AD NUMBER

ADB215487

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Specific Authority; Sep 96. Other requests shall be referred to Commander, Army Medical Research and Materiel Command, Attn: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012.

AUTHORITY

USAMRMC ltr, 4 Dec 2002

AD_____

CONTRACT NUMBER DAMD17-96-C-6033

TITLE: Development of Modified Biodegradable Polymers for Osmotically Driven Biodegradable Implant Therapeutic System (OBITS) for (PANDA)

PRINCIPAL INVESTIGATOR: Jer-Wen Hsu, Ph.D.

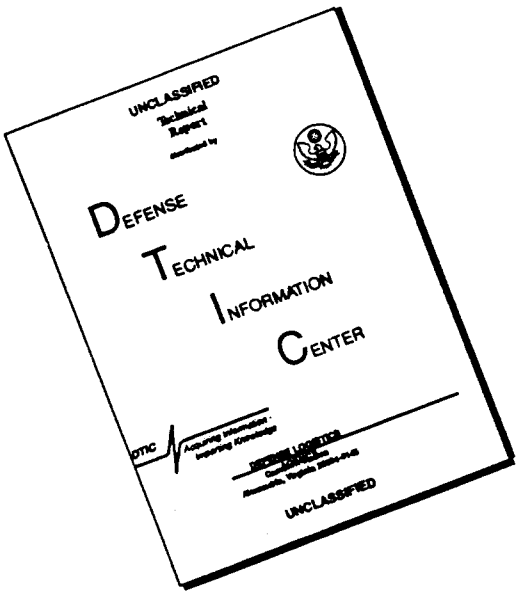
CONTRACTING ORGANIZATION: DPD, Inc.
Lansing, MI 48906

REPORT DATE: September 1996

TYPE OF REPORT: Final

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

DISCLAIMER NOTICE



THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1996	Final (3/15/96 - 9/14/96)

4. TITLE AND SUBTITLE Development of Modified Biodegradable Polymers for Osmotically Driven Biodegradable Implant Therapeutic System (OBITS) for (PANDA)

5. FUNDING NUMBERS
DAMD17-96-C-6033

6. AUTHOR(S)
Jer-Wen-Hsu, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
DPD, Inc.
Lansing, MI 48906

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick
Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (Specific Authority, Sep 96). Other requests for this document shall be referred to Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

The ultimate goal of the proposed project is the development of a novel drug delivery system which is capable of providing long-lasting pain relief utilizing local anesthetics while reducing the debilitating side effects associated with current pain management therapies. In Phase I research the technical and commercial feasibility of developing a controlled release delivery system based on the microporous membranes was demonstrated. Microporous membranes were fabricated from biodegradable polymers using various hydrophilic water soluble agents. It was demonstrated by SEM that upon contact with water the hydrophilic agents leave the polymer forming a microporos membrane. The kinetics of pore formation studies indicated that pores were formed very rapidly in the membranes. The transport studies indicated that pores were formed in the membranes and the transport of the drugs across the membranes is dominantly through the pores formed within the membranes thus eliminating drug/polymer interactions. The long term mechanical testing indicate that the mechanical integrity of the membrane does not deteriotc after prolonged exposure to buffer used to mimic biological system. The desired technical performance of the cast membranes make the technical feasibility of the proposed drug delivery system based on the microporous membranes developed in Phase I of this research extremely promising.

14. SUBJECT TERMS Biodegradable Polymers, Microporous Membrane, Drug-Polymer Interaction, Zero Order Release; Local Anesthetics; Reduced Side Effects, Pain Management; Therapeutic System

15. NUMBER OF PAGES
27

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	limited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Principal Investigator's Signature

9/96

Date

CONTENTS

Results of Phase I work

INTRODUCTION

Statement of the Problem

The proposed project concerns the development of a stable biodegradable drug delivery system which is capable of effectively and safely delivering drugs while virtually eliminating all polymer/drug interaction, allowing the application of the proposed technology to both Polar and Nonpolar drug substances. Initially, the proposed drug delivery platform will be used to develop a system for local anesthetics in treatment and mitigation of pain. The advantages of a controlled release system for local anesthetics include better management of pain with a significant reduction of toxicities and side effects (loss of motor function and sensation) of these drugs (Maniar et al., 1994).

The proposed OBITS delivery system has significant military applications by reducing the pain afflicted on military personnel during combat, thereby maintaining the maximum functional capabilities of the military personnel. The military implications of the OBITS-PANDA system are significant since the incidence of traumatic injury increases significantly during acts of war. The experience of pain which in itself can be debilitating is universal following traumatic injury. The OBITS-PANDA system utilizing local anesthetic is anticipated to effectively alleviate pain without loss of motor function. This offers tremendous advantage in the battlefield arena since by eliminating debilitating conditions, the military personnel will be functional for continued engagement of enemy and/or execution of more efficient maneuvering and evacuation scenarios of wounded personnel which will be of significant strategic value.

The proposed system has significant civilian applications as well since pain is the most common cause of human suffering and is the primary reason for physician visits (Frolund et al., 1986). The disability associated with pain impairs the quality of life of millions of people throughout the world, furthermore there is no permanent cure for severe pain at the present. The Nuprin Pain Report prepared in 1985 (sternbach, 1985) estimated the prevalence rates for pain lasting greater than three months to be 10% for joint pain, 9% for backache, 5% for headache, and 5% for muscle pain. Although no figure for total pain prevalence was given, the results presented are significant since they are measures of chronic pain lasting greater than three months. In another study by Von Korff et al., (1988), the prevalence rate for pain greater than a day was determined to be 41% for backache, 26% for headache, 17% for abdominal pain, and 12% for chest and facial pain. It is estimated that each year over 40 percent of Americans have acute or chronic pain which requires therapy by health care professionals.

Chronic pain alone is estimated to afflict over 70 million Americans, and of these, 50 million are either partially or completely disabled either temporarily or permanently, resulting in the estimated loss of over 700 million workdays per year. This, together with the health care costs and payments for compensation, quackery, etc., are estimated to cost

the American public over 60 billion dollars annually (Bonica, 1979). More recently, annual health care costs of back pain alone were estimated to be as high as $24.3 billion in the US (Frymoyer, 1991), as compared to $10.3 billion for AIDS (Hellinger, 1992).

Currently, existing therapies primarily rely on morphine and related narcotics for pain management, however these therapies are so sedating at high doses that they alter the state of conciseness of the patients. At times the loss of conciseness is so sever that the patients can not even recognize their surrounding including family membranes, this severely reduces the quality of life of the patient and increases the level of care, effort and cost associated with patient care. The use of narcotics has another major disadvantage in that the patients run an increased risk of becoming addicted to the various narcotic agents utilized. The degree of suffering, morbidity, and disability associated with pain can be markedly decreased through improved application of local anesthetics.

The proposed OBITS-PANDA system is anticipated to improve the therapy and care of patients suffering from pain by providing a steady release of lidocaine over a long period of time while reducing the potential side effects. Specifically, the use of the OBITS-PANDA system can be localized to the site of administration adjacent to region of pain generation and sensation. This localized administration of the system is anticipated to virtually eliminate systematic levels of drug thus eliminating any potential side effects and/or toxcities associated with the use of the OBITS system. The primary advantage of the OBITS-PANDA system using local anesthetic is effective management of pain over a extended time frame utilizing drugs which do not have sever addicting or sedating properties. Furthermore, since the local anesthetic in their application will be administrated in a localized region of interest the remaining regions of the body are not affected. Thus, the remaining regions are capable of functioning normally without any detrimental reduction in performance or sensations associated with the pain therapy. These attributes are expected to significantly increase the quality of life of the patient while decreasing the cost and work load of the health care professional.

