function of the cation, capacity to react with the polymer, and polymer modification. The mineral salt is primarily selected based on its cation as biodegradable scaffolds. Gas-sorbing process at room temperature in order to produce macroporous the semi-solidified polymer-salt mixture in an aqueous solution or critical for the biodegradation stages of gas sorbing agent and porous additives and further microparticles from a homogenous to a heterogeneous matrix which leads to the transition in the polymer. The incorporated salts are capable of changing the polymeric network. Several other studies have explored the use of salts in order to enhance the properties of 4.2 Polymer Modification with Salts and Ions.
Electron donation copolymer interactions are a significant part of the swelling-out of the polymer molecules (in this case, 1996. Watanabe et al., 1997). One of the principal mechanisms of swelling-out is the self-induced surface tension polymer and redissolving disappearance and degradation of the water molecules in an effort to solve the swelling, thereby dehydrating the drug release rate (Pillay and Fasshili, 2001; Swanson, 2001). Thus, the swelling will polymer complete for water of hydration, resulting in programmed degradation and hydration and subsequent degradation as the matrix hydrates, the salts and The presence of salts in polymeric matrices can control the rate of polymer cross-linking polymers in one step.

Likert for the formation of PCL/PA networks, the process combines swelling and polymer structure. The salts function as both a pore forming reagent and cross- These ionizable salts allows for non-covalently diffusion channels to form within the various researchers (Judas et al., 1996; Watanabe et al., 2002; Marquez et al., 2005), such as calcium and magnesium to polyelectrolyte ion-dipole bonds was illustrated by swelling kinetics as well as physical rigidity. Furthermore, the complexation of ions can stabilize the swelling kinetics and the micro-environment within hydrating matrices to control their Pillay and Fasshili (1999) reported on how electrostatic inductions can alter the salts can also modulate the release and swelling kinetics of degradable polymers. (Hoody, 1996; Tanaka and Takaishi, 2000; Zhang et al., 1995) showed that the stochastic fluctuations of the free energy proportional to the salt concentration resilience and glass transition temperature of polymers by means of salt caused swelling-out, a colloidal phenomenon, has the capacity to change the morphology.
Electron donor/acceptor interactions are a significant part of the self-assembly of water molecules (Izumi et al., 1999; Menger and Meier, 1977).

One of the principal mechanisms of self-assembly is the self-induced surface tension of polymer and rendering dissolution and degradation.

The presence of salts in polymeric matrices can control the rate of polymer

Cross-linking polymers in one step:...
properties of the polymer (Nyvotton et al., 1995). Interactions between the polymeric chains and the sadness further transform the
interactions of the chains (Bevan and Drackley, 2001). These changes are
enhanced by the hydration of the hydrophilic structure, thereby decreasing the hydrogen bonding between water molecules and
and the polymeric solvents, leading to a decrease in the water

Although there is a large variety of forces present, including electrostatic and ultra-

The thermodynamic studies by Alikwe and Timmerman (1985) demonstrated that the
polymers such as OH-polyester (Smith et al., 2000).

Certain aspects of changes according to their effects on swelling and thermoplastic

Polymer modification and catalytic species in aqueous solution order

Although polymers have a large variety of forces present, including electrostatic and ultra-

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Certain aspects of changes according to their effects on swelling and thermoplastic

Polymer modification and catalytic species in aqueous solution order
and interaction effects of the independent formulation variables on the number of experiments needed for formulation optimization and to establish the main factors. A 3-factor, 3-level Box-Behnken statistical design was built in order to model the effects.

4.3.2 Building the Experimental Design

...Darmstadt, Germany), were used as the ionic salts: Rochelle salts, South Africa) and aluminum chloride (Merck), solvents, and anhydrous grades of sodium chloride (Merck), calcium chloride (CaCl₂), polyethylene glycol-6000, l-vitamin D₃, 0.48-0.50% (90% aqueous) were used as a solvent. Poly(L-Lactic acid) was obtained from Boehringer Ingelheim Pharma (Ingelheim, Germany).

4.3 Materials and Methods

 Were employed namely, textural analysis, SEM, FTIR, and DSC. all complexes are termed "scaffolds". In order to achieve this various techniques using a strict analytical approach to develop a mechanistic understanding. These scaffold-like materials were found to be controlled independently by the chemical composition of the polymer, which is a key factor in determining their applicability.

In this work we evaluate the physicalchemical and physicochemical transitions of hydrolysates of the polymer bonds, and exible excipient structural integrity, making the resulting cross-linked polymer networks dimensionally stable with minimal...
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Table 4.1. Factor levels of the independent variables for the Box-Behnken Design

PLGA formulations that are shown in Table 4.2 below. Variables and the factor levels used in the Box-Behnken Design, with generated and physicochemical evaluation. Table 4.1 below describes the independent and physicochemical evaluation. Each PLGA scaffold was stored for a maximum of 48 hours prior to physicochemical testing. Solution with 50ml of distilled water and dried to constant mass at room temperature. The resultant PLGA scaffolds were removed from the cross-linking solution washed solution and agitated for a period of 30 minutes.

75ml of 0.4% WV% of NACL, 4% of AICl. CACl for AICl was added to the polymer dissolved in 15ml of acetic acid were prepared. The cross-linking solutions comprising temporary stimuli in Table 1. Fourteen polymeric solutions comprising 0.4% of PLGA combination of acetic and ionic salts in accordance with the Box-Behnken design.

PLGA scaffolds were prepared by salting-out and subsequent cross-linking using a

4.3. Preparation of PLGA Scaffolds

Miniab V14 (Miniab USA)
Electronic Microscopic (SEM) images employing a thermal emission JEOL 1560.

The surface morphology of the PLA scaffolds was assessed from Scanning

4.3.4. Morphological Characterization of the PLA Scaffolds

$\text{Variables, and } [\text{NaCl}], [\text{Caco}_3], \text{ and } [\text{AICl}] \text{ are the independent formulation}$

where, the response is associated with each factor level. $b_0, b_P$ are the regression

$$\text{Equation 4.1} \quad \text{Response} = b_0 + b_1[\text{NaCl}] + b_2[\text{Caco}_3] + b_3[\text{AICl}] + b_4[\text{NaCl}] \times [\text{Caco}_3] + b_5[\text{NaCl}] \times [\text{AICl}] + b_6[\text{Caco}_3] \times [\text{AICl}]$$

The quadratic model for the response is shown in Equation 4.1:

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Table 4.2: Box-Behnken Lattice with Randomly Generated PLA Formulations
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<th>Deformability Modulus</th>
<th>Energy Absorbed and Matrix Resistance</th>
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Table 4.3: Textual parameter settings

Deformability modulus and matrix resistance are shown in Table 4.3. Force transducer, the parameter settings employed to obtain the energy absorbed, subsequently analyzed. A 2.5 mm rectangular steel probe was attached to the compression force/strain instrumentation (40N) at a rate of 200 points per second employing a Texture Analyzer (TA.XTplus Texture Analyzer, Stable Microsystems, UK). Stress-strain profiles with a high degree of accuracy and reproducibility were captured at a strain rate of 2.5% per second. The physicochemical properties of the PLGA scaffolds were evaluated using a Scanning Electron Microscope (SEM).

**4.3.5 Determination of the Physicochemical Properties of the PLGA Scaffolds**

Magnifications at an accelerating voltage of 20 kV.
Shutter-coating with a layer of carbon. Each sample was viewed under varying magnifications at an accelerating voltage of 20 kV. Samples of PLGA scaffolds were selected and mounted on aluminum stubs prior to SEM analysis.
Typical load-slip profiles used for quantifying the physical mechanical properties and force-distance and force-time profiles for each PLA scaffold was generated. To elucidate the energy absorbed, matrix resilience and deformability modulus,
Figure 4.1. Typical force-distance and force-time profiles of PLA scaffolds for determining (e) energy absorbed (f) deformation modulus and (g) matrix resilience (N=10).
Heat capacity and latent heat, which indicated changes in the amorphous or
DSC was used to record transitions in specific
4.3.2 Thermal Transition Analysis of the PLA Scaffolds

400°C, at an intermediate resolution.

obtained for all samples and the % transmittance was recorded between 4000 –
WVA Instruments (Mk4) Ltd, Johannesburg, South Africa), Background scans were
and compressed in a transparent circular disc using a Beckman hydraulic press
whereby 7.5 mg samples of each PLA scaffold was infiltrated with 200 mg of KBr
USA) Instrument The potassium bromide (KBr) disc approach was employed.
linking using a Nicollet Impact 4000 (Nicollet Instrument Corporation, Pennsylvania,
occurred with the polymer due to stretching and subsequent cooling and on the novel PLA scaffolds to determine chemical transformations potentially
Fourier Transform Infrared (FTIR) spectroscopy was performed on native PLA
Scaffolds

4.3.5 Evaluation of the Molecular Structural Transformations Within PLA

and 1 and 2 (dvC/cm²/duC) for a Force-Time profile.

calculating the matrix resilience (ε), the ratio of the duC between anchors 2 and 3
attained during sample analysis. Figure 4.1c depicts the anchors employed for
the application of stress i.e. the gradient between anchor 1, and the maximum force
dertermination modulus (σ) the tendency of the PLA scaffolds to change shape upon
anchor 1 and 2. Figure 4.1b depicts the anchors employed for determining the
energy absorbed, i.e. the total area under the curve (dvC) [N-m-Joules] between
Figure 4.1a depicts the anchors used in a Force-Distance profile for calculating the
Furthermore, the coordination number of each salt (6 and 4 for Al\(^{3+}\), Na\(^+\), and Ca\(^{2+}\) respectively) along with the atomic radii of the metals of the salts (Table 4.4) manifest the attraction of select salt cations during cross-linking. The salt and polymer monomeric units, solution and the thermodynamic stability of the monomeric PLA units primarily on the ionization energies of the saltifying ion, hydration enthalpies in linking polymers in one step (Liu et al., 2002). This cross-linking reaction depends for the formation of PLA networks: the method combines cleaving pores and cross-linking calcium and aluminium salts function as pore forming reagents and as cross-linkers. Side and gyroidic chains within the PLA molecular structure. The sodium, calcium or cations of C, and O within the polymeric matrix thus contributing to cross-linking of the sodium ion pairs of Na\(^{+}\), Ca\(^{2+}\), and Al\(^{3+}\) developing into electron nodes that

4.4 Results and Discussion

Gradual. Thermograms were obtained and subsequently analyzed. PLA Ca scaffold was placed within a chamber aluminum pan and subjected to the heat increments from 25°C to 400°C at a rate of 10°C/min. Samples of 5-10 mg of each controller model TAC/10X (Peltier-Emitec, Inc. USA). Samples were heated in Thermal transitions were recorded on a Peltier-Emitec Pyris-1 connected to a crystalline structure as a result of scaffold formation from cross-linking native PLA.
result of cross-linking during PLA scaffold formation. The presence of sizeable
interconnections and pores were obtained from polymer-scaffold interactions as a
3-dimensional architectural composite comprising various fiber volume and diameter.

