An Exploration of Design Parameters – The Development of a Temperature Responsive Prostaglandin E_1 Implant for Treating Penile Erectile Dysfunction

by

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An Exploration of Design Parameters - The Development of a Temperature Responsive Prostaglandin E_1 Implant for Treating Penile Erectile Dysfunction

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Abstract

The objective is to make a penile implant which would release drug on demand to treat erectile dysfunction. The triggered delivery of prostaglandin E_1 (PGE1) and a model drug, propranolol (PRO), across a temperature-responsive membrane, and the stability of PGE1 were examined.

Porous polyethylene (PE) membranes were absorbed with an alkane, the melting point of which corresponds to the release-trigger temperature. The alkanes were selected because of their inertness which would maintain PGE1 stability in the

implant. Permeability through these membranes can be controlled by varying the temperature above or below the melting point of the absorbed substance.

PRO permeabilities through docosane-absorbed PE membranes at 37°C and 45°C was reproducible, giving an on-off permeability ratio of 378(± 65). Similarly, the on-off permeability ratio through docosane-eicosane-absorbed membranes at 37°C and 42.5°C was 235(± 56). However, PGE1 permeation through these membranes was undetectable, primarily due to its low docosane/water distribution coefficient.

The membrane concept can be applied to the delivery of other drugs.

Polyethylene membrane were reproducible at 37 °C and 42.5 °C for 5 cycles of temperature oscillation. The permeability of PRO at 37 °C was 7.87 (± 0.66) × 10^{-10} cm^2/s, and at 42.5 °C, was 1.85 (± 0.41) × 10^{-7} cm^2/s, giving an on-off ratio of 235 ± 56. The results demonstrated that the responsive membrane triggered by a temperature change could yield reproducible and reversible PRO permeabilities. Moreover, the "on" and "off" permeabilities are significantly different to be of practical use.

Repeated permeation experiments using PGE1 as the solute showed that PGE1 was not able to pass through the thermal-responsive membrane. By measuring the octanol/water and docosane/water partition coefficients of PGE1 and PRO, the observed difference in membrane partition behaviour was attributed to PGE1's small docosane/water partition coefficient.

Solute permeability through the membrane used in this study can be controlled by varying the membrane temperature above or below the melting temperature of the membrane-modifying substance. Although PGE1 was not able to partition across the membrane, the high on-off permeability ratio achieved with PRO provides promise for the development of a thermal-responsive implant using this membrane and a suitable drug. The investigated thermal-responsive drug-delivery system can be applied in other clinical situations where drug is to be released on demand.

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1.0 Introduction

After years of responsive drug delivery research, many concepts to trigger on-demand release of drugs have been identified, yet few such delivery systems are in clinical use. It has been demonstrated that drugs can be delivered in response to physical changes such as temperature, pH, and light.[1] The need now is to integrate and test such responsive drug delivery concepts within the context of specific therapeutic applications. Penile erectile dysfunction, a condition where a drug is needed only on demand, is a clinical scenario in which the application of responsive drug delivery can be tested.

The human body can endure only minimal fluctuation from the norm. For a responsive device placed inside the body, the drug-release trigger should be in a form that is physiologically tolerable. The core temperature of a human body can range from 37 to 42 °C. Skin can tolerate slightly higher temperatures. Pain usually does not occur until the skin surface temperature reaches 45-50 °C.[2] As a result, induced temperature change can be used as a signal for responsive drug release.

The long term objective of this research is to develop, by integrating an existing responsive drug-release concept, a drug-containing thermal-responsive penile implant to treat erectile dysfunction. When the proposed device is implanted in a patient, upon application of external heating, it could release a desired amount of drug to the cavernosal cavity. The implant has the potential to provide an easy

on-demand treatment for impotent patients. Prostaglandin E_1 (PGE1) is a drug which has been approved for intracavernous[3] or intraurethral[4] use to treat erectile dysfunction. The specific objective of this thesis is to explore the feasibility and design parameters of a PGE1-containing thermal-responsive implant.

1.1 Statement of the Problem

Penile erectile dysfunction is an under-reported disease.[5] The embarrassment of revealing the problem as well as the lack of noninvasive therapy cause many impotent men to avoid seeking treatment. The administration of intracavernous injections can be painful and troublesome.[6] Other treatments, such as hormonal drugs[7] and topical application of vasodilating drugs[8], are not very effective. Traditional impotence treatments are not well accepted. Although widely marketed, a recently introduced oral drug, sildenafil,[9] is contraindicated with co-existing nitrate therapy. Yet the majority of impotent patients are seniors who are predisposed to cardiovascular diseases and require the systemic use of vasodilators. Without proper intervention, erectile dysfunction may demolish ego, affect social interactions and diminish the quality of life of the patient. There is a need to provide treatment options that are efficacious, have general patient acceptance, and have minimal drug interactions and side-effects.

1.2 Overview of Implant Design Concept

The proposed penile implant consists of a drug reservoir encapsulated by a thermal-responsive membrane, as shown in Figure 1.1. The cylindrical implant has a diameter of 0.3 cm, a length of 3.5 cm and is to be surgically inserted into one of the cavernosal cavities of the penis. The implant does not release drug at body