Brief Description of OBITS system

The development of the proposed Osmotically driven Biodegradable Implant Therapeutic System (OBITS) revolves around the utilization of the microporous membranes developed during Phase I of this project. These microporous membranes will be utilized in a novel controlled release system depicted in the figure below

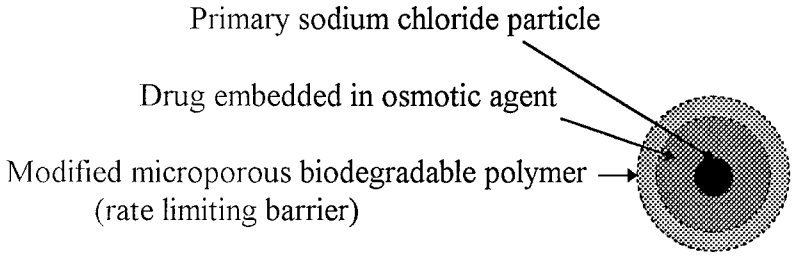


Figure 1. The OBITS-PANDA System utilizing the microporous biodegradable membrane developed during Phase I of this project.

The proposed dosage form utilizes sodium chloride particles as seed material upon which the drug and any additional osmotic agents necessary can be deposited by fluid air coating. The microporous biodegradable membrane developed in first part of this research will then be coated upon the drug loaded particle to provide the rate limiting coat. In this fashion the core material containing the drug as well as the osmotic agent establishes the osmotic pressure and hence the osmotic flow across the membrane. This osmotic flow will then drive the drug across the water channels formed in the microporous membrane. In this fashion the drug/polymer interaction is significantly reduced allowing the application of the proposed system to both polar and non-polar drug compounds. Furthermore, the proposed system can be designed to deliver drugs in a constant zero order release rate (Zentner et al., 1985; Wesselingh, 1993).

The proposed OBITS system is superior to other controlled release systems currently utilized such as the matrix system in which the drug is dispersed in the polymeric matrix. Due to the dispersion of the drug within the matrix, there is a tremendous amount of drug/polymer interactions (Jacobs and Mason, 1993; Shah et al., 1992). This inevitable drug-polymer interaction is at the root of making these devices inappropriate for both polar an nonpolar drug compounds. Furthermore, zero order constant release of drug from these systems is rarely obtained. Our proposed system will practically eliminate all drug-polymer interactions, making the system applicable to both polar and nonpolar drug compounds.

The objective of Phase I research was the development of microporous membranes fabricated from poly (DL-lactide-co-glycolide family of biodegradable polymers currently approved for medical applications (Frazza and Smith, 1971; Brady et al., 1973). The microporous membranes were fabricated using the biodegradable polymer and water soluble pore formers. The hydrophilic pore formers, upon contact with water in the biological tissue would dissolve and leave the membrane, forming a microporous membrane with fine pores or water channels in the membrane (Zentner et al., 1985; Thombre et al., 1989). The various pore formers identified were used along with the polymer in various solvent systems to prepare membranes. The membranes cast utilizing the above pore formers were characterized by studying i) kinetics of pore formation, ii) scanning electron microscopy of the membranes iii) permeability of local anesthetics across the membranes, iv) the long term mechanical properties of the membranes, and.

Selection of pore forming agents

The primary focus of our efforts have been on the fabrication of membranes with various pore formers using different organic solvents and aqueous-organic solvent mixtures as proposed in the Phase I proposal. Membranes were cast using 65:35 poly (DL-lactide-co-glycolide) and various pore formers using acetone, actone/water (95/5 v/v%), acetone/water (80/20 v/v%), dioxane, dioxane/water (95/5 v/v%), dioxane/water (80/20 v/v%), ethyl acetate, and ethyl acetate/water (95/5% v/v%). Solvent systems containing more water were not pursued since the polymer did not have sufficient solubility in these mixtures (Lambert et al., 1995). The solubility of the polymer and various pore formers at the end of 24 hours of intermittent agitation were visually estimated. The data is summarized in the Table 1, 2, and 3.

As is evident in Tables 1, 2, and 3, the acetone and dioxane solvent systems dissolved the biodegradable polymer most effectively. The addition of a small quantity of water at the five percent by volume level in the solvent system increased the solubility of the pore formers without having a detrimental effect on the solubility of the polymer. The addition of water at the twenty percent by volume level in the solvent system increases the solubility of the pore former significantly. Most of the pore formers under investigations are soluble in this solvent system. The addition of water in the solvent systems both at the 5% level and the 20% level did not have a detrimental effect on the solubility of the polymer which is consistent with observations of Lambert and coworkers (1995).

At the end of solubility observations, membranes were cast from the mixtures prepared and allowed to dry. The membranes were examined visually upon drying. The primary observation on the formed membranes was that in cases were both the pore former and polymer were dissolved in the solvent system, the membranes were homogenous in nature. When either the pore former or polymer was not completely dissolved in the solvent system the membranes appeared to be non-homogenous in nature. The non-homogenous nature of these membranes can be attributed to the fact that some solid particles were not

completely dissolved and were randomly dispersed in the film. Therefore, subsequent efforts were primarily focused on systems where both the polymer and the pore former were completely dissolved.

Table 1. Solubility of 65:35 poly (DL-lactide-co-glycolide) (200 mg) and various pore formers (50 mg) in 2.5 ml of various neat solvents.

Pore Former	Pure Solvent System		
	Acetone	Dioxane	Ethyl acetate
None	100% of polymer	100% of polymer	≈50% of polymer
Sodium Chloride	100% of polymer ≈20% of sodium chloride	100% of polymer ≈20% of sodium chloride	≈50% of polymer ≈10% of sodium chloride
Mannitol	100% of polymer ≈10% of mannitol	100% of polymer ≈10% of mannitol	≈50% of polymer ≈5% of mannitol
Poly Ethylene Glycol 400	100% of polymer 100% of PEG 400	100% of polymer 100% of PEG 400	≈50% of polymer 100% of PEG 400
Plyoxomer LF 62	100% of polymer 100% of LF62	100% of polymer 100% of LF62	≈50% of polymer 100% of LF62
Citric Acid	100% of polymer 100% citric acid	100% of polymer 100% citric acid	≈50% of polymer ≈50% of citric acid
Sorbitol	100% of polymer ≈10% of sorbitol	100% of polymer ≈10% of sorbitol	≈50% of polymer ≈20% of sorbitol
Sodium Bicarbonate	100% of polymer ≈20% Bicarbonate	100% of polymer ≈10% Bicarbonate	≈50% of polymer ≈20% Bicarbonate
Sodium Lauryl Sulfate	100% of polymer ≈10% of SLS	100% of polymer ≈60% of SLS	≈50% of polymer ≈10% of SLS
Malic Acid	100% of polymer 100% of malic acid	100% of polymer 100% of malic acid	≈50% of polymer ≈40% of malic acid
Glucose	100% of polymer ≈10% of glucose	100% of polymer ≈10% of glucose	≈50% of polymer ≈10% of glucose
Ascorbic Acid	100% of polymer ≈20% of ascorbic	100% of polymer ≈20% of ascorbic	≈50% of polymer ≈10% of ascorbic
Glycerin	100% of polymer 100% of glycerin	100% of polymer 100% of glycerin	≈50% of polymer 100% of glycerin

Table 2. Solubility of 65:35 poly (DL-lactide-co-glycolide) (200 mg) and various pore formers (50 mg) in 2.5 ml of various organic-aqueous solvent mixtures at 95/5 v/v% level.