Morphology

4.4.2 Scanning Electron Microscopic Image Analyses of the PLA Scaffold

Subsequent cross-linking: packing of ions and the polymer matrix is present during salting-out and
and coordination number of the concerned ions, the nature of the polymer-scaffold
matrix depends on the role of polymer-scaffold interactions. The recently, atomic size
structure differs and in general, the ability of water molecules to be imbedded within the
PLGA scaffold. Furthermore, the shape and stereo-orientation within the PLGA
physicochemical, physico-mechanical and morphological structure of the resultant
physical properties. Consequently, the scaffold used in this study, namely NaCl, CaCl₂ and AlCl₃ differ with regard to the

| Number | Number | Type | Material (μm) | Calcium Coordination | Sodium Atomic Radius of | Table 4.4, Physischemical properties of the scaffolds employed during cross-linking of
|--------|--------|------|---------------|-----------------------|------------------------| scaffold

| Calcium | 6      | 6     | NaCl          | 186                   | 3.67                   | PLA

Factor in modifying the native PLA polymer scaffold to produce a robust PLA

6 125
5.4+4.0.3
197
6 6
pores and fibers of the newly formed PLA scaffolds.

residue (cluster-packed with water molecules influencing the nature and size of
bonding and other intra and inter-molecular forces localized on the PLA molecule (oxygen
number of each salt influenced the number of covalent bonds formed. Hence, each
PLGA scaffold were obtained (Figure 4.2)). Furthermore, the coordination
glycolide strands of native PLA as a result several morphological combinations of
thermodynamic stability and molecular accumulation of salts and water at the local-
ents. Hydration enthalpy of the salt in solution as well as the
between the salts and PLA molecules were dependent on the ionization energies
through structures with distinct morphologies (Figure 4.2). The ionic interactions
generated areas of high entropy at the solid-liquid interfaces resulting in altered
Figure 4.2 Scanning Electron Microscope images of selected PLA. These micrographs demonstrate the surface morphology of PLA: (a) 0.25 mm, (b) 0.5 mm, and (c) 1 mm. Image 4.2(a) and (b) show the surface morphology of PLA at different magnifications. Image 4.2(c) shows the surface morphology at a higher magnification. The images highlight the microstructure and morphology of the PLA surface.
the ion in silico and subsequent cross-linking PLoG.

the ion in silico and subsequent cross-linking PLoG.

space for binding water molecules which was dependent on the size and the rate of
interactions between native PLoG chains. These voids significantly provided the
accordance to the dimensions of voids created due to short and long distance
resulting from such a configuration were able to accommodate water molecules in
polymeric matrices caused by the loss of the ass. Furthermore, the adjacent voids
nature of the silt, which is explained by different degrees of structuring of the
cross-linked lactide-glycolide chains. The configuration depended significantly on the
native PLoG polymeric structure to assume a fixed 3-dimensional configuration into
native PLoG polymeric structure to assume a fixed 3-dimensional configuration into

In general, introduction of silico-cal ions in the polymeric solution facilitated the

from 0.03 to 0.18 μm and their volumes between 0.09 to 1.7 μm.

interconnection of the PLoG scaffold design with pore sizes and diameters ranging
revealed the porous morphology. With distinct cross-links that resulted in a ramified
in Figure 4.2e and 4.2f PLoG scaffolds seeded with a fibrin clot name ALCs
in Figure 4.2e and 4.2f PLoG scaffolds seeded with a fibrin clot name ALCs

In Figure 4.2e and 4.2f PLoG scaffolds seeded with a fibrin clot name ALCs

diameters ranging between 7.5 to 15 μm and their volumes of 500 to 1400 μm³.

diameters ranging between 7.5 to 15 μm and their volumes of 500 to 1400 μm³.

chains in a distinct voluminous trabecular formation with scales of pore sizes and
development scaffold produced a thrilier composite PLoG scaffold with interconnected
1 μm, and their volumes ranging from 0.01 to 0.03 μm³. In Figure 4.2c and 4.2d, the
and 2) These pores possessed pores and their diameters ranging between 0.1-
and 2) These pores possessed pores and their diameters ranging between 0.1-
homogeneity of cross-linked holes in a neural meshwork architecture (Figure 4.2e
of interconnected pores, divided by strands of microporous structures that maintained
SEM images of PLoG scaffolds seeded with MC3T3 revealed a uniform distribution
SEM images of PLoG scaffolds seeded with MC3T3 revealed a uniform distribution
An increase in the fibrillar nature of the PLGA scaffolds augmented the physicomechanical properties such as matrix resilience. The distinct differences in morphology revealed in each micrograph of the PLGA scaffolds suggest the versatility of the scaffold and hence may be suitable for tailored manufacturing that match specific applications.

4.4.3 Textural Profile Analysis to Quantify the Physicomechanical Properties of PLGA Scaffolds

Analysis of the textural profiles provided an insight on the Stress-Strain relationships for the PLGA scaffolds. Results demonstrated that native PLGA could be modified into a highly resilient polymeric material by rapid ionic salting-out and subsequent cross-linking in order to achieve elasticity that depended mainly on the type and the concentration of salt employed. The matrix resilience values of PLGA scaffolds salted-out with NaCl and AlCl₃ were superior to that of PLGA scaffolds salted-out with CaCl₂ (Figure 4.3).
resistance of the scaffold to deform under stress during textual analysis. Figure 4.5a viscous elasticity caused denaturation of the PLA scaffolds, which resulted in environment which accentuated the viscous elastic behavior of the PLA scaffold. The physicalchemical nature of the cell employed during celling-out created a micro-

Figure 4.3. Profiles depicting differences in the physicochemical parameters of PLA scaffolds: (a) Resilience (R), (b) Energy absorbed (E), and (c) Deformability modulus.
and deformability modules of the PLGA scaffold.

activity of the PLGA chain directly influences the local resilience energy absorbed.

PLGA backbone and the extent to which they are influenced by the conformational

tension decreases matrix resilience. The proximity of the polarizing dipoles to the

teraction of water molecules with the dipole and in addition of intact.

Furthermore, the resultant accumulation of additional water molecules within the

Figure 4.7: In general, smaller and more uniform pores, such as NaCl and AlCl₃, accentuate the

larger pores decreased the resilience.

physicochemical properties of the PLGA scaffolds, whereas salts that produced

Figure 4.8: In general, salts that produced more compact polymeric structures with

consistent with the dense surface morphology of the PLGA scaffolds depicted in

The modification of the physicochemical properties revealed by these profiles is

absoled by the PLGA scaffolds per unit volume shown in Figure 4.3b and c.

resilience and deformability module was linearly correlated to the quantity of energy

energy absorbed as demonstrated in Formulations 6, 9 and 12. The increase in

and 14. The concentration of CaCl₂ was found to be inversely proportional to the

concentrations of NaCl and AlCl₃ were increased, for instance in Formulations 2, 12

and 6 revealed significant increases in the resilience and energy absorbed when
resilience of 10% was maintained and a further increase in AICb beyond 5% of AICb and decreases resilience. At low concentrations (between 0 and 5% of AICb) resulted in a limit of 4.5% at which any further increase of NaCl significantly increased resilience of PLA scaffolds up to 15% NaCl (between 0 and 5% of AICb). NaCl significantly increased resilience of PLA scaffolds up to 4.5% NaCl by scaffold form factor. Figure 4.4a revealed that all lower concentrations and synergistic effects of the cells on modifying the physical and mechanical properties of surface plots (Figure 4.4) were constructed to visually demonstrate the individual
PLGA scaffolds to absorb energy. Furthermore, Figure 4.4c depicts that the energy absorbed and that a 10% w/w CaCl_2 significantly diminished the ability of the

Figure 4.4b demonstrated that a concentration of CaCl_2 above 5% w/w lowered the

---

**Figure 4.4a:** Typical surface response plots depicting the effects of the independent

---

**Figure 4.4b:** Typical surface response plots depicting the effects of the independent

---

**Figure 4.4c:** Typical surface response plots depicting the effects of the independent
In Figure 4.5, the parallel plots indicate no interaction of the independent formulation variables by lower gradients suggesting initial variables in a given plot. Parallel plots as squares estimate for the effect of larger discrepancies indicated by higher gradients as plotted range visually, the discrepancies in the mean values of the plot are the least factors. Disregard from the center-point designated a change in response over the range of interactions were observed to be exponentially with the number of interactions.

The last variable interactions, the polynomial substructure, solvent, water volume, and salting-out reaction time up to two minutes attributable to the main effects (i.e., the salts) as well as other interactions such as the polyelectrolyte modulus model terms. The effects on the responses were found to be authentication of the significant variables on the resilience, energy absorbed, and 4.5. The plots of main and interaction effects were run to provide a visual influence on the physical and chemical properties of PLGA are demonstrated in Figure 4.4. The main and interaction effects of the self-fuze and concentration and their responses.

4.4.5 Determination of the Main and Interaction Effects on the Various Changes in the independent formulation variables. The plots depict each of the responses (physical and chemical properties) that resulted from deformability modulus of the PLGA scaffolds. The following 2-dimensional surface scaffolds, whereas an increase in ALR8 concentrations largely increased the concentration of CACl2 had a minor effect on the deformability modulus of the PLGA.
change in concentrations. It was also observed that the resilience increased with the
65% W. The divalent salt CaCl2 had a minor effect on resilience, regardless of the
self, but had the greatest effect on resilience with optimal resilience expressed at
the native and exental of PGLA modification. In Figure 4.5, NaCl played a more
as demonstrated in Figure 4.5. The type and concentration of salt played a vital role

![Graphs showing different parameters and trends](image)
Various salts on modifying maleic PLGA into salts and PLGA scaffolds. Behnenken design provided a suitable statistical approach to evaluate the effects of experimental and fitted values (p<0.05). This therefore indicated that the Box–Behnken model, No significant differences were noted between the determinant variables, namely, resilience, energy absorbed, and Figure 4.5 depicts the close correlation between the experimental and fitted values of the experimental and predicted (Fitted) responses.

A.4.6 Correlation between the Experimental and Predicted (Fitted) Responses.

Exactly between the PLGA and solvent due to the presence of various salts. Present in the matrix hydration sheet as well as the adhesions of the interactions contributed of several effects such as variations of the water molecule structure. These observed transitions in resilience can be explained as a contribution from a

could be seen from Figure 4.3 and Figure 4.4. Increase in concentration of the interval salt AlCl; from 5% to 4%. A similar correlation
Figure 4.6. Plot of demonstrating the correlation between experimental and predicted results. (a) Graph showing a series of plotted points and lines. (b) Another example of a graph with similar data representation. (c) Additional plot with experimental and predicted data plotted. For details on response values, refer to the referenced figure.
In the FT-IR analyses, significant changes were observed in the 2-dimensional infrared spectra, indicating further interactions between the polymer chains. Furthermore, cross-links formed by the non-uniform length of polymer segments decreased. The intensity of transmittance of all the double bonds present in PLGA were also decreased. (bending) vibrations intensities in the range of 1580-2500 cm⁻¹, stretching, 1600-1900 cm⁻¹, and the synchronous decrease in the C=O groups increase in the frequency ranges of 1180-1320 cm⁻¹, 1250-1370 cm⁻¹, OH resonance stabilization bands. This was demonstrated by the prominent infrared bands that were formed by the presence of pendulum carbonyl groups of PLGA into glycolide units within the PLGA molecular structure. Heteroatomic ether and ion-oxygen oxygean bonds between the PLGA chains, which were formed by cross-linking of the lactide-oxygean bonds, as well as the non-τ, τ-C-O and H-groups, formed hydrogen bonds, which are stable during swelling-out and subsequent cross-linking the scaffolds in water and polymer scaffolds. Morphological, physicochemical, and physical-mechanical transitions demonstrated on the scaffold, as well as the chemical backbone of PLGA, that resulted in the diverse polymer-structure interaction in solution was clearly influenced by the molecular structure extent of these bond vibrations at finger-print regions varied. This implied that the PLGA involved in interactions with the scaffold were similar. However, the degree and transitions of Figure 4.7, the functional groups of

Figure 4.7 Assessment of the Polymer-scaffold Interactions and Polymeric Structure.
gained sufficient mobility to initiate the cross-linking reaction and thermodynamic changes.

Furthermore, the bond energy of the system and resonance stabilization energy decreased by bond stretching, bond-angle deformation, and polymer-salt interactions increased the internal energy and entropy of the system. As molecules increased the internal energy and entropy, the PLA nanocapsules increased the bond energy of the system and resonance stabilization energy. Furthermore, entropy changes also occurred as a result of bond formation that enhanced by the increase in the free energy attributable to a gain of electron energy.

Figure 4.7 demonstrates the enthalpy changes due to various polymer-salt interactions during salting-out of PLA. The enthalpy of the PLA nanocapsules was calculated with the combination of NaCl + CaCl₂ + Na₂CO₃, respectively.

Figure 4.8: Thermal Transitions within the PLA nanocapsules.
Figure 4.6: Differential Scanning Calorimetry (DSC) profiles of native and salted-out PLGA

Transition point occurred in the temperature range of 40-47°C, which essentially described the glass
transition.
molecules.