Pore Former	Organic Solvent / Water (95% v/v) Mixtures		
	Acetone / Water	Dioxane / Water	Ethyl acetate /Water
None	100% of polymer	100% of polymer	≈50% of polymer
Sodium Chloride	100% of polymer ≈30% of sodium chloride	100% of polymer ≈30% of sodium chloride	≈40% of polymer ≈10% of sodium chloride
Mannitol	100% of polymer ≈20% of mannitol	100% of polymer ≈20% of mannitol	≈30% of polymer ≈10% of mannitol
Poly Ethylene Glycol 400	100% of polymer 100% of PEG 400	100% of polymer 100% of PEG 400	≈50% of polymer 100% of PEG 400
Plyoxomer LF 62	100% of polymer 100% of LF62	100% of polymer 100% of LF62	≈50% of polymer 100% of LF62
Citric Acid	100% of polymer 100% citric acid	100% of polymer 100% citric acid	≈50% of polymer 100% of citric acid
Sorbitol	100% of polymer ≈20% of sorbitol	100% of polymer ≈20% of sorbitol	≈15% of polymer ≈20% of sorbitol
Sodium Bicarbonate	100% of polymer ≈25% Bicarbonate	100% of polymer ≈20% Bicarbonate	≈15% of polymer ≈20% Bicarbonate
Sodium Lauryl Sulfate	100% of polymer ≈15% of SLS	100% of polymer ≈15% of SLS	≈25% of polymer ≈15% of SLS
Malic Acid	100% of polymer 100% of malic acid	100% of polymer 100% of malic acid	≈60% of polymer ≈50% of malic acid
Glucose	100% of polymer ≈20% of glucose	100% of polymer ≈20% of glucose	≈40% of polymer ≈20% of glucose
Ascorbic Acid	100% of polymer ≈50% of ascorbic	100% of polymer ≈50% of ascorbic	≈45% of polymer ≈15% of ascorbic
Glycerin	100% of polymer 100% of glycerin	100% of polymer 100% of glycerin	≈50% of polymer 100% of glycerin

Table 3. Solubility of 65:35 poly (DL-lactide-co-glycolide) (200 mg) and various pore formers (50 mg) in 2.5 ml of various organic-aqueous solvent mixtures at 80/20 v/v% level.

Pore Former	Organic Solvent / Water 80% v/v Mixtures	
	Acetone / Water	Dioxane / Water
None	100% of polymer	100% of polymer
Sodium Chloride	100% of polymer 100% of sodium chloride	100% of polymer 100% of sodium chloride
Mannitol	100% of polymer ≈70% of mannitol	100% of polymer ≈95% of mannitol
Poly Ethylene Glycol 400	100% of polymer 100% of PEG 400	100% of polymer 100% of PEG 400
Citric Acid	100% of polymer 100% citric acid	100% of polymer 100% citric acid
Sorbitol	100% of polymer 100% of sorbitol	100% of polymer 100% of sorbitol
Sodium Bicarbonate	100% of polymer ≈80% Bicarbonate	100% of polymer ≈70% Bicarbonate
Sodium Lauryl Sulfate	100% of polymer 100% of SLS	100% of polymer 100% of SLS
Malic Acid	100% of polymer ≈80% of malic acid	100% of polymer ≈50% of malic acid
Glucose	100% of polymer ≈30% of glucose	100% of polymer ≈70% of glucose
Ascorbic Acid	100% of polymer 100% of ascorbic	100% of polymer 100% of ascorbic
Glycerin	100% of polymer 100% of glycerin	100% of polymer 100% of glycerin

Based on the observation that both the pore former and the polymer should be completely dissolved in the solvent mixture in order to obtain homogenous membranes and the fact that the presence of water in solvent mixture increases the drying time necessary to form the membranes, the pore formers citric acid, glycerin, and poly ethylene glycol 400 in the acetone solvent system were chosen for future studies. Dioxane was not used as it also evaporates slowly compared to acetone. However, as the poly ethylene glycol membranes were not quite dry at the end of 24 drying time, poly ethylene glycol 8000 was used instead of poly ethylene glycol 400. The primary reason is that poly ethylene glycol 8000 is solid at room temperature. This is not a major change since both compounds are chemically identical in terms of their composition. Upon selection of the pore formers and the solvent system, membranes were cast to in order to determine various properties of the membranes that are required in order to design and fabricate the proposed OBITS-PANDA (Osmotically driven Biodegradable Implant Therapeutic System for Polar And Nonpolar Drug Applications) dosage form.

Kinetic Determination of Pore Formation

The kinetic of pore formation in the membranes is an indication of the time frame required for the formation of pores or water channels within the cast membranes following contact with aqueous media (Zentner et al., 1985; Thombre et al., 1989). It is desirable to have pore formers that leach out of the membranes in a short time frame this reduces the lag time associated with the proposed dosage form. Dosage forms which have short lag times are ideal since they require little to no initial loading dose to maintain effective coverage for the patient during the first several hours.

Two different experimental methods were used to determine the kinetics of pore formation form the cast membranes. The first method was a simple gravimetric method in which the cast membranes were initially weighed and subsequently placed in phosphate buffer (pH=7.4) . At predetermined time points, the membranes were removed and allowed to air dry in presence of dririte for at least 24 hours and subsequently reweighed. Based on the initial and final weights obtained, a percent weight loss was calculated. The data for citric acid appears in Table 4. It is evident that the weight loss from the membranes occurs in a very short time frame (i.e. less than 15 minutes).

Table 4. Gravimetric analysis of release kinetics of citric acid from 65:35 Poly (DL-lactide-co-glycolide) membranes. The membranes were cast using acetone and contain 20% (w/w) citric acid.

Incubation Time	Percent Weight Loss	Mean (SD)
15 min.	0.99, 4.12, 2.46, 2.14	2.4 (1.1)
30 min.	2.32, 2.69, 13.20, 2.67	5.2 (4.6)
60 min.	3.81, 3.17, 3.20, 1.87	3.0 (0.7)
2 hours	2.57, 4.04, 5.45, 3.21	3.8 (1.0)
4 hours	7.01, 3.13, 6.55, 5.32	5.5 (1.5)
6 hours	3.46, 3.81, 6.90, 3.31	4.3 (1.4)
8 hours	-1.29, 5.33, 3.53, 2.93	2.6 (2.4)

In addition to the gravimetric method a poteniometric method was used in determining the release profiles of citric acid from the cast membranes. The poteniometric method measured of the pH or mV of the water upon placement of the membranes in distilled water as a function of time (Fig 1 & Fig 2). The change in the pH or mV is predominately associated with the release of citric acid or malic acid from the membrane into the distilled water. Therefore, a change in the mV or pH as a function of time is indicative of the release kinetic of these pore forming agents from the membranes. Based on the change in mV or pH in Figure 1 & 2, it is speculated that the pores in these membranes are formed within hours (approximately two hours or less).

Both the gravimetric method and the poteniometic methods indicate that the pores or water channels are formed rather rapidly within the membranes. The rapid kinetics of pore formation are encouraging since the lag time associated with the proposed controlled release delivery platform is minimized and/or practically eliminated, increasing its technical and commercial feasibility.