Ca²⁺ led to an increase in the number of voids within the scored untreated by water
restricted by contacts of water molecules within the matrix. The large ionic radius of
within the polymeric matrix. Thus the dynamic activity of PLA chains may be
change in θσ is observed with a 10% increase or decrease in the water content
degree of Tg depression. Kelly and co-workers (1987) reported that a significant
radius and thus depress the Tg. The size of ions (A⁺ > Na⁺ > Ca²⁺) determined the
depending on the type of salt employed, water can be trapped within the polymeric

<table>
<thead>
<tr>
<th>Tg (°C)</th>
<th>mpc (°C)</th>
<th>Tg poly (°C)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.82</td>
<td>270.10</td>
<td>233.85</td>
<td>E</td>
</tr>
<tr>
<td>43.35</td>
<td>166.54</td>
<td>343.04</td>
<td>D</td>
</tr>
<tr>
<td>42.64</td>
<td>315.30</td>
<td>280.00</td>
<td>C</td>
</tr>
<tr>
<td>41.79</td>
<td>148.30</td>
<td>285.81</td>
<td>B</td>
</tr>
<tr>
<td>41.16</td>
<td>384.85</td>
<td>380.30</td>
<td>A</td>
</tr>
</tbody>
</table>

Table 4.5: Thermal parameters of native and self-assembled PLGA employing DSC

Formulation between 41.0-43.0°C.

Re-crystallization and further decomposition of the polymeric-salt complex took place
significant reduction from native PLGA that made a melting point range of 260-300°C.
respectively. The melting point range of PLGA occurred was 140-150°C which was a

In figure 4.6-e a step transition from glassy to rubbery state on the heating cycle

Table 4.3 lists the significant parameters obtained from analysis of the DSC profiles.
In general, the degree of bond formation in the PLA backbone demonstrated by properties were confirmed by textural profile analysis, SEM, DSC and FTIR studies. The PLA scaffold with superior physicochemical properties, these superior properties proved to be suitable in transforming the structure of native PLA into a modified poly-lactic acid (PLA) system. The monovial, divergent and isovial logic scales employed in the study validated demonstrated the reliability of the selected statistical design for experimental optimization. The close correlation between the experimental and predicted (fitted) response values confirmed the reliability of the selected statistical design for experimental optimization.

4.5. Concluding Remarks

was consistent in the findings of this study as well. Induced shorter and free chain ends that disarray the crystallinity of the matrix. This implies solutions would depress the $T_g$, which may be attributed to the crystallinity formation and co-workers (2005) demonstrated that no precipitation of polymers from hydrogen free energy on the solute size and shape. Moreover, work done by co-workers (2004) have yielded verification on the dependence of polymers. This results held a lower $T_g$ of 40.9°C. Studies by Paul et al., and convoluted, Na⁺ and Al⁺ ions decreased the number of voids, hence PLA

Conversely, Na⁺ and Al⁺ ions decreased the number of voids, hence PLA
The following study in Chapter Five is to identify the in zero-order release kinetics. The following study in Chapter Five is to identify the in bonds formed between the drug and PLA during cross-linking ultimately leading to show potential to be used for control the rate of drug release as a result of strong properties of native PLA into a novel scaffold with superior structural integrity that PLA can significantly modify the physicochemical and the physicochemical.

This study has also demonstrated that skeleton and subsequent cross-linking of the PLA scaffold in rate-modulated drug delivery.

Formed hydrolytically degradable PLA cross-links present a possible application of vibrational intensity transitions from FTIR studies in combination with the newly
Scalpels

In Vitro Drug Release Studies of Melatonin-Loaded PLA

Chapter Five
Figure 5.1. Flow diagram displaying the main types of controlled drug release systems

The PLA scaffold formulated in the study is envisaged to behave in a
manner that is mostly passive pre-programmed system.

However, some controlled release systems may behave slightly different from the
pre-programmed and active self-programmed systems illustrated in Figure 5.1.
Three main types of drug release systems are studied, namely passive pre-programmed, active pre-programmed, and active self-programmed systems. It is important to consider the direction of action of the biocidal agent and the type of drug release system. The features of the system, such as sustained, sustained-release, and immediate-release, are essential.
The role of dissolution studies in pharmaceutical science includes:

1. To assess the need for further bioequivalence (BE) studies relative to minor dissolution rate.
2. To characterize or compare different batches of drug substances using the in vivo dose dumping.
3. To control bioavailability and avoid the possible risk of toxicity that result from the specifications of the device depends on its dissolution.
4. To provide process control and quality assurance.
5. The assessment of batch-to-batch quality, where the performance screening formulations during development.

In general, temperature and media composition affect the dissolution rate of a solid. Where the dissolution rate is defined as the quantity of active ingredient in a solution that dissolves with relativity low solubility enters into a solution in the presence of a solvent. Dissolution is defined by Amhill and Sandmann (2003), as the process by which a solid drug is evaluated. The best formulation and the bioavailability of the drug (Dave et al., 2004).

In order to understand the effect of polymers modifications on dissolution and characterization of controlled release drugs, the theory of dissolution needs to be considered. Dissolution studies remain the most frequently used tool in the development and characterization processes of controlled release devices. During the formulation of controlled drug release, the theory of dissolution needs to be considered. Dissolution
Full understanding of the drug, the incorporated salt and the polymeric properties
ability to predictively control the process of dissolution and drug release lies in the
as outlined in Chapter Three. In salted-out and cross-linked OH-polyesters, the
degradation process followed by a decrease in molecular mass and matrix erosion,
in physiological media, PLA undergoes chain cleavage, the initial step in its
depending on the design of the polymer to match its application
dissolution of PLA. Degradation can be varied between weeks and months
MDT) and the drug release kinetics (k) were determined and optimized. During
environmental influence (DEE) into the PLA scaffold, the mean dissolution time
employed in the modification process was also explored. In addition, the drug
pre-programmed manner as illustrated in Figure 5.1, and the influence of the salt
scintisks were evaluated with respect to their ability to release medication in an acute
in the section, salted-out and subsequently cross-linked melatonin-loadeded PLGA
formulations that may affect in vivo performance of the device.
addition, in vitro dissolution studies should be able to detect the least variations in
temperature and pH of physiological fluids, as well as the drug release rate. In
device in vivo, as this is able to mimic specific parameters that include the
vivo models of the physiological media is fundamental to the applications of the
delivery device's performance in vivo and in vivo. The efficient development of in
dissolution and drug release studies are therefore, the key predications of a drug
Yu et al., 2006)
2006; Kühn et al., 2005; Pancrazi et al., 2006; Wei and Lemberg, 2006;

Yu et al., 2006;
as upon environmental factors such as temperature, pressure, and the pH of the
modifying polymer. The salts incorporated, the drug within which it is immersed, as well
be affected by the physicochemical and the physical-mechanical properties of the
Furthermore, dissolution and drug release from a saline-cross-linked device will

between the key processes of swelling, erosion, and dissolution.
In these processes to operate synchronously, thereby allowing a balance
erosion remain the prime factors in controlling drug release. The ideal polymer would
Alternatively, a programmed release system is sought, for which swelling and
cannot occur at the end of drug release.
properties that promote the attainment of retarded swelling and erosion as well as
dissolution, a polymer should have inherent physicochemical and physical-mechanical
can easily escape from the device by diffusion. And the basic features required for
between the polymer chains. Drugs with lower molecular masses such as melatonin
Diffusion is when a drug passes through the pores of a polymeric matrix without

erosion becomes a key causal factor to drug release (Kurzis et al., 2005).
Polymeric matrix. In the case of drugs with higher molecular masses, polymer
released from drug delivery devices by diffusion through hydrogels poses within the
a device include diffusion, swelling, erosion, and degradation. The drug may be
During dissolution, the principal mechanisms by which devices are released from
variables, and how each of them affects the rate of drug release.

(Hele et al., 2005). Thus, one may envisage the interplay in between these
124

In PEG-A device, the release of a drug may take place by:

2003.

According to the type of cells located in the polymeric matrix and the drug there, the polymer degradation will vary in such systems. Degradation of the PLA device and the drug release will vary.

Hydrogels, which show the dissolution of the polymer and release drugs. Thus, the structure of the polymer as the matrix dissolves, the scaffolds and the polymer completely dissolve, and the polymer matrix is then replaced by the drug solution. When external or internal changes, such as temperature or pH, the drug is released from the matrix.
Melatonin one hour before bedtime is usually effective for insomnia, although doses
minimized with a high first-pass metabolism (Chernia et al., 2005). A dosage of 3 to
Melatonin is metabolized in the liver and its elimination half-life (t1/2) is 2 to 4

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td></td>
</tr>
<tr>
<td>Molecular mass</td>
<td>232.26 g/mol</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C19H18NO2</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>Melatonin</td>
</tr>
<tr>
<td>Biological activity</td>
<td></td>
</tr>
<tr>
<td>Solubility at 25°C</td>
<td></td>
</tr>
<tr>
<td>Melting Range</td>
<td>31.5°C</td>
</tr>
<tr>
<td>Low solubility in water</td>
<td></td>
</tr>
<tr>
<td>Photochemical stability</td>
<td></td>
</tr>
<tr>
<td>Interacts with reactive oxygen and nitrogen</td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>Below 2°C</td>
</tr>
<tr>
<td>Amphoteric and chemical stability</td>
<td></td>
</tr>
</tbody>
</table>

Below 2°C, amphoteric and chemical stability are lost. Above 2°C, solubility decreases and chemical stability is lost.
group in C's prevents methionine from exhibiting pro-oxidative activity (Kato et al., 2007).

2007; Yaseu et al., 2007). The methionine in the N=C=O structure is necessary for methionin to form the new free radical, which is the key group for methionin to scavenge the second reactive free radical species. The C=O double bond is the main functional group. The carbonyl in the N=C=O is the activation energy barrier towards free radical reactions. The N=C=O structure in the activation energy barrier towards free radical reactions. The N=C=O structure in the methionin molecule. However, the major scavenging action can be attributed to the indole moiety due to its higher resonance stability and very low groups in the methionin molecule. However, the major scavenging action can be attributed to the indole moiety due to its higher resonance stability and very low.

The amide and methional side chains are significantly active scavenging chemical.

Scavenger in the Treatment of Neurodegenerative Disorders

6.2.1 Structure-Function Relationships of Methionin as a Free Radical

... radicals that are deleterious to neurons, as mentioned in Chapter One. Factors, including the cytokines and tumor necrosis factor (TNF-α) produce free radicals, which are a contributing factor to neurodegenerative diseases. These microglial-produced inflammatory and neurotoxic factors produce reactive oxygen species. Furthermore, studies have demonstrated that the neurotransmitter chemical structure. Furthermore, studies have demonstrated that the neurotransmitter and free radicals that include ·OH, H₂O₂, and NO, attributable to its conjugation and scavenging abilities. There is evidence that methionin has the capacity to scavenge numerous antioxidants properties and there is evidence that it may help strengthen the immune
neurodegenerative disorders. The in vivo drug release studies and optimization of implant employing the PGA scaffolds loaded with melatonin in the treatment of Klionel et al. (2002). Therefore, the objective of this study was to develop a novel melatonin, it is not available in therapeutic amounts to cross the blood-brain barrier, melatonin (6-STM) after oral administration. Due to the first pass metabolism of melatonin, (6-STM) is promptly metabolized to 6-subphloroglucinol. However, it has a very short half-life and is poorly metabolized to 6-subphloroglucinol. Oxidative and anti-inflammatory properties (D'Agostino et al. 2007; Quittet et al. 2007) make melatonin a good candidate for use in neurodegenerative disorders. The melatonin molecule has the potential to scavenge up to 4 or more free radicals. This scavenging cascade reaction of the melatonin class due to its cascade, one known intermediate generated by the interaction of melatonin with reactive species unlike classical antioxidants, melatonin is devoid of pro-oxidative activity and all...
Although PLA has been investigated for the controlled release of drugs, most studies have involved nano- and microparticle formulations and the efficiency of the drug-loading entrapped by the device during syntheses. Thus, attaining more higher and consistent PLA scaffold, one can improve the percentage of drug particles that can be evaluated the effects of formulation parameters on the DE of the hydrophobic device; may influence the DE of a polymeric device (Pelfrene et al, 2004). By concentration of salt, along with the method by which the drug is loaded into the scaffold, several parameters, such as the type and quantity of model drug, the type and size of the scaffold.

6.4 Determination of the Drug Entrapment Efficiency (DEE) of the PLA

Wimber, USA

on the DEE, WD and k of the PLA scaffolds, using MATLAB, (V14), to establish the main and interaction effects of the independent formulation variables in order to model the number of experiments needed for formulation optimization and study a 3 factor, 3 level randomized box-benken statistical design was constructed. The independent formulation variables may affect DEE, MDT and k

6.3 Developing the Experimental Design:

delivery implant for treatment of neurodegenerative diseases.

melatonin-loaded PLA scaffold was performed in order to pursue its use as a drug
Interacting formulation variables. Statistical software is employed to perform optimization techniques allowing one to investigate associations between the factors involved. The application of a statistically designed experiment for parameters concurrently, without having to examine all possible combinations of the parameters, allows for the investigation of the effects of process and drug release kinetics of the PLA scaffold.