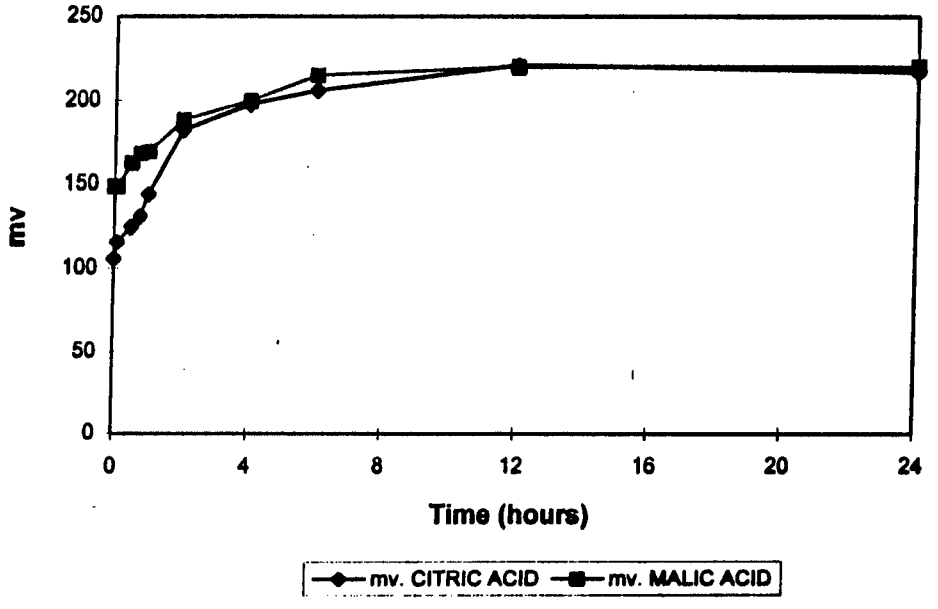


Figure 1. The measured potential as a function of time for polymeric membrane containing 20% (w/w) citric acid or malic acid.

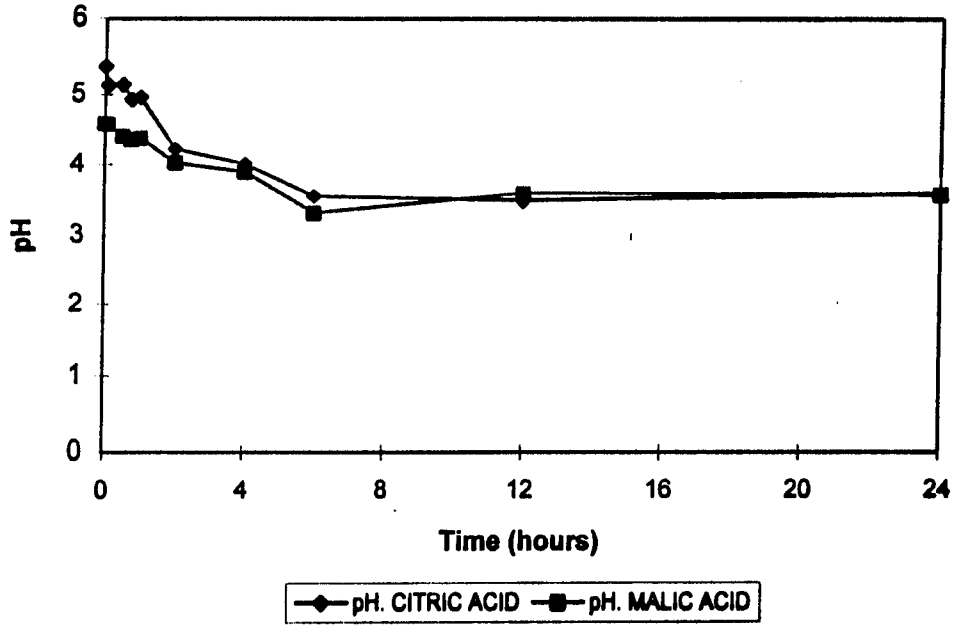


Figure 2. The measured pH as function of time for polymeric membrane containing 20% (w/w) citric acid or malic acid.

Scanning Electron Microscopy (SEM) of the Cast Membranes

The key to the proposed technology is the formation of pores or water channels within the membranes which allows for the transport of the drug across the membranes through the water channels formed (Wesselingh, 1993). The transport of drug through the water channels is superior to simple diffusion through the polymeric membranes or release of drug through bulk erosion of polymeric systems. In case of simple diffusion of the drug across the polymeric membrane there are numerous physcio-chemical quantities of both drug and polymer which control the release profile of the drug these parameters include, the free volume of the polymer, the molecular size of the diffusant, the partition coefficient of drug in the polymeric membrane, and various other physico-chemical quantities which are indicative of the extent of drug polymer interactions (Higuchi, 1988; Shah et al., 1992; Jacobs and Mason, 1993). In the case of bulk erosion of the polymer once again there are numerous parameters associated with polymer drug interactions controlling the release of the drug from the polymer. The proposed OBITS-PANDA system based on the porous membrane virtually eliminates the interaction of the drug with the polymer since the transport occurs through the water channels.

Scanning electron microscopy was used as a tool to demonstrate the formation of these water channels within the membranes upon placement of the membranes in an aqueous media to allow for the leaching of the water soluble pore formers from the cast membranes. The membranes were cast using 65/35 poly(DL-lactide-co-glycolide) for the polymer using acetone as the solvent. The membranes examined were polymer only (no pore former present), polymer with 20% (w/w) citric acid as pore former, and polymer with 20% (w/w) glycerin as pore former before and after storing the membranes in 0.1 M phosphate buffer at pH 7.4 for 48 hours. The additional storage of the membranes in the buffer mimics the aqueous biological media which allows for the water to dissolve and leach out the pore formers from the membranes (Vert et al., 1991). The scanning electron micrographs appear as figures 3-8.

As is evident for the polymer only membrane (Fig. 3), there are no pores within the membrane initially. Furthermore, after storing the membrane in buffer for an additional 48 hours no pores develop within the membranes (Fig. 4). For the membranes using citric acid (Fig. 5) as the pore former, there were no pores present initially and the citric acid appears to be distributed on the surface of the membrane. However, after storing the membrane in the buffer for 48 hours (Fig. 6) numerous well defined pores with uniform size distribution were formed in the membrane. This observation is of significant value to the technical feasibility of the proposed approach in that there is conclusive evidence that pore formers are formed. For the membranes using glycerin as pore former (Fig. 7) initially some pores are randomly distributed within the membranes. After storage of these membranes in buffer for an additional 48 hours, a significant number of pores formed within the membrane. These pores are circular. These observation indicate the pores are indeed formed in membranes using citric acid or glycerin upon placement of these membranes in an aqueous media to allow for the leaching of the water soluble pore formers from the membranes.

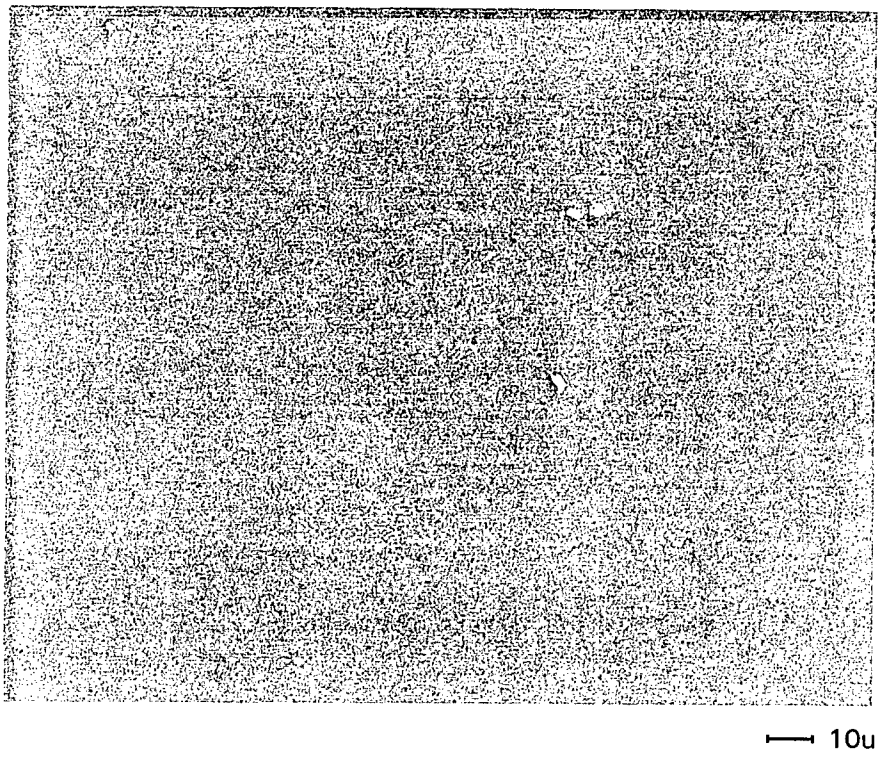


Figure 3. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with no pore former present.