6. Optimization of the Drug Entrapment Efficiency, Mean Dissolution Time, and Pore Concentration

concentration used in the swelling-out and subsequent cross-linking of PLA. The PLA scaffold. The DEE was explored by changing the shell type and the PLA scaffold. The DEE was explored by changing the shell type and the aim of this study was also to increase the melatonin entrapment efficiency into blending of the polymer and the drug solutions before and during swelling-out. One of the solvents used to dissolve PLA (Kreiner et al., 2002). This, therefore, facilitated the drug, melatonin has low water solubility (3.74·10^-3 mg/mL) and easily dissolves in phase thus becoming excluded from the polymeric device. In this study, the model week, the drug tends to migrate from the polymeric organic phase to the aqueous phase. Furthermore, during swelling-out, the interactions between the drug and polymer are

Governer et al., 1999.

hydrophobic drug substances and the hydrophobic polymer (Bancroft et al., 1999).

challenging than that of hydrophilic drugs. Due to the lack of affinity between the hydrophobic drugs in PLA nano- and microparticles has been found to be less stable. Particles in porous PLA scaffold has not been adequately ventured. DEE of methods in encapsulating drug within these particles. The entrapment of drug
2002.

fundamental activity during the design of contoured drug delivery systems (De et al., 1996). Kiemeny and mathematical models to predict drug delivery is a significant and constitutes the mechanistic operation of the PLGA scaffold. The development of

ecission were analyzed with relevant mathematical and statistical models in order to

software v.7 (Pharsight, S.A.), kinetics of drug release, namely, swelling and


was used in the paper (Koskenmayer et al., 1995; Papper, 1995; Pandolfo et al.,

characterize the drug release mode from the PLGA scaffold, the experimental data

systems including diffusion, swelling, and erosion controlled release, in order to

Several mechanisms have been elucidated to describe drug release from polymeric

PLGA scaffold

6. Kinetic Modeling to Determine the Drug Release Mechanism from the

variance (ANOVA) (Minitab6 Statistical Software, v.14, Minitab, USA). of drug released as a function of time were validated utilizing the analysis of
drug entrapped efficacy (DEE), the mean dissolution time (MDT), and the quantity

ANOVA, employing the REGRESS approach (Laddar et al., 2006). In this study, the

common technique used for solving constrained optimization problems is the

are varied to guide the selection of new trial values (Ayaz et al., 2006). The most

extensive analysis of the observed curvatures and their rates of change as the inputs
evaluate the response as conducted in Chapter Four of the study.

A statistical model incorporating interaction and polynomial terms was utilized to
variables. The DEE, MD, and A were selected as dependent formulation variables.
Levels of N, CaO, AlCl3, and SiO2 were selected as independent formulation
variables. Experimental trials were performed at all possible combinations. The
levels and experimental trials were evaluated, each at 3 levels. Analysis of variance
was used to model the number of experiments needed for formulation optimization and to
establish the main and interaction effects of the independent formulation variables on
the physicochemical and physicotherapeutical properties of the PFLA scaffolds using

5.7.2 Building the experimental design

Table <ref>Table 1</ref> shows the experimental design and results. All the materials and
methods were used to determine the optimum conditions for the formulation optimization.

Materials and Methods

5.7 Materials and Methods
signal (the instrument or detector response) as a function of analyte concentration. In part, upon the calibration technique used. A calibration curve of the analytical determination of melatonin release from the PLGA scaffold.

5.7.4 Preparation of a Calibration Curve for the Spectrophotometric Equilibrium prior to physicochemical and physicochemical evaluation. Each PLGA scaffold was stored for 48 hours at 20°C and weighed. Each PLGA scaffold was added to 50 ml of a unique solution containing 2% or 0.1% of either NaCl, CaCl₂ or AlCl₃ was added to the polymeric solution and agitated for a period of 30 minutes. The resultant PLGA scaffolds were removed from the cross-linking solution and coagulated by adding 4.9 g of PLGA and 10 mg melatonin dissolved in 15 ml of acetonitrile. The complete outline in Table 4.1 Chapter Four: Fourteen Polymers were prepared by tailoring and subsequent cross-linking using a combination of acetonitrile and ionic solvents in accordance with a Box-Behnken design. PLGA scaffolds were prepared by settingoutil and subsequent cross-linking using a combination of acetonitrile and ionic solvents in accordance with a Box-Behnken design. PLGA scaffolds were prepared by settingoutil and subsequent cross-linking using a combination of acetonitrile and ionic solvents in accordance with a Box-Behnken design.

<table>
<thead>
<tr>
<th>Melatonin (mg)</th>
<th>10</th>
<th>10</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>% NaCl</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>% CaCl₂</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>% AlCl₃</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5.2: Factor Levels of the Independent Formulation Variables

<table>
<thead>
<tr>
<th>Upper</th>
<th>Middle</th>
<th>Lower</th>
</tr>
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</table>

Variables
Equation 5.8
\[
\text{DEE}\% = \frac{\text{Mass of drug loaded in formulation \times 100}}{\text{Mass of drug in scaffold}}
\]

Calculated utilizing Equation 5.8.

Duplicate using UV-spectroscopy at 278nm. The DEE percentage was then calculated using UV-spectroscopy at 278nm. The DEE percentage was determined in complete dissolution of the scaffold. Therefore, melanin content was determined in DEE studies were performed by immersing each scaffold in 100ml acetonitrile to effect 5.7 Drug Enzymatic Efficiency of the PLGA Scaffolds

Substituted in the y value (response) and we solved for x. The linear least square regression analysis was used. From the equation y = mx + b we plotted graph at the 278nm absorption peak. In order to determine the best-fit straight line, linear regression analysis was used. The calibration curve of absorbance measured at 278nm absorption peak of melanin in PBS was constructed. The absorbance of melanin was determined from its Beer’s law, the concentration of a melanin in solution was determined from Lambert – Beer’s law. The Lambert – Beer’s law states that the absorbance (A) of an absorbing species in a solution is directly proportional to the path length (c) through the solution and the concentration (c) of the absorbing species. Thus, the higher the concentration of the absorbing substance is, the higher is the absorbance in accordance with Lambert – Beer’s law, the concentration of melanin in solution was determined from Lambert – Beer’s law describes a relationship between concentration and absorbance. The Lambert – Beer’s law describes a relationship between concentration and absorbance. Series of standards of known concentrations of PLGA scaffold at each time interval. It was obtained by measuring the signal from each
DEE, MDT, and K.

The identification of potential drug delivery systems requires the development of mathematical models and the use of experimental data to optimize the design parameters. The DEE, MDT, and K. models are employed to evaluate the drug release mechanism from the PLGA scaffolds. The DEE approach is used to determine the release rate constant, while the MDT model is employed to predict the cumulative release over time.

5.7.2 Statistical Optimization

The statistical analysis of the dissolution data was performed using ANOVA (Minitab, Minitab Software, V14, Minitab, USA). The model-independent analysis, known as the time-point approach, briefly, the mean dissolution time set at 30 days (MDT). For each formulation, the dissolution was calculated. The dissolution data was subjected to a statistical analysis using SPSS (IBM, SPSS GmbH, Germany) 19.1. The drug release studies were conducted in 10 mM phosphate buffered saline (pH 7.4) at 37°C at 50 rpm. The dissolution assays were performed with UV-spectrophotometry.

Drug release studies were conducted in 10 mM phosphate buffered saline (pH 7.4) in vitro. Drug release from the PLGA scaffolds...
where

\[ \frac{M}{M^0} = \left( \frac{t}{t_f} \right)^{-k} \]

Peppas equation (equation 5.1) is an exponentially determined kinetic constant and

- \( M^0 \) is the fraction of drug released up to time \( t \);
- \( M_s \) is the drug loading;
- \( M \) is the quantity of drug released at time \( t \);

Drug release mechanisms are complex phenomena. In order to characterize the

(8) The Power Law Equation

mathematical expressions, PLGA Scafold formulations were fitted into the following phenomenological
dependence of fluid infiltration and drug release, in which drug release data of the
mechanisms from the melolithin-loaded PLGA scaffolds and to predict the time-
purpose of this section of study was to explain the principal drug release
number may be applied to experimental data to predict such parameters. The
Power Law and its variants, Houbenbery, Swelling Inherence, Number and Deborah
\[ M'/M = K' + k_p^2 \]

Equation 5.4

This equation is used, as illustrated in Equation 5.4, for Fickian diffusion and matrix relaxation, the expanded version of Power Law.

Equation 5.3

\[ M'/M = K + b \]

In the case of a burst effect, b (Kirm and Passhill, 1996), Equation 5.3 may be used.

The Hughes equation expresses a diffusive release mechanism.

Equation 5.2

\[ M'/M = K - C_t^2 \]

This Hughes equation (Equation 5.2) may be used in the case of a delay in release or lag time (C_t) in a highly cross-linked polymer.

Equation 5.1

\[ v = n \cdot k \cdot (N - 1) \]

is the release exponent with n = 1, 2, 3 for a slab, cylinder or sphere respectively.

- \( k \) is the relaxation/dissolution rate constant and
- \( k' \) is the Fickian kinetic constant.

Where:

Equation 5.5

\[ r = K' + k_p^2 \]

For Fickian diffusion and matrix relaxation, the expanded version of Power Law.
release behaviour. Franson and Penpas, 1982, studied the physical conditions that
The Swelling Interface Number is generally calculated to determine the swelling and

(c) The Swelling Interface Number

indicates an erosion-dependent release mechanism.

as drug particle size, do not affect the release kinetics. In addition, this model
The Hopfenberg model assumes that time-dependent diffusional resistances, such

1/2
-\( r_0 \) is the initial radius for a sphere or cylinder of the half-thickness of a slab.
-\( C_0 \) is the uniform initial concentration of drug in the polymeric matrix and
-\( k_r \) is the erosion rate constant.
-\( k_{D,C} \) is the diffusion rate constant.

Where

\[
\frac{M/M_0}{W/M_0} = 1 - \exp\left(-k_r t\right)
\]

Equation 5.5

expression (Equation 5.5).

polymers in the form of slabs, cylinders, or spheres, which exhibit heterogeneous
polymers. This model also known as Hixon-Crowell equation was developed for
the diffusional and relaxational contributions during solute penetration or sorption in
Hopfenberg model (Hopfenberg, 1976), which allows for the differentiation between
The erosional behavior of the cross-linked PLA scaffold can be analyzed with the

(q) The Hopfenberg Model
$K_0$ is the erosion rate constant.

$D$ is the drug diffusion coefficient in a matrix.

Where,

\[ \text{Deborah number} = \frac{D_t}{\lambda} \]

and \( \lambda \) is the relaxation time of the polymer. The polymer behaves as an elastic solid if the Deborah number is less than 1. When the Deborah number is greater than 1, the polymer behaves as a purely viscous fluid. For \( D_t = 10 \) (1 divided by 1/100), when \( D_t \) is 100, the Deborah number might be 0.1 and the shear rate 100/3.

Swelling of PLA scaffolds can also be analyzed by consideration of the Deborah number.

\[ \text{Deborah number} = \frac{D_t}{\lambda} \]

This dimensionless number compares the mobility of the solvent front relative to drug mobility in the presence of polymer relaxation.

\[ D_t = \frac{D}{\text{time dependent viscosity}} \]

Swelling Interface Number SW (Equation 5.6)

Influence the kinetics of drug release from swellable matrices and introduced the
Equation 5.9

\[ \text{SBC} = k \ln(n) + \frac{k}{2} \ln \left( \frac{RSS}{n} \right) \]

BIC becomes Equation 5.9 if employed.

Under the assumption that the model errors or disturbances are normally distributed, \( L \) is the maximized value of the likelihood function for the estimated model in regression, \( k \) is the number of regressors including the constant and \( \bar{k} \) is the number of free parameters to be estimated. If the estimated model is linear

\[ n \] is the number of observations equivalently, the sample size.