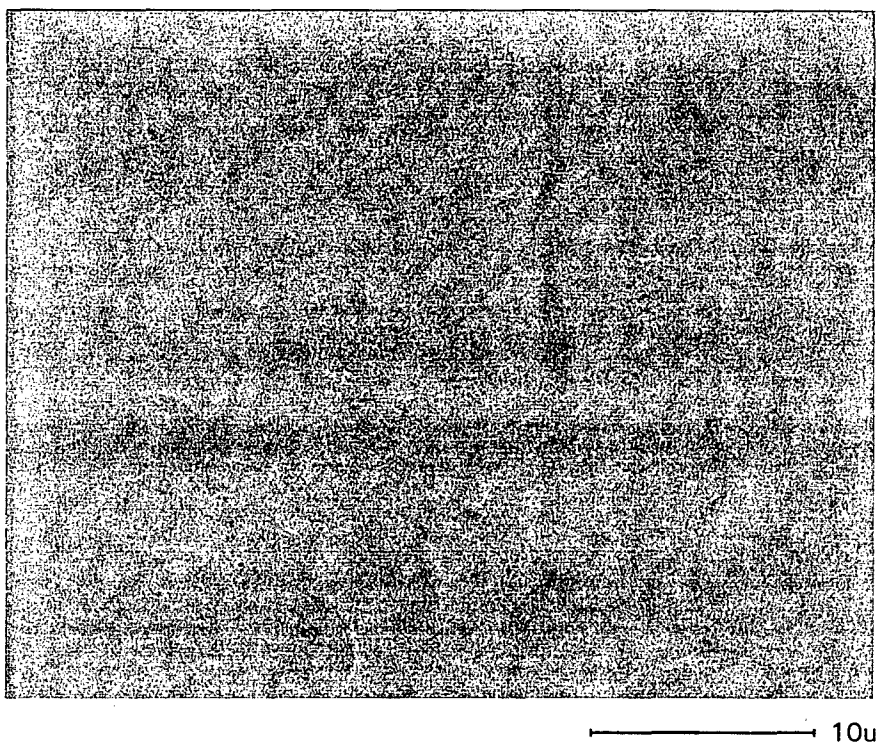


Figure 4. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with no pore former present after additional storage of the membranes in 0.1 M phosphate buffer (pH 7.4) for 48 hours.

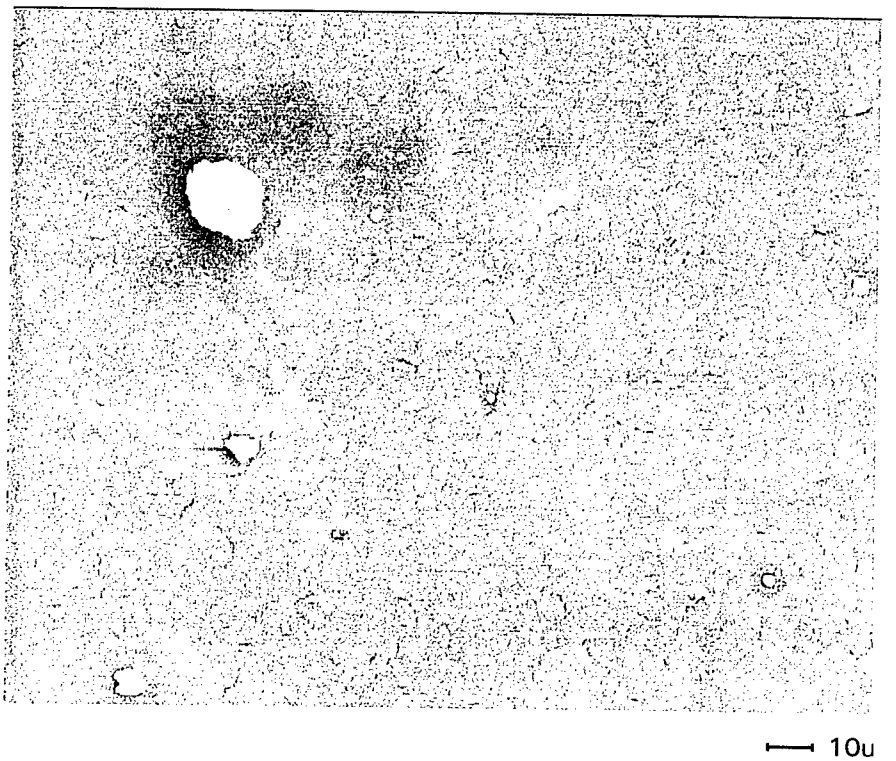


Figure 5. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with citric acid (20% w/w) as the pore former.

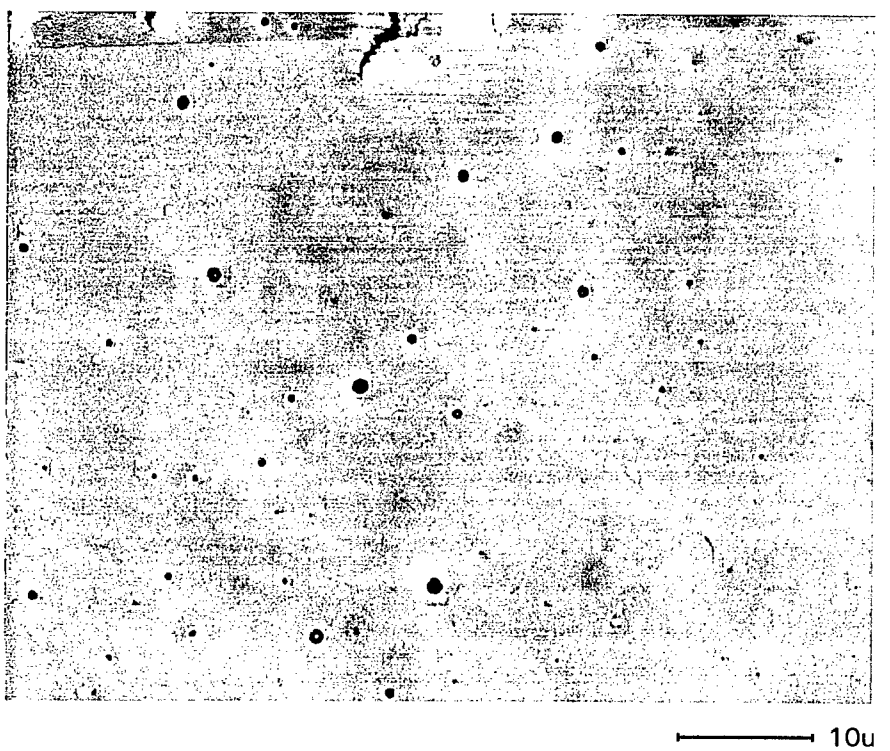


Figure 6. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with citric acid (20% w/w) as the pore former after additional storage of the membranes in 0.1 M phosphate buffer pH (7.4) for 48 hours.

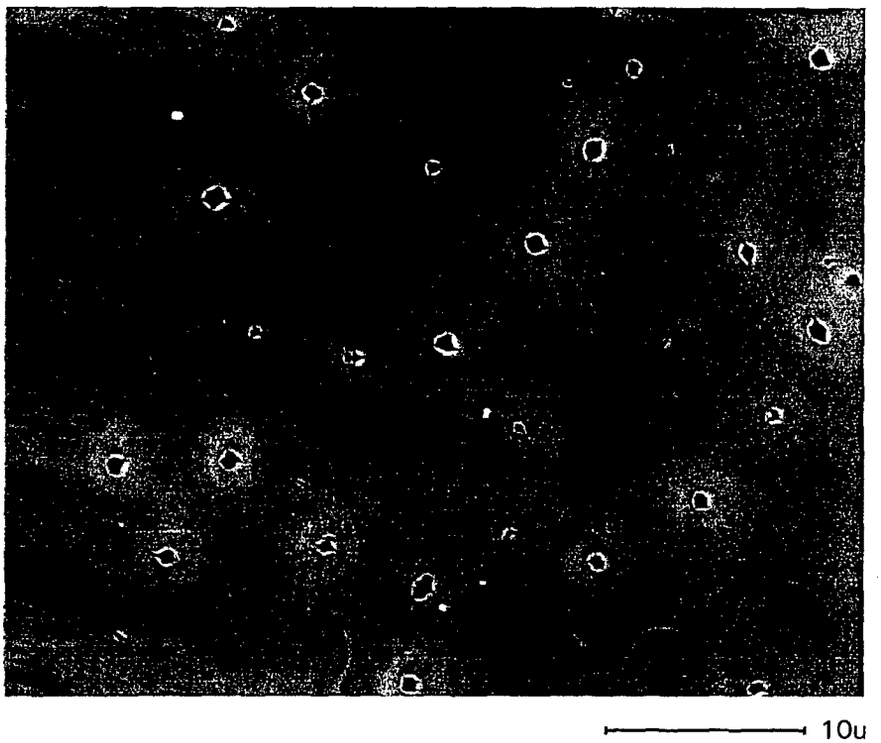


Figure 7. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with glycerin (20% w/w) as the pore former.

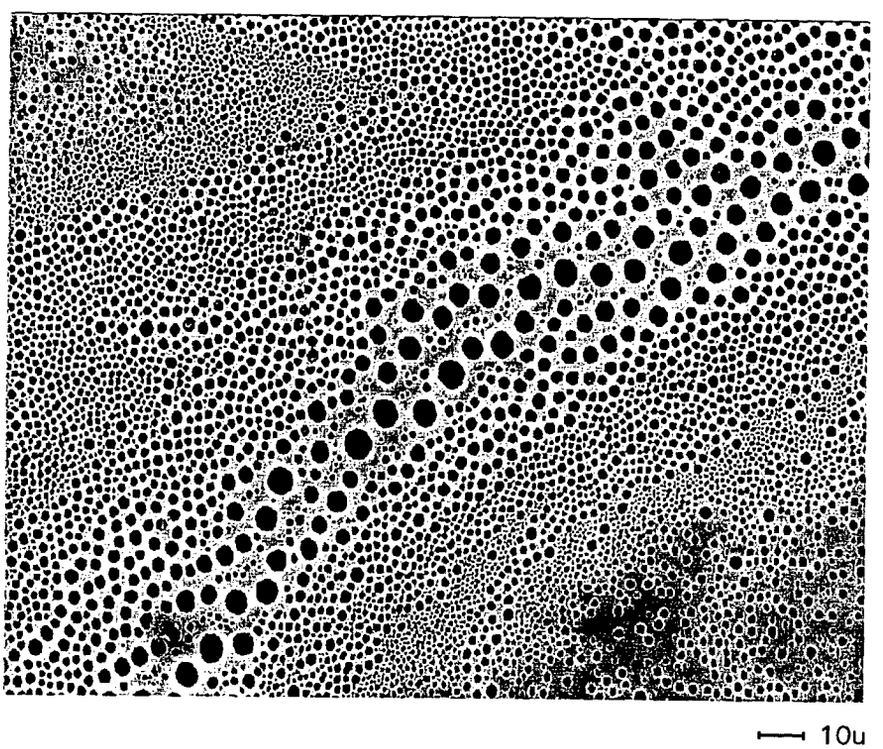


Figure 8. SEM of polymeric membrane cast from 65/35 poly(DL-lactide-co-glycolide) with glycerin (20% w/w) as the pore former after additional storage of the membranes in 0.1 M phosphate buffer (pH 7.4) for 48 hours.

The SEM data obtained is very enlightening and conclusively indicates that pores (water channels) are formed within the membranes using citric acid or glycerin as pore former which is highly indicative of the future technical feasibility of the proposed OBITS-PANDA delivery platform.

Permeability of Lidocaine Across the Cast Membranes

The transport property of lidocaine across the membranes containing no pore former and the three pore formers chosen were determined in order to demonstrate the mechanism of transport across the membranes containing the pore formers. The mechanism of transport across membranes containing pore formers was anticipated to be predominately through the water channels formed in the membranes after the pore formers come in contact with an aqueous media (Wesselingh, 1993). Therefore, the transport of lidocaine across membranes containing pore formers is anticipated to be significantly greater than the transport of lidocaine across membranes with no pore former (control membrane). The demonstration that the mechanism of drug transport across the membranes is through the formed water channels has strong implications in that the drug/polymer interactions are significantly reduced and virtually eliminated. Furthermore, the control of drug release across the polymeric membranes will primarily depend on the number of pores or water channels that are formed in the polymeric membranes as opposed to various physico-chemical properties of the polymer and the drug such as partition coefficient or diffusion coefficient of the drug in the polymer. This minimization of drug polymer interaction provides significant advantage in controlling and obtaining zero order constant drug release (Zentner et al., 1985; Thombre et al., 1989).

The transport of the drug across various polymeric membranes containing pore formers and polymeric membrane with no pore former was determined using vertical Ussing chambers (Kompella et al., 1993). The membranes were cut into appropriate size and soaked in distilled water for 12 hours prior to the experiment. The experiment was carried out using phosphate buffered saline (pH=7.4) at 37°C. At various predetermined time points samples were withdrawn from receiver side of the chamber and analyzed for drug. The cumulative amount of lidocaine transported across the membranes as a function of time was calculated and the results are shown in Figure 9.

As is evident from Figure 9 the lidocaine transport across the membrane with no pore former is extremely small as compared to membranes with pore formers. The rank order of the pore formers for lidocaine transport were poly ethylene glycol 8000, glycerin, and citric acid. The different ranking of the various pore formers is associated with the number and size of pores or water channels that form as a result of incorporation of the pore former within the membrane. The SEM observations indicated a lower number of well defined water channels are formed with citric acid as compared to glycerin. This is consistent with the lower amount of lidocaine being transported across membranes using citric acid as opposed to glycerin.