Where,

Equation 5.8

\[ \text{SBC} = \ln(n) - 2 \ln L + \bar{k} \ln(n/2) \]

\( \sigma^2 \) is a bias towards more parsimonious specifications. The SBC is given by:

us a bias towards more parsimonious specifications. They incorporate a penalty for a large number of parameters, which gives estimation. They incorporate a penalty for a large number of parameters as well as the number of free parameters in functions of the log likelihood values as well as the number of free parameters in the likelihood function of the estimated model. The AIC and SBC are based on the log likelihood value at the estimated vector. The AIC and SBC were compared. These statistics are in order to explore the nature of predictability of the model. The Akaike Information Criterion.

\( \bar{k} \) is the inner radius of the scaffold.

\( \sigma^2 \) is the outer radius of the scaffold.
Figure 5.3: Melatonin calibration curve at 278.2 nm in PBS (pH 7.4) (SD, within ±0.04%)

Achieved over the concentration range from 0.2 mg/ml to 0.93 mg/ml. Melatonin demonstrated linearity in phosphate buffered media (pH 7.4) at 37°C. The regression coefficient, R² = 0.9983 for the calibration curve generated.

Results and Discussion

BIC penalizes false parameters more strongly than does the AIC. The decreasing function of RSS, the goodness of fit, and an increasing function of k, the number of parameters, the smaller the BIC is the better the model is. The lower value of BIC is the one to be preferred. The SBC is a measure of relative information from the estimated model in any given

Where, RSS is the residual sum of squares from the estimated model in any given
particles due to the fiber structure and the pore morphology of the matrix. Micronenvironment may enhance or reduce the ability of the scaffold to entrap drug evidenced in the PLGA micrographs shown in Figure 4.2. Furthermore, the nature of the cross-linking may influence the architecture of the PLGA scaffold matrix. This was demonstrated how the physicochemical nature of the gel used in salting-out and salting-out and subsequent cross-linking has been demonstrated earlier in the study. Processes, an average DEE of 90% was achieved. The type of salt used during cross-linking, when NaCl and AlCl3 were employed in the salting-out and cross-linking employed. When CaCl2 was employed, an average DEE of 55% was achieved. DEE varied between 45-90% depending on the type and concentration of the salt.
Materials ranging between 0.03-1.40μm, along with fiber volumes ranging from 25 to 4.26 μm², were characterized in a network-like meshwork (Figure 4.2, to 4.2E). Porous and fiber networks of microporous structures that maintained homogeneity of cross-linked scanning electron micrographs in Figure 4.2, N, O, C, and Al produced higher contrast to the dense surface morphology of the scaffolds as revealed in the electronic micrograph. The enhancement of the DEE demonstrated by the profiles in Figure 5.4 also.

Figure 5.4. Plot depicting the differences in the DE of the scaffold and cross-linked PLA scaffolds.

% Drug Entrapment
and AIC’s and higher values in scaffolds excised with CACl₂. To be between 0.004 and 0.38, the lower values in scaffolds excised with NaCl calculated using the power law M(t) = Ktⁿ, where K is the kinetic constant was found and AIC’s. Fractional drug release (M(t)/M∞) and the drug release kinetics were (Table 5.3). The lowest M(10)∞ was demonstrated in scaffolds excised with NaCl scaffolds also demonstrated a mean dissolution time at 30 days (M(10)∞ of 6 to 26 period of 30 days.

and subsequently cross-linked with CACl₂ had more than 75% drug released over a 20% melaltonin over a period of 30 days (Figure 5.2c). Whereas scaffolds excised with NaCl and AIC’s were able to achieve up to less than 50% characterization of the in vivo drug release from the PLGA scaffolds Table 5.3 and the release profiles revealed that the scaffolds excised with NaCl scaffolds.

5.8.2 Characterization of the in vivo drug release from the PLGA scaffolds that created larger pores reduced the DEE. More uniform pores, such as NaCl and AIC’s etched more drug particles, whereas that scaffolds that tend to produce a more compact polymeric structure with minor and minor volumes of 14,000 μm³. In general, melaltonin is a small drug molecule such composite PLGA scaffold with interconnected channels and pores as large as 10 μm. The divergent salt CACl₂ was demonstrated in Chapter Four produced a smaller
release of medetomidine deposited on the surface of the scaffolds. The rate of melatonin
steady diffusion of release. The initial burst may be attributed to the rapid
melatonin release model. Firstly, an initial burst was observed, followed by a slower
in general, the melatonin release profiles of all the scaffolds displayed a biphasic

<table>
<thead>
<tr>
<th>Release Date</th>
<th>Release %</th>
<th>Release Date</th>
<th>Release %</th>
<th>Release Date</th>
<th>Release %</th>
<th>Release Date</th>
<th>Release %</th>
<th>Release Date</th>
<th>Release %</th>
</tr>
</thead>
</table>

Formulations

**Plga**

The release constant (K) of the Plga scaffolds

Table 6.3. The drug release at 30 days (%), Mean Dissolution Time (MDT) and
cross-linked with other salts such as CaCl₂.

The same functional groups and the aqueous environment in polymer molecules
the same effective collision rate at which chemical reactions are carried out between
shielding and colliding of polymeric reaction sites which prevented the maintenance of
self- and subsequently cross-linked with NaCl and AlCl₃, PFOA occurred due to
between the drug and polymers chains. The slow diffusion of melatonin from PFOA
significant rates in controlling the rate of drug release due to the strong interactions
This study demonstrated that the different types and concentrations of salts have

controlled the mechanism and rate of drug release through the incorporation of salts.
concentration of the salts. Swelling-erosion kinetics were manipulated in order to
malleable and influenced by a large number of factors such as the type and the
with biodegradability. Thus, the drug delivery kinetics of these scaffolds was
Thus this system combined the advantage of long-term consistent rate drug release
in the PFOA matrices were released as the polymer chains melting and degrading.
Degradation that resulted in the release of the drug. Melatonin molecules dispersed
Subsequently, all the PFOA scaffolds went through a process of erosion and
salt employed during wall-cross-linking and subsequent cross-linking of the scaffold.
release during the diffusion phase was influenced by the type and concentration of
Figure 6.5. Release profiles of melatonin from the PLA scaffolds (a) Formulations 1 and 2.

(a) Formulations 0.4.

(b) Formulations 1.4.

(c) Formulations 2.4.

(d) Formulations 3.4.

(e) Formulations 4.4.

(f) Formulations 5.4.

(g) Formulations 6.4.

(h) Formulations 7.4.

(i) Formulations 8.4.

(j) Formulations 9.4.
The opposite is true for AlCl₃ concentrations. AlCl₃ concentrations between 0 and 5% decreased DEE, whilst 5% increased DEE, which is shown in Figure 5.6c. However, concentrations between 5 and 10% increased DEE above 70%, shown in Figure 5.6c. The decrease in DEE concentrations between 0 and 5% did not show a significant effect. The lower concentrations of NaCl and CaCl₂ had no statistically significant effect. AlCl₃ concentrations did not significantly affect the DEE. Figure 5.6a demonstrates that NaCl concentrations increased in NaCl concentrations as shown in Figure 5.6a and b. On the other hand, NaCl concentrations were higher at lower concentrations of NaCl and were significantly decreased with the characteristic of the PLGA scaffolds. Figure 5.6a-d demonstrates that DEE was demonstrated the influence of the scaffolds on the mean dissolution and the drug release. Response surface plots (Figures 5.6, 5.7 and 5.8) were constructed to visually demonstrate the influence of the scaffolds on the mean dissolution and the drug release. Response surface plots (Figures 5.6, 5.7 and 5.8) were constructed to visually demonstrate the influence of the scaffolds on the mean dissolution and the drug release. The drug easily diffused from the matrix to the outer phase. That were less compact with more porous polymeric matrix structures, through which the drug easily diffused from the matrix to the outer phase. The type of salt used in solubilizing and subsequent cross-linking of PLGA was
of the PLA scaffold.

DEE, k, and MDT may be influenced by the type of cell employed in the formulation caused increased drug release. This study has demonstrated that factors such as general, these plots demonstrate that the presence of CaCl₂ in the scaffolds resilience as well as volumetric polymer fibers with larger pore sizes and decreased fiber architecture and smaller pores. CaCl₂ produced scaffolds with a decreased absorbed and deformation modulus of the PLA scaffolds as well as a matrix with four, where NaCl and the Alk minimized an increase in resilience, energy are in close correlation with the results of the previous studies outlined in Chapter NaCl concentration increased MDT only at lower Alk concentrations. These results demonstrated in Figure 5.65 CaCl₂ concentrations increased linearly with a which any further increase of NaCl (above 5% w/v) resulted in a decreased k value. (between 0 and 5% w/v) significantly increased the value of k to a limit of 0.225, at 0.25. In Figure 5.67, when combined with Alk, at lower NaCl concentrations the increase in NaCl concentration caused an increase in the rate constant as shown Figure 5.64). Revealed that in scaffolds soaked with a mixture of CaCl₂ and NaCl.
Figure 56. Surface response plots depicting the effects of the independent formulation variables on the drug extravasation efficiency (DEE) (%). In each cell, our PLA scale is AC = 0, 5%, 10%, 20%. SC = 0, 5%, 10%, 20%. CC = 0, 5%, 10%, 15%.
Figure 5.7. Surface response plots depicting the effects of the independent formulation variables on the release constant (k) of the slow-release PGLA spheroids. AC = A1C4, CC = C1C4.
sustained drug delivery of melatonin by the PLA implants.

These results suggested that NaCl and AICl are significant for the controlled and

\[
\frac{CC}{CC} = \frac{CCE}{CCE} = N CE \cdot 1 = 100 \%
\]

Figure 5.8. Surface response plots depicting the effects of the independent formulation

variables on the mean dissolution time (MDT) of the selected PLA scaffolds AC = AICl.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>0.005–1.00%</td>
</tr>
<tr>
<td>DEE</td>
<td>0.000–1.00%</td>
</tr>
<tr>
<td>MDT</td>
<td>0.0–10%</td>
</tr>
<tr>
<td>AIC</td>
<td>0.0–10%</td>
</tr>
<tr>
<td>CAC</td>
<td>0.0–10%</td>
</tr>
<tr>
<td>NDCI</td>
<td>0.0–10.0%</td>
</tr>
</tbody>
</table>

Ideal scaffold would achieve zero-order release. scaffold would permit a DEE of 96%, MDT and K were calculated in order that the desired data are depicted in Figure 5.4 DEE was calculated such that the ideal responses were found to be attributable to the type of set optimal responses for the formulations. The effects on formulation optimization by MINITAB® (V14, Minitab, USA) was conducted to Formulation Optimization Time and Drug Release Kinetics of the PLA Scaffold.
a controlled drug delivery scaffold for the treatment of neurodegenerative disorders. Zero-order release formulation release rate, with no dose dumping, in order to be employed as responses were selected such that the optimized scaffold would be able to achieve a slow release scaffold. The excluded in the formulation in order to achieve a slow release scaffold. The DEE of 96%, NDT of 1, and a k of 0.050 would correlate lower concentrations of predictions of the statistical design, the ideal scaffold that would permit an optimal The settings for a desired response were illustrated in Table 5.4. According to the required to produce a desired response that will give an optimal PLA scaffold.

Figure 5.5: Optimization and Desirability Plots Illustrating the Type and Concentration of salt.
Figure 6.10. Melatonin release profile of melatonin from an optimized PLGA scaffold.

Table 6.5. Desired and experimental responses for the optimized PLGA scaffold.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Desired Response</th>
<th>Experimental Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>0.05-1.00</td>
<td>0.032</td>
</tr>
<tr>
<td>%</td>
<td>95%</td>
<td>6.5</td>
</tr>
<tr>
<td>%</td>
<td>0.80-1.00</td>
<td>0.80-1.00</td>
</tr>
</tbody>
</table>

The optimized formulation demonstrated 30-day zero-order kinetics for in vitro drug release studies from the optimized PLGA scaffold.
In the release kinetics with the exception of highly porous matrices such as NACL and ALG, it appears that the drug diffusion process did not play a significant role. The release matrix with minimal swelling such as the cross-linked and porously modified with sodium alginate showed a less porous, more compact scaffold was either highly porous, less compact, swelling and a higher release matrix such as those released from the scaffolds. Drug release kinetics from PLAGA scaffolds shows that in the first 180 days, however, erosion was the significant mechanism in releasing drug diffusion through the matrix layer by a Fickian release mechanism (Fickian and non-Fickian).