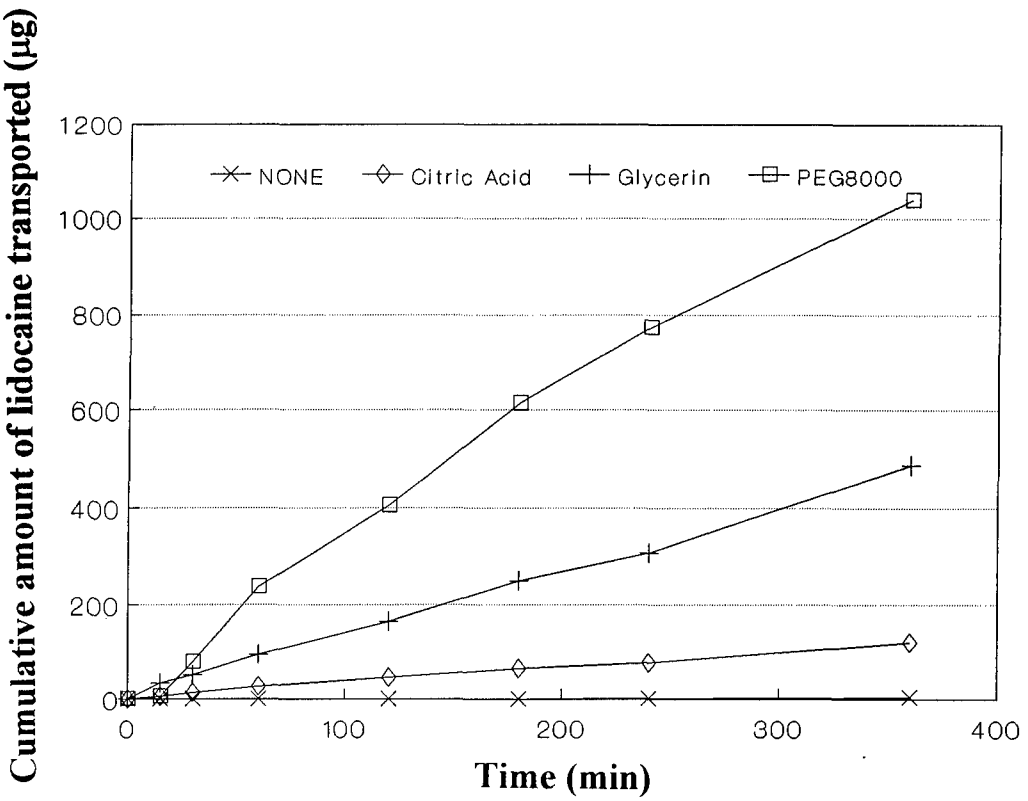


Figure 9. The cumulative amount of lidocaine transported across the various cast membranes. The pore formers were used at the 20% w/w level. (n=3)

Based on the tremendous increase in the transport of lidocaine across the membranes cast using pore formers and the SEM pictures as compared to control membrane with no pore former, it is evident that water channels are formed in the polymer. These water channels allow for the transport of drug through these water channels as opposed to the diffusion of the drug through the membrane itself thus reducing the drug/polymer interactions significantly making the technology suitable in practical applications to polar and non-polar drugs (Wesselingh, 1993; Zentner et al., 1985). By minimizing the drug/polymer interaction further advantage is gained in that zero-order constant release of the drug becomes possible. The transport data obtained further supports the technological feasibility of the proposed OBITS-PANDA technology.

Long-term Mechanical Property of the Cast Membranes

The primary objective of this testing was to assure that the membranes maintain their integrity during implantation in biological systems. The long term mechanical integrity of the membrane was evaluated to ensure that no change in the mechanism of drug release occurs over the desired release time frame. Furthermore, the maintenance of the mechanical integrity reduce the chances of dose dumping associated with catastrophic failure of the membrane (Sinko et al., 1993). The long-term mechanical testing was performed on the cast membranes as a function of storage time in 0.1 M phosphate buffer pH=7.4 (Aulton, 1982). The phosphate buffer was used to simulate the storage of the membranes in the more complex biological systems where the polymer will be utilized (Vert et al., 1991). The tensile strength of the various polymeric membranes cast were determined as a function of storage time in buffer and plotted (Figure 10).

As is evident from Figure 10, the membranes utilizing glycerin and poly ethylene glycol 8000 as the pore former have slightly lower strength than the membranes cast using no pore former. This is due to the introduction of the pore or water channels in the polymeric membranes containing the pore formers which slightly weakens the mechanical strength of these membranes as compared to the membranes with no pore former (control membranes). The tensile strength of all the membranes cast decrease slightly as a function of storage time possibly due to slight bulk erosion or introduction of polymeric degradation to lower molecular species. At any rate, the decrease is slight and deemed to be insignificant for our application.

The long term mechanical data indicates that the membranes maintain their mechanical integrity after prolonged storage time in buffer used to mimic the more complex biological systems. This is of positive impact on the technical feasibility of the proposed OBITS-PANDA platform since the possibly of dose dumping due to mechanical failure of the proposed dosage form is significantly reduced.

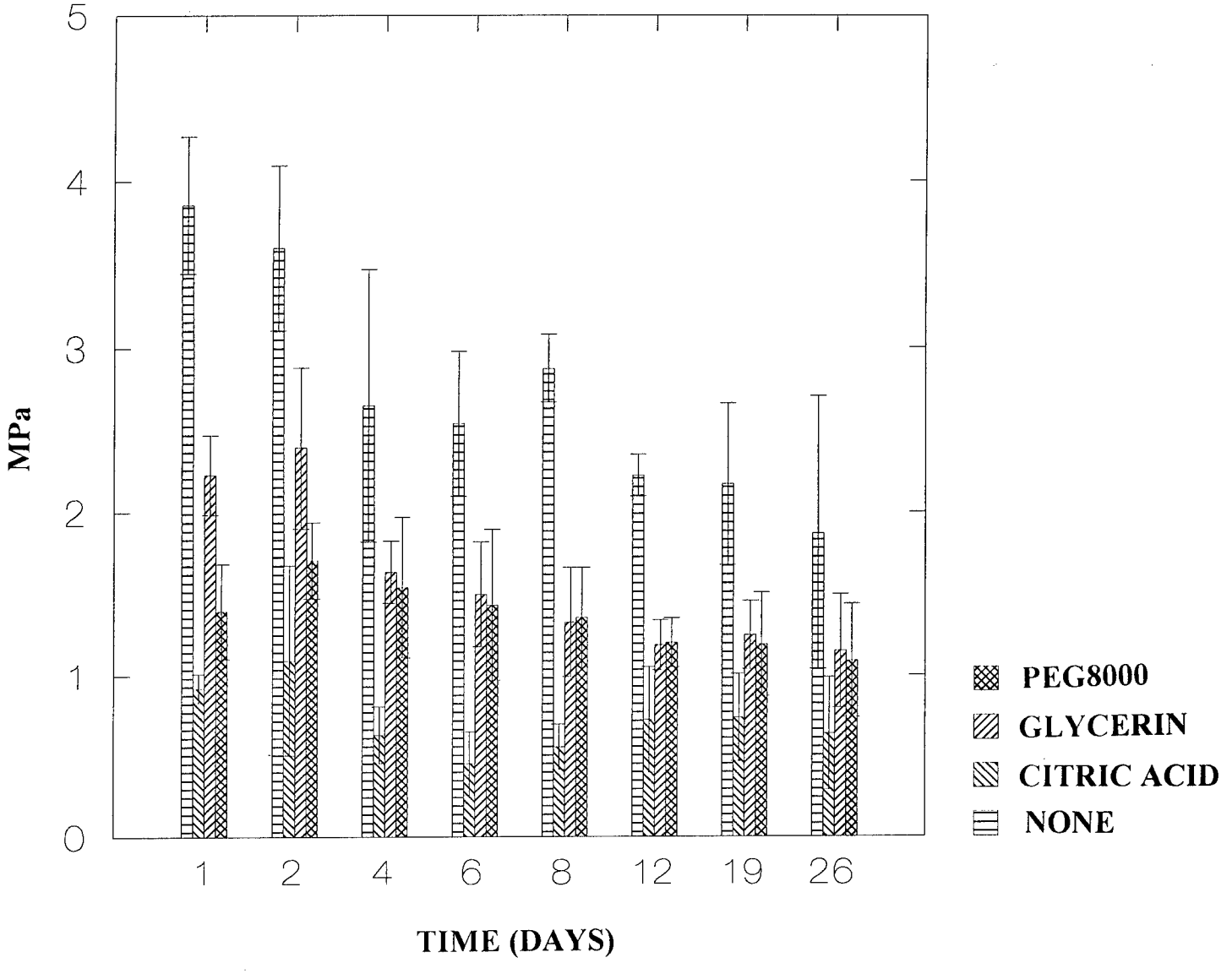


Figure 10. Long-term mechanical strength of the cast membranes as a function of storage time in pH 7.4 phosphate buffer. (n-4)