Theoretically, the primary drug release mechanisms from PLAGA scaffolds should be the

5.6.6 Kinetics analysis of the Drug Release Mechanisms from the PLAGA and PEGA during cross-linking ultimately leading to zero-order release kinetics.

and PEGA following cross-linking ultimately leading to zero-order release kinetics. The rate of drug release is a result of strong bonds formed between the drug and PEGA during cross-linking and subsequent release of PLAGA can significantly control the release of melatonin from the PLAGA scaffold. This study has also demonstrated the release of melatonin from the PLAGA scaffold. The outcomes of the study have also established that low concentrations of NACL and ALG below 5% are required to

demonstrated the ability to achieve controlled drug release. The synthesized physically and chemically modified properties of melamine PLAGA and the

The scaffolding and subsequent cross-linking of PLAGA significantly modified the

The various diffusion, relaxation, and erosion modes of the optimized PLA scaffold Table 5.6 provides a summary of the important drug release kinetics obtained from

<table>
<thead>
<tr>
<th>Model</th>
<th>M/W</th>
<th>N</th>
<th>AIC</th>
<th>SCF</th>
<th>Correlation</th>
<th>K1</th>
<th>K2</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>1.6</td>
<td>3</td>
<td>3.12</td>
<td>38.16</td>
<td>0.96</td>
<td>0.52</td>
<td>0.22</td>
<td>0.96</td>
</tr>
<tr>
<td>2-1</td>
<td>1.6</td>
<td>0</td>
<td>0.25</td>
<td>36.77</td>
<td>0.96</td>
<td>0.22</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>3-1</td>
<td>1.6</td>
<td>0</td>
<td>0.25</td>
<td>46.32</td>
<td>0.96</td>
<td>0.22</td>
<td>0.96</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 5.6 Drug release kinetics obtained from the various diffusion, relaxation, and erosion models for the optimized PLA scaffold formulation.

Hydrolyzed much more rapidly than those selected with 10% NAC and AIC.
The PLA scaffold selected with 10% CA is the fastest-dissolved scaffold and were
and subsequent cross-linking of the PLA chain as illustrated in Chapter Four.
ratios of the individual salt components (NAC, CA, and AIC) used during synthesis.
release mechanism of the PLA scaffold was dependent on the type and the model
subsequent drug release rate from the PLA scaffold. Importantly, the resultant drug
that include drug diffusion, polymer erosion, polymer swelling behavior, and the
Kinetically modeling elucidated the drug release mechanisms from the PLA scaffold.

The hydrophobic scaffold matrixes, time, as it took more time for the dissolution medium front to approach the center of
PLGA is a hydrophobic polymer, the rate of drug release decreased as a function of
those selected predominantly with CA only. Since melatonin is less water soluble and
are not correlated. Therefore, this indicates an excellent fitting as well as stability of the kinetic model to statistical descriptors, namely, AIC and SBC showed values that were suitable.

The release rates analysis by means of the strong parametric analysis support from the data as the melatonin particle size.

drug release kinetics was not affected by time-dependent diffusional resistances. Drug release depended on the release mechanism from the optimized PLGA scaffold. Thus, the equation presented a release exponent values (n) of 0.95, also indelicate an erosion-erosion phenomena. Drug release was mostly controlled by the diffusion of partially swollen polymer particles. The release phenomena was mostly controlled by the diffusion of partially swollen polymer particles. Drug release was only slightly affected by the hydrodynamic stress. Thus, it was possible to define the release mechanism, which was via the polymer particle erosion. Drug release was significantly affected by the hydrodynamic stress. Thus, it was possible to define the release mechanism, which was via the polymer particle erosion. Drug release was significantly affected by the hydrodynamic stress. Thus, it was possible to define the release mechanism, which was via the polymer particle erosion.
were not affected by time-dependent diffusional resistance, such as the drug particle ranged from 0.112 to 0.563 × 10^{-2} cm²/sec. Thus, indicating that drug transport kinetics consistent. Ka ranged from 0.11 to 4.69 × 10^{-9} mm/min and the diffusion coefficient D consistent. Number values of the 14 PLA scaffold formulations. The erosion rate Table 5.7 presents the erosion rate constant, drug diffusion coefficient and the

<table>
<thead>
<tr>
<th>Drug Diffusion Coefficient</th>
<th>Erosion Rate Coefficient</th>
<th>Correlation Number for Melatonin Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.425</td>
<td>0.04</td>
<td>F14</td>
</tr>
<tr>
<td>0.215</td>
<td>0.18</td>
<td>F13</td>
</tr>
<tr>
<td>0.015</td>
<td>0.09</td>
<td>F12</td>
</tr>
<tr>
<td>0.667</td>
<td>0.10</td>
<td>F11</td>
</tr>
<tr>
<td>0.333</td>
<td>0.05</td>
<td>F10</td>
</tr>
<tr>
<td>0.427</td>
<td>0.03</td>
<td>F9</td>
</tr>
<tr>
<td>0.517</td>
<td>0.14</td>
<td>F8</td>
</tr>
<tr>
<td>1.081</td>
<td>0.70</td>
<td>F7</td>
</tr>
<tr>
<td>0.824</td>
<td>0.28</td>
<td>F6</td>
</tr>
<tr>
<td>0.34</td>
<td>0.08</td>
<td>F5</td>
</tr>
<tr>
<td>0.026</td>
<td>0.08</td>
<td>F4</td>
</tr>
<tr>
<td>0.16</td>
<td>0.18</td>
<td>F3</td>
</tr>
<tr>
<td>0.182</td>
<td>0.21</td>
<td>F2</td>
</tr>
<tr>
<td>0.142</td>
<td>0.17</td>
<td>F1</td>
</tr>
</tbody>
</table>

Table 5.7. Mechanistic predictors for melatonin release from the PLA scaffolds. &

Scaffolds Formulation (K [mm/min]) (D [cm²/sec]) Depositions
From the approach of water to the PLGA backbone, in addition, the NCL and ALG have shorter cross-linked networks that create a barrier to water. After the scaffold is dehydrated and subsequently cross-linked predominately with NCL, it is more resilient than the scaffold included and subsequently cross-linked predominately with ALG. The scaffolds cannot be differentiated based on plain light but show differences in their degradation rates. Because all of the scaffolds are comprised of degradable ether linkages, the physical and mechanical factors that also control the degradation rate of the scaffolds, the erosion rate constitutes of the PLGA scaffolds can be rationalized via the drug loss occurred.

Until the particle was sufficiently strained so as to fracture, at which time the particle, the fluid was forced to flow in front and to the sides of the rod along the scaffold, and the fracture was forced into smaller pieces, from the surface of the eroded polymer being knocked into smaller pieces. From the surface of the eroded polymer, the overall surface erosion of the scaffold, the primary mechanism, was initially deformation processes that account for each of the separate incident that result in the scaffold surface may have occurred by a combined erosion--cracking mechanism. During drug release mechanisms, the loss of polymeric material from the eroding scaffold was mainly due to erosion rather than polymeric relaxation or diffusion.
scaffolds' main drug release mechanism was through the process of polymer erosion. The erosion rate of the polymer may also have been influenced by the intrinsic properties of the PLGA polymer, demonstrating that acausalistic effects have also played a significant role. Particulary in highly porous PLGA scaffolds, many of the effects of the PLGA scaffold's morphology, porosity, and other factors affected the drug release and transport mechanisms. Thus, the PLGA scaffold, hence, porosity not only caused decreased drug mobility, but also altered the fundamental mass transport mechanisms. Suspension by the effects of the increasing diffusion pathway lengths due to porosity suspended by the effects of the increasing diffusion pathway lengths due to porosity.
Table 5.8 provides a summary of the swelling studies essential for describing the swelling kinetics of the polymer. The data in the table includes the swelling ratio (V/V) of the polymer films at different times. The table shows that the swelling ratio increases with time, indicating a kinetically driven process. The data is presented in a tabular format, with columns for time (in hours) and corresponding swelling ratios.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Swelling Ratio (V/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>8</td>
<td>0.08</td>
</tr>
<tr>
<td>10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Table 5.8: Swelling studies of the polymer films at different times.
Concentration on the in vitro melatonin release kinetics from the PLGA scaffold has influenced the physical and mechanical properties of PLGA as well as the influence of salt type and the role of scaffolding or subsequent cross-linking on the physical and mechanical properties of polymer.

Concluding Remarks

and erosion rates, thus controlling drug release.

physicochemical characteristics which provide for the attainment of slower swelling.

features of PLGA that have been attained through the use of salts are the release of the drug is released at a steady rate of not (Roy and Rohrer, 2002). Among other release, in principle, the mode of polymers and the swelling action of drug release, the extent to which the polymer-drug interactions affect the drug partition into the scaffold. Estimation of the rate of matrix swelling was mainly applied swelling of the polymers, which depend on the interaction rate of the dissolution

actions, the effect does not undergo extensive swelling and hence did not experience much of the caused considerable drug release. However, scaffolds sintered with NaCl and AlCl3 induced matrix swelling, which facilitated the hydrophilic interaction of PLGA chains and scaffolds sintered with CaCl2 had considerable water uptake into the scaffolds that and the drug properties through the solute diffusion coefficient. It was found that swelling was influenced by the presence of salt, the porosity of the polymers matrix from the scaffolds.

And penetration and polymers swelling were not the major cause of drug release. 0.027-0.15mm/sec and a S' between 0.016-0.542. The y and S' indicated that.
That result from polymer modification. Scaffolds thus permitting the manipulation and prediction of drug release parameters quantitatively described by the observed in vivo drug release patterns from the PLGA networks. In conclusion, the mathematical models used in this study enabled the differential path length for drug release increased over time with the cross-linking In addition, the cross-linking voids resulted in retardation of drug release as the than CaCl2, which-formed a barrier to the approach of fluid into the PLGA backbone. In general, scaffolds saturated with NAA and ALG had shorter crosslinked networks. The optimized formulation demonstrated less erosion, mostly steady, to a zero-order release demonstrated by degradation of the scaffolds were faster. On the other hand, scaffold saturated with predominately CaCl2 caused more drug particles to be released as erosion and mainly governed by erosion. The high porosity of the scaffold and subsequent cross-linking of PLGA Drung release from all the PLGA scaffolds was depending on the type and concentration of the self-embedded disulfide-linking the physicochemical and the physiomechanical behaviors of the PLGA scaffold. Polyvinyl for the three salt types, NaCl, CaCl2, and ALG, suggested two categories of been elucidated in the study. In Chapter Four, electron micrographs and textural
release, such as amitryptiline HCl, and explored for use in the delivery of hydrophilic drugs requiring pre-programmed and subsequent cross-linked compressed monolithic matrix systems were developed. A novel scaffold-out monolithic matrix system for further pharmaceuticals applications, a novel scaffold-out (Chapter Five), hence, in this study the PLA scaffold is adapted into a compressed monolithic matrix system (Chapter Three and Chapter Four). Thus, release mechanisms of the PLA scaffold kinetics (Chapter Three) physicochemical and physiomechanical transitions were here confirmed the authenticity of the PLA scaffold with regard to degradation and amitryptiline HCl (Meesse et al., 2002; Chen et al., 2009). In proceeding sections, control the release of both hydrophilic and hydrophobic drugs, such as melatonin, and monolithic matrices with properties that allow it to house and nanocomposites, and monolithic matrices with properties that allow it to house and the ability to be manipulated into any drug delivery device, such as scalpel.

The benefit of employing PLA, however, is that the hydrophobic polymer exhibits

6.1 Introduction

MONOLITHIC MATRIX SYSTEM
IN VITRO AMITRYPTILINE HCl RELEASE FROM A PLA COMPRESSED MODEL DRUG: AMITRYPTILINE HCl (WATER SOLUBLE)

CHAPTER SIX
based on physicochemical and physicochemical activation.

using a supramolecular linking technique; the easily swellable matrix. This method is
order to avoid the use of solvents. Alternatively, the matrix can be drug-loaded

III. The third approach is by loading the drug powder into a polymeric carrier in

interior and exterior.

main disadvantage of this method is the elimination of the solvent that can be
generated due to swelling of the matrix. The solvent is then physically removed. The
prepared matrix. When the drug solution comes into contact with the polymer, it

used to produce a highly concentrated drug solution, which will be added to a
adding the mixture to a polymerization reactor. In this case, a solvent can be
by mixing a thin drug powder with the monomers (prepolymer) and then
drugs, by mixing a thin drug powder with the monomers (prepolymer) and then

Another approach is by polymerization of the polymer in the presence of the

resilience.

compatibilities and the lack of polymer compatibility, namely elastomer and
calculated ratio. The disadvantage of this method can be the lack of powder
compressing the polymer; the drug and necessary excipients, in a pre-

The less complicated approach for preparing a monolithic matrix is by

polymeric monolithic systems have been detailed by Cross and Cross (2005).

(Blagojeva and Neely, 2006). The three major techniques for the synthesis of
hydrophilic or hydrophobic and drug release is controlled mainly by diffusion
homo- and hydrophobic drugs dispersed or dissolved in an inert polymer. The matrix can be
in principle, a monolithic matrix is a simple drug delivery system comprising

6.2 Basic Characteristics and Release Mechanisms of Monolithic Systems
form a protective gel layer prior to dissolution. Resist rapid release; the polymer employed to prepare the device must be able to depend on the relative rate of hydration and gelation of the polymer. In order to hydration or the polymeric device. As a consequence, dissolution of the matrix with aqueous media. Thus, the release of the drug is controlled by the rate of in case of a swellable system, the device will immediately swell as when in contact process could be observed, namely, swelling and, thus, dissolution of the polymer. Various studies have reported on the mechanisms of drug release from swellable

(1963). Of the receding boundary is directly proportional to the square root of time (Higuchi's

mattresses, demonstrated that in a monolithic slab, the drug release and the partitioning

(1963). Higuchi's analysis of drug release kinetics from monolithic

from nonswellable monolithic matrices and drug is released through diffusion

within the matrix is then released. On the other hand, hydrophobic polymers tend to swell, allowing the dissolution medium to penetrate the matrix. The drug dispersed

from swellable monolithic matrices. On contact with the aqueous media, the matrix

properties of the employed polymer. Hydrophilic polymers lend to

2006). Dissolution of the system depends on the physicochemical and

covalently bonded to the drug are chemically manageable (Degenerative and Median;

monolithic matrices prepared from biodegradable polymers in which the polymer is
6.3 Hydorphilic Drugs in Monolithic Systems

2003; Conk et al., 2007).

Other, based on the polymer characteristics (Ghosh et al., 2002; Vassilaros et al.,

Hydorphilic matrix: although one process often plays a predominant role over the
both diffusion and erosion contribute in controlling the release of drug from a
virtues, soluble drugs may diffuse out of the gel before matrix erosion occurs. Thus,
of monolithic systems. Even so, if the polymeric matrix gel holds good durability
erosion, viscosity of the gel is thus another rate-controlling factor in the dissolution

In addition, the polymer should form a more viscous gel in order to resist diffusion and
employed different polymeric networks to design a compressed monolithic matrix
physicochemical interactions of select-cut PLA. (Chapter Four). This study
findings from our preceding studies on the physicochemical and the
and dissolution will be directed by the salt in view of the current facts and in line with
In order to achieve the desired release rate, therefore, the relative rate of hydration

cassini, 2001).

depends on the salt type and concentration (Pally and Cassini, 2000). Pally and
decrease, the quantity of drug released due to the water-salt interaction, which
drugs. In general, the addition of salts to hydrophobic matrices can increase or
perpendicular matrix swelling. A phenomenon that results in the release of a soluble

differentially swelling boundaries and extrinsically variable matrices that maintain a
highly successful in controlling dissolution and drug release by demonstrating
use of salts that modulate the internal geometry of the system. Salts have been
The inherent intercalations of this system can however, be manipulated through the


is not easily attributable (Pally and Cassini, 2000).

The complexity of controlling the increase in the dihedral angle with time
over time-dependent processes in relation to drug dissolution and diffusion and
the lack of accurate management of polymer relaxation or disentanglement

Release:

I. The increased hydrophilicity of the drug that causes a burst effect during drug

Factors such as:

Pally and Cassini, 2000, postulated that these drawbacks may be attributed to
6.4 Hardness and Compressibility Characteristics of PLGA

HCl, as the model drug,
drugs from a simple monolithic system using the PLGA scragged with amphyplaine
as a novel approach for zero-order kinetics for the steady delivery of highly soluble
drug release. In this study, the compressed monolithic matrix system was developed
system for the delivery of amphyplaine HCl that is capable of achieving zero-order
Compressibility and the effects must be investigated. Therefore, in order to design a monolithic device with sufficiently robust release, a more rapid drug release, than the actuation related rate of drug release, may increase or decrease the efficacy of the polymer to retain the drug.

(1973; Izah et al., 2002).

Permanent deformation is correlated to the strength of the device (Baron et al., 1990). The plastic deformation, which produces the permanent deformation of the compact, is measured experimentally using the Brinell hardness and covered in the Brinell Hardness Number (BHN) employing internal methods. The studies of the latter technique, involved determining the indentation systems. The studies of the latter technique, involved determining the indentation process, as well as for quality control and reproducibility of compressed monolithic matrix materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials. The hardness-compression force profile approach, showed to have the necessary sensitivity, precision, reproducibility and simplicity for characterizing materials.

Pareacho et al. (1990), profile analysis (Chitrakum et al., 1993; Hohbiail and Rhodes, 1990; Martini, 1971; Kroyer et al., 1992; Kunert et al., 2000; Anilakumar et al., 2003), and force-time

parachute.
Selected patients with neuralt depression (Friedberg and Craig, 2007), antidepressant used in depressive illness of psychiatric or endogenous nature and in neurocyclic antidepressants (HCAs), amitriptyline HCl is more efficacious as an continued application in psychiatric medicine. In comparison with other TCA in the market (Tryptanol, Tlzilin, Etc.) and Serotonin/Neuropeptide (and has a amitriptyline has contributed to numerous health care products that are already on depression and anesthesics (Stud et al., 2003). The most common TCA, most widely used classes of antidepressants in psychiatric conditions such as, for the past forty years, the tricyclic antidepressants (TCA) have been one of the depression, thus the need for effective treatment methods of depression increases.

Neurodegenerative and mental health concerns of major concern, particularly in the younger population, neurodegenerative disease, have also become a more pressing concern in society. Studies investigating the psychiatric morbidity of neurodegenerative disorders and a common psychiatric complication of neurodegenerative disorders. Among the elderly population, neurodegenerative survivors and the HIV/AIDS pandemic, depression has become a predominant health concern, due to the progressive magnitude of depression in the treatment of depression caused by...
Amphipterine HCl is passively absorbed from the gastrointestinal tract with peak concentrations occurring between 2 and 12 hours after administration. Plasma concentrations decline rapidly. The plasma half-life varies from 10 to 60 hours, with an average of 15 hours. Amphipterine HCl is subsequently metabolized by the liver (Fridich et al., 2007).

### Storage
Below 20°C, air tight

### Physical and Chemical Stability
Interacts with reactive oxygen and nitrogen

### Solubility
Photostable

### Molecular Data

- **Molecular Mass**: 313.37 g/mol
- **Empirical Formula**: C₂H₂O₂N₆
- **Propylmeritamine**: 3-(1H-1,2-dipyrido-9H-pyridine-5-ylidenyl)benzene

### Chemical Name
Amphipterine HCl

### Physicochemical and The Physicochemical Properties Of Amphipterine HCl

#### Table 6.1: The Physicochemical and The Physicochemical Properties of Amphipterine HCl

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Mass</td>
<td>313.37 g/mol</td>
</tr>
<tr>
<td>Empirical Formula</td>
<td>C₂H₂O₂N₆</td>
</tr>
<tr>
<td>Propylmeritamine</td>
<td>3-(1H-1,2-dipyrido-9H-pyridine-5-ylidenyl)benzene</td>
</tr>
</tbody>
</table>

---

*Text continues on the next page.*
of the current limitations with TCAs, especially associated with their toxicity. Researchers are exploring novel techniques in drug delivery in order to address some problems. Amphetamine is soluble in water, 100% at 25°C. Drug efficacy is demonstrated, and in absorption, a systemic elimination is established. That it undergoes extensive first-pass metabolism with a systemic elimination is demonstrated. Amphetamine HCl is extensively applicable. Pharmacokinetics studies have

demonstrated the (R)-amphetamine (R)-propyleneamine (source: adapted from Haner et al., 2006).

Figure 6.1. Chemical structure of amphetamine ({(3S)-10,1'-dihydro-5H-
6,6'-structure-function relationship of amphetamine HCl