Summary and Conclusions

The technical and commercial feasibility of developing a controlled release delivery system based on the microporous membranes was demonstrated. For this purpose, various hydrophilic water soluble pore formers were tested for their solubility in different solvent systems and membranes containing these solutes were fabricated. Based on the solubility of the pore formers and the homogeneity of the membranes, three pore formers were identified for further study. Further studies using the selected pore formers confirmed that the membranes cast using the pore formers possessed the properties that were required to design and fabricate the proposed dosage system. The following are the properties of the membranes that support the technical feasibility of the proposed dosage form:

- The kinetics of pore formation studies indicated that pore formers are released very rapidly from the membranes upon contact with water. Because of such rapid pore formation in the membranes little or no lag time is anticipated with the dosage form designed and fabricated from these membranes.

- While 100% polymeric membranes was virtually impermeable to lidocaine, 80% polymeric membranes containing 20% pore formers were highly permeable to lidocaine. These transport results support the fact that pores are formed in the membranes following contact with water and that the transport of the drugs across the membranes cast using the selected pore formers is predominately through the pores which are formed within these membranes. This observation is of positive impact on the project since the drug transport occurs through the water channels formed in the membranes the interaction between the drug and the polymer is virtually eliminated.

- The scanning electron microscopy results conclusively demonstrated the formation of water channels upon contact with an aqueous buffer were formed in the membranes cast with hydrophilic solutes. No such pores were observed in the membranes containing polymer only.

- The long term mechanical testing indicates that over a one month time frame in which the membranes were stored in a phosphate buffer to mimic the biological media there was a minor decline in the mechanical strength of the membranes. This is also of positive impact on the project since the mechanical integrity of the membrane does not deteriote significantly even after a month therefore the possibility of dose dumping (release of all of the drug at once due to mechanical bursting and/or failure) is significantly reduced.

The above observations support the technical feasibility of the proposed dosage form which is extremely positive. By virtue of the membranes fabricated in this study the proposed OBITS-PANDA delivery system will start releasing the drug soon after contact

with water present in the body. The release will be controlled by the size and number of pores, the thickness of polymeric coat, and the concentration of drug and osmotic agent incorporated within the delivery system. These parameters can be maintained constant throughout the release profile, thereby, zero-order constant release is expected from the dosage form. The superior performance properties of the proposed OBITS-PANDA dosage form in terms of anticipated zero order release profile and reduction of side effects and toxicities warrant follow-on research and development activities toward the commercial implementation of the proposed technology.

REFERENCES

Aulton, M., "Assessment of the mechanical properties of film coating materials" International Journal of Pharmaceutical Technology and Product Manufacture, 3, 9, 1982.

Bonica, J.J., Liebeskind, J.C. and Albe-Fessard, D., "Perface" Advances in Pain Research and Therapy, Vol. 3, edited by H.L. Fields et al, Raven Press, New York, 1979.

Brady, J. M., Cutright, D. E., Miller, R. A., Ballistone, G. C. "Resorption rate, route of elimination, and ultrastructure of the implant site of polylactic acid in the abdominal wall of the rat" J. Biomed. Mater. Res., 7, 155, 1973.

Frazza, E. J. and Schmitt, E. E. "A new adsorbable suture" J. Biomed. Mater. Res. Symp., 1, 43, 1971.

Frolund, F., Frolund, C. "Pain in general practice" Scand. J. Prim. Health Care, 4, 97, 1986.

Frymoyer, J., Cats-Baril, W., "An overview of the incidence and costs of low back pain" Orthop Clin N Am, 22, 263, 1991.

Hellinger, F., "Forecasting of the costs of medical care for persons with HIV: 1992-1995" Inquiry, 29, 356, 1992.

Higuchi, T. "Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices", J. Pharm Sci., 1988, 5, 622-624.

Jacobs, I. and Mason, N. "Polymer Delivery Systems Concepts" In Polymeric Delivery Systems: Properties and Applications, ACS Symposium Series 520, edited by El-Nokaly, M., Piatt, D., and Charpentier, B., American Chemical Society, Washington, DC. 1994.

Kompella, U., Kim, K., Lee, V., "Active chloride secretion in the pigmented rabbit conjunctiva", Current Eye Research, 12, 1041, 1993.

Lambert, W., Peck, K., "Development of an insitu forming biodegradable poly-lactide-co-glycodie system for the controlled release of proteins", J. Controlled Rel., 33, 189, 1995.

Maniar, M., Domb, A., Haffer, A., Shah, J., "Controlled release of local anesthetic from fatty acid dimer based polyanhydride" J. Controlled Rel., 30, 233, 1994.

Mhando, J., Wan Po, L. "Controlled release of local anesthetic agents from liquid-solid emulsion gels", 62, 249, 1990.

Shah, S., Cha, Y., Pitt, C., "Poly (glycolic acid-co-DL-lactic acid): diffusion or degradation controlled drug delivery?" J. Controlled Res., 18, 261, 1992.

Sinko, P., Kohn, J., "Polymeric drug delivery systems: An Overview" In Polymeric Delivery Systems: Properties and Applications, ACS Symposium Series 520, edited by El-Nokaly, M., Piatt, D., and Charpentier, B., American Chemical Society, Washington, DC. 1994.

Sternbach, R. "Survey of pain in the united states: the Nuprin Pain Report" Clin. J. Pain, 1, 49, 1986.

Thombre, A., Zentner, G., Himmelstein, K., "Mechanism of water transport in controlled porosity osmotic devices" J. Membr. Sci., 40, 279, 1989.

Vert, M., Li, S., Garreau, H., "More about the degradation of LA/GA-derived matrices in aqueous media" J. Controlled Res., 16, 15, 1991.

Von Korff, M., Dworkin, S., Le Resche, L., Kruger, A., "An epidemiologic comparison of pain complaints" Pain, 32, 173, 1988.

Wesselingh, J. "Controlling diffusion", J. Controlled Res., 24, 47, 1993.

Zentner, G., Rork, G., Himmelstein, K., "Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds" J. Controlled Rel. 2, 217, 1985.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 4 Dec 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB218773
ADB223531
ADB230017
ADB223528
ADB231930
ADB226038
ADB224296
ADB228898
ADB216077
ADB218568
ADB216713
ADB216627
ADB215717
ADB218709
ADB216942
ADB216071
ADB215736
ADB216715
ADB215485
ADB215487
ADB220304
ADB215719
ADB216072
ADB222892
ADB215914
ADB222994
ADB216066
ADB217309
ADB216726
ADB216947
ADB227451
ADB229334
ADB228982
ADB227216
ADB224877
ADB224876
ADB227768
ADB228161
ADB229442
ADB230946
ADB230047
ADB225895
ADB229467
ADB224342
ADB230950
ADB227185
ADB231856
ADB229914
ADB229497
ADB230947
ADB282209
ADB270846
ADB282266
ADB262442
ADB256670