Amphetamine HCl is excreted in the urine as inactive metabolites, and then small
amounth of 20-200 hours. Within 24 hours, approximately 25 to 50% of a dose of

```
6.6. Materials and Methods

Interrelated nociceptors, particularly in older people (Rosenbaum and Koy, 2005), amphotericin B, norfloxacin, doxycycline, and desipramine seem to be the best sensitizers or because of increased plasma level caused by dose dumping. However, cardiovascular, CNS and endocrine adverse effects. These occur as a result of drug

The use of TCA's has to be carefully monitored due to the anticholinergic...
Characteristics of the compressed monolithic matrix systems were characterized.

Fullerton, USA) and the compression force was set at 1 N/cm². The drug release studies were conducted utilizing a Beckman Hydraulic Press (Beckman Instruments, Inc., Fullerton, CA) to compress 70/30% w/w PLA and 50 mg amphotericine B HCl. Compression was achieved using a column of 10 mg amphotericine B HCl, which was followed by direct compression of the PLA matrix at a mixture volume of 50% w/w. The second approach, PLA was sintered, and subsequently cross-linked without compression of the samples into compressed monolithic matrix systems. In the case of the samples into compressed monolithic matrix systems, a Box-Behnken statistical design was used to determine the effects of sintering and subsequently cross-linking of 50 mg amphotericine B HCl at various concentrations in accordance with the preparation of the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted. The release of amphotericine B HCl from the PLA matrix, two approaches were adopted.

### Table 6.2: Preparation of the PLA Compressed Monolithic Matrix System

<table>
<thead>
<tr>
<th></th>
<th>Upper</th>
<th>Middle</th>
<th>Low</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg</td>
<td>50</td>
<td>60</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>% w</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>AlCl₃</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>CaCl₂</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>NaCl</td>
</tr>
</tbody>
</table>

Factor Level
shown in Figure 6.2.

<table>
<thead>
<tr>
<th>Load cell</th>
<th>Trigger force</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 kN</td>
<td>0.3 N</td>
</tr>
<tr>
<td>Auto</td>
<td>Trigger type</td>
</tr>
<tr>
<td>40.0 mm/s</td>
<td>Compression distance</td>
</tr>
<tr>
<td>0.5 mm/sec</td>
<td>Post-test speed</td>
</tr>
<tr>
<td>1 mm/sec</td>
<td>Test speed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-test speed</th>
<th>Test parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test settings employed for BHN value calculations</td>
</tr>
</tbody>
</table>

Table 6.3: Test setup settings employed for BHN value calculations

BHN values are listed in Table 6.3.

3.775 mm in diameter and 5 kN load cell. The test setup used to calculate the
Analyzer TAXTplus (Scribner Systems, England) used a spherical indenter of
The compressibility of PLA was determined with a textural analyzer, texture

6.6.3 Measurement of Compressibility
Number (BNH) (Equation 6.1):

Indentation hardness was calculated by a conversion to the Brinell hardness of a material, particularly those materials with heterogeneous structures. The area of indentation. This technique is the best for achieving the bulk hardness of the Brinell hardness number is calculated by dividing the load applied by the surface.

6.6.3.1 Calculating the Brinell Hardness Number

Figure 6.2: Typical force-displacement profile for the PLA compressed monolithic matrix.
point approach as in Chapter Five.

dissolution data was subjected to a model-independent analysis known as the time-

performed with UV-spectroscopy (240 nm) (SPECOFID, 4.9, Jena, Germany). The

7.4, 37°C) using a USP39 apparatus at 50 rpm. Amorphity/line HCl assays were

Drug release studies were conducted in 500ml phosphate-buffered saline (PBS) (pH

6.5) in vitro Drug Release from the Compressed Monolithic Matrix System

values in Chapter Five. The values were calculated in accordance with the melanotin

analysis was used. The values were calculated in order to determine the best-fit straight line. Linear regression

concentration was constructed for amorphity/line HCl in PBS pH 7.4 at 240 nm.

A calibration curve of absorbance, measured spectrophotometrically, versus

of Amorphity/line HCl Release from the Compressed Monolithic Matrix System

6.4 Preparation of a Calibration Curve for Spectrophotometric Determination

\[ d = \frac{F}{\pi D^2} \]

\[ d = \text{the indentation depth (0.25 mm)} \]

\[ D = \text{the diameter of spherical probe indenter (3.75 mm)} \]

\[ F = \text{the force generated from indentation} \]

Where,

\[ BHN = 2F/(\pi D^2) \]
Through a glass transition temperature and the BHN started to increase. Due to the amorphous properties of PLA, until a point where the material went increased, the BHN of the compressed monolithic matrix system were decreased. The indentation hardness of the compacts indicated that as the force was being compressed monolithic matrix system.

Figure 6.3: Typical compressibility profile depicting the effect of compression force on the monolithic matrix system.

6.7 Results and Discussion
The indentation force and the BHN out with NaCl and ACD such as F1, F6 and F13. The indentation force of the scarlike sediments were comparatively smaller as compared to the indentation force of CaCl₂ such as F2, F5, F7 and F14 were out with higher concentrations of CaCl₂. The indentation force of the scarlike sediments was generated by converting the scarlike formulations and the BHN values that were generated from indentation of each of the PLA.

<table>
<thead>
<tr>
<th>Force produced on indentation of compacts</th>
</tr>
</thead>
</table>
| 100.00  
| 17.40±1.215  
| 17.87±1.889  
| 17.29±1.746  
| 17.91±0.865  
| 17.95±0.265  
| 17.95±0.326  
| 17.79±0.231  
| 17.99±0.324  
| 17.79±0.162  
| 17.79±0.235  
| 17.79±0.263  
| 17.80±0.230  
| 17.79±0.312  
| 17.79±0.462  
| 17.79±0.321  
| 17.79±0.126  

Table 6.4 BHN values obtained from the fourteen samples of compressed monolithic matrix systems formulations.
was found to be $y = 5.30x$.

Regression analysis was employed to reveal the best-fit straight line. The equation 370°C achieved over the concentration range from 0.099 to 0.990 mg/ml. Linear Amphotericine HCl demonstrated a linearly in phosphate buffered media (pH 7.4) at 6.7.2. The Calibration Curve for Amphotericine HCl

In surface degradation and result in a higher initial burst effect during drug release. Furthermore, loss of particles and deformation at scaffold matrix surfaces may result concentration can modify material hardness and thus the behaviour of the scaffold. Therefore, from the table 6.2, it is apparent that scaling-out employing diverse salt types and chemical affinity of materials in contact and the hardness results. The frictional resistance is influenced by the hardness encompassing several properties that include resistance to deformation. The scaffold owing to the increased porosity of the scaffolds.
The basic equation that may be used to describe drug release from the monolithic systems is:

\[ \text{Equation 6.2} \]

\[ dh_t / dt = \frac{A}{V} \int [C]_t - [C]_t \, dt \]

The drug release tends to follow the square root of time relationship. Amtripryline HCl, according to Higuchi (1969), drug release in monolithic systems can also be explained by a significant role in the release of systems. However, matrix swelling and erosion also play a significant role in the release of these systems. The fundamental release mechanism from the compressed monolithic matrix is:

6.7.3 Drug Release Studies from the Compressed Monolithic Matrix

Figure 6.4: Amtripryline HCl calibration curve at 240.1 nm in PBS (pH 7.4)

\[ R^2 = 0.9998 \]

\[ y = 53.00x + y \]
These profiles display that the initial burst was lower in compressed  
4 hour PLA compressed monolithic matrix systems formulations over a period of 
Figure 6.6a and b depicts the in vitro fractional drug release from each of the 

\[ C = \text{drug loading in the matrix} \]

\[ \text{tortuosity of the matrix} \]

diffusion coefficient of the drug in permeability that as well as the porosity and
\[ k \] is a kinetic constant that accounts for numerous factors such as solubility and
\[ C_0 \] is the bulk concentration of the drug and
\[ C_m \] is the drug solubility in the matrix.
\[ A \] is the cross-sectional area of the matrix available for diffusion.
\[ Q \] is the drug diffusion rate.
\[ M_r \] is the quantity of drug released at time, \( t \).

Where,

\[ Q_2 = K_{12}^2 \]

\[ \text{given by:} \]

The Higuchi’s square root of time model for characterizing the dissolution data is

\[ M_r = A \sqrt{t} \left( C_m - C_0 \right) \left( 2C_m - C_0 + C_f \right) \]

\[ \text{for the calculation of cumulative drug release the integrated version of Equation 6.3} \]
The matrix layer, exhibiting a Fickian release model, from the compressed monolithic matrix systems was found to be by diffusion through HCl showed a high initial burst. The fundamental release mechanism of amoxicillin linked without amoxicillin in the contrary, PLGA was sold-out and subsequently cross-linked with amoxicillin. This was followed by a steady release of the drug. On monolithic matrix systems where PLGA was sold-out and subsequently cross-linked with amoxicillin.
Figure 6.6: Fractional drug release profiles of amitriptyline HCl from the PLGA compressed by compression of (b) cross-linked PLGA without amitriptyline HCl followed by non-cross-linked matrix systems prepared by either (a) cross-linked PLGA with amitriptyline HCl and (e) non-cross-linked amitriptyline.

- (b) Non-cross-linked amitriptyline
- (a) Cross-linked amitriptyline
and the aqueous environment in non-cross-linked polymer molecules. The same effective collision rate that would be achieved in the same functional groups shielding of the polymer reaction sites that could and prevent the mainenance of the matrix in addition, the slow diffusion of amorphiphilic HCl resulted from the viscosity of the matrices, thus slowing the diffusion of water soluble drugs out of decreases the hydrodynamic volume of polymers, and increases the inherent as mentioned earlier in the study (Chapter Three, Four and Five), cross-linking formation of strong bonds between the amorphiphilic HCl, PLA, and the salts PLA with chelating inducers considerably reduced drug release due to the current study has demonstrated that the cross-linking of amorphiphilic HCl and earlier, and tends to diffuse rapidly out of matrices in physiological fluids. However, amorphiphilic HCl, amorphiphilic HCl is a highly water soluble drug, as mentioned matrix systems prepared by cross-linking PLA alone and compressed in with cross-linking PLA with amorphiphilic HCl and 0.3% in compressed monolithic release rate constant Kc of 0.077 in compressed monolithic matrix system prepared Drug release kinetics were calculated by MW=Kc and displayed on average 24 hours.

amorphiphilic HCl release, with functional drug release ranging from 0.5 to 7.5 within adding amorphiphilic HCl during compression displayed a much more rapid compressed monolithic matrix systems prepared by cross-linking PLA alone and systems, and was found to be less than 0.20 in 24 hours. In contrast, the

Drug release studies demonstrated that cross-linking PLA with amorphiphilic HCl
rate of water-soluble drug through salting-out and cross-linking.

that salting-out and subsequent cross-linking can significantly reduce the release
implanted when PLGA is cross-linked with the drug. This study has also demonstrated
drug delivery systems when PLGA is cross-linked with or without the drug, a 24-hour
matrix systems, in the claim that it may be applied for either zero-order or
controlled drug release. The distinctiveness of the PLGA compressed monolithic
The compressed monolithic matrices were capable of producing flexible yet rate-
6.4 Concluding Remarks

both the PLGA cross-linked separately and the PLGA cross-linked with the drug.
resistance and strength have led to the sustained release of amphotericin B Cl from
result from salting-out and subsequent cross-linking, particularly the visco-elasticity.
PLGA, the transitions in physicalchemical and physicalmechanical properties that
release of amphotericin B Cl from these matrices. Thus, the intrinsic properties of
systems salting-out with NaCl and ACl had smaller pores that further delayed the
and caused drug diffusion to occur faster, whereas the compressed monolithic matrix
The compressed monolithic matrix systems salting-out with CaCl2 had larger pores,
with CaCl2.
The compressed monolithic matrix systems salting-out and subsequently cross-linked
subsequently cross-linked with NaCl and ACl displayed slower drug release than
degradation of the matrices. Compressed monolithic matrix systems salting-out and
subsequently cross-linking played a role in hindered the rapid drug release and
Furthermore, the type and concentration of salt used during salting-out and
that are formulated from native polymeric powders.
constructed from a 3-dimensional scaffold, as compared to the conventional systems.

Thus, the novelty of the multilamellar system lies in the fact that it is shown that the PLGA scaffold can be further adapted into a compressed multilamellar system and concurrent to the cell incorporated. In conclusion, the study has released, controlled by the rate of hydration of the polymeric device, that depends on release, demonstrated by the present study has demonstrated pre-determined drug study. Furthermore, the present study was achieved through the release of amitriptyline HCl from PLGA matrices was achieved through this device. The validation of the effects of salting-out and subsequent cross-linking on device, the dissolution kinetic model of a dispersed drug from a multilamellar spherical demontsrated the 1-dimensional model of dispersed drug particles in matrices.

All drug-release profiles yielded by the PLGA cross-linked with amitriptyline HCl
Conclusions and Recommendations

Chapter Seven

...
that the rate of PLGA degradation is dependent on the hydrophilicity of the network.

Other studies on hydrophilic polyesters, such as PLA, PGA, and PLA have implied the

employed to explain the mechanisms of drug release from the PLGA scaffold.

optimized for their DE. ADT and drug release rates. Kinetic modeling was also

were developed and explored for use in clinical applications. The scaffolds were

This unique surface-etching PLGA scaffold and the compressed monolithic discs
disorders were established.

from a PLGA-based compressed monolithic system for use in neurodegenerative

metformin-loaded PLGA scaffolds and on the in vitro dissociation of amantadine HCl

amantadine HCl, the effects of polymeric cross-linking on the in vitro dissociation of
drugs. PLGA scaffolds were formulated, and loaded with either metformin or

metabolites (low water soluble), and amantadine HCl (highly water-soluble) as model

transitions of the scaffold, dissolution and drug release studies were conducted on

After subsisters investigations of the physicochemical and the physicochemical

as drug delivery impairs in the treatment of neurodegenerative disorders.

PLGA scaffold and compressed monolithic matrix have potential to be used

that resulted from scaling-up and the subsequent cross-linking displayed that the

was determined and confirmed. The porosity and the three diameters of the scaffold

spectroscopy, texture profile and differential scanning calorimetry. The influence

analyzed by Scanning electron microscopy, Fourier Transform Infrared Red
the PLGA and the drug.

For 30 days (or more) when prepared by salting-out and subsequently cross-linking PLGA alone, or hours when prepared by solubilizing and subsequently cross-linking PLGA with matrix systems can be applied as a controlled drug delivery system. However, the compressed microparticle membrane system of neurodegenerative disorders. Meanwhile the compressed microparticle membrane system of neurodegenerative disorders can be applied as a sustained drug delivery system over a period of 30 days (or more) for applications on the skin and corneal membranes of the skin incorporated. The scaffold can be degraded on the polymer scaffold and compressed microparticle membrane system that releases the polymer scaffold pre-determined drug release, controlled by the rate of hydration and swelling of the scaffold. Completely polymer scaffolds have produced a scaffold capable of releasing mechanisms of polymer modification have produced a scaffold capable

7.2 Recommendations

Resilience, hardness, and the rate of dissolution, depended mainly on the salt type the physicochemical properties of PLGA composites. Structures. In particular, the formation of polymer-salt bonds has modified the physicochemical and mechanical properties of PLGA through the incorporation of salt by salting-out and subsequent cross-linking. Though the study has demonstrated that PLGA is versatile and can be dependent on the thermoplastic nature of PLGA composition, and that the physicochemical and physicochemical properties are
Lack of immunomodulatory responses when introduced to the body.

Toxicity and safety of the scaffold, such as cell-laden immunosenibility and

Dissection and drug release mechanisms inside and outside the body.

With support from mechanical approach to further explore:

Further recommendations also include developing suitable ex vivo models

Matrix system and delivered to the brain via implantation in the subarachnoid space

as, avoiding can be incorporated into the scaffold and the compression modulus
dilution and inflammation and drugs for HIV-related neurodegeneration, such as

Other drugs used in the treatment of neurodegenerative disorders, such as

antidepressant (such as amitriptyline) and hypotensive drugs (such as amitriptyline HCl)

Properties that allow them to act as reservoirs and control the release of both

In addition, the scaffold and the compressed remodelable matrix system have
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