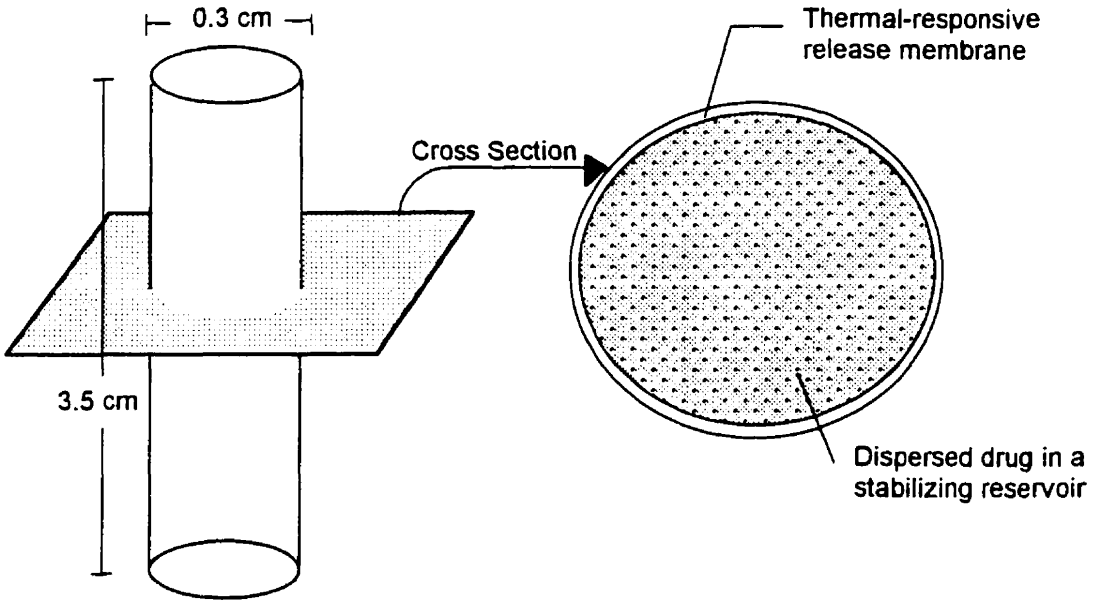

Figure 1.1 Proposed dimensions of the thermal-responsive drug-containing penile implant.

temperature. When the patient desires an erection, heating the implant membrane using an external heater can trigger the release of drug. The heating mechanism can be in the form of microwave or focusable ultrasonic wave, which targets the

heating of the implant and not the surrounding tissues. Selection of the trigger temperature is critical. It should be higher than temperatures that may be reached during a fever and lower than the skin's pain and burn thresholds. As the temperature of the implant is raised above the membrane's transition temperature, the drug is released from the implant and exerts its local pharmacological effect on penile tissues. Although the responsive release concept can be applied to any impotence drug, the regulation of PGE1-release from the implant was studied. Since no prior experience was available in such thermal-responsive device development, this thesis focused on identifying factors which would guide the design and ensure the feasibility of such an implant.

1.2.1 Clinical Requirements and Design Specifications

The pharmacological and clinical requirements of a penile implant containing the selected drug, and the design specifications that they dictate are described below.

(1) *The implant must reproducibly release PGE1 and exert pharmacological effect when and only when an external heating trigger is imposed.*

When the patient activates heating of the implant, the implant must reproducibly release a pharmacologically effective dose of drug upon triggering, while permitting no drug release when not activated. In the absence of the thermal-

trigger, the implant must release little or no drug, ensuring no pharmacological effect in the "off" state. The "off" permeability should be reproducibly low, irrespective of the number of "on" cycles experienced by the implant. Moreover, the required dose for pharmacological effect may be individualized by controlling the duration of heating.

(2) *The implant must respond fast to the application and removal of the external-heating trigger.*

To minimize the amount of patient anticipation, the pharmacological effect should manifest no later than 20 minutes after device activation. In other words, within 20 minutes of heating the implant to the trigger temperature, a pharmacologically effective dose of drug should be released. Drug release should stop after heating is discontinued. Cooling of implant is accelerated by enhanced blood flow to the cavernosal area, as the clinical response to the impotence drug manifests.

The required dose of intracavernously delivered PGE1 is usually no more than 20 μg per erection.[10] Using PGE1 as an example, to ensure a reasonable response time between the initiation of the on-trigger and the appearance of clinical effect, the required flux of PGE1 across the activated membrane should be no less than 20 μg in 20 minutes. Assuming that only the cylindrical surface of the implant is permeable to the drug, the average thickness of the membrane to be 50 μm, and the drug reservoir is saturated in PGE1, the minimum required permeability of PGE1 through the activated membrane is 3.2×10^{-7} cm^2/s.

(3) *The implant should provide sufficient drug for 6 months of use.*

The encapsulated drug should remain stable at body temperature inside the implant. Prostaglandin E_1 is a labile substance. It must remain stable for at least 6 months in the implant at body temperature. The drug reservoir material should be able to inhibit the degradation of drug during storage so that the drug in the implant remains stable until released.

(4) *The implant shape and size should be anatomically compatible, and easily insertable.*

The proposed implant should resemble the size of a mini-cigarette, with 0.3 cm diameter by 3.5 cm length, so that it could be easily inserted into the cavernosal cavity. The proposed dimensions are illustrated in figure 1.1.

(5) *The device must be safe to implant and use.*

The implant should be made from materials that have an established record of safe use and are biocompatible with penile tissue. Furthermore, the external heater should be able to focus on the implant, and thus selectively heat the device and not the surrounding tissues.

1.3 Objectives and Scope of the Thesis

With the above functional characteristics for the implant in mind, the specific objectives of this thesis are as follows:

(1) *To identify a pharmaceutical vehicle which would maintain the stability of PGE1 for 6 months at physiological temperature. The vehicle should also allow rapid diffusion of PGE1 when the implant is heated.*

(2) *To develop and characterize a thermal-responsive-release membrane for the encapsulation of PGE1 reservoir.*

(3) *To evaluate the feasibility of making a responsive-release, implantable PGE1 device using the thermal-responsive membrane.*

To meet the above objectives, the following studies were conducted in this thesis. Firstly, the stability of PGE1 in selected pharmaceutical vehicles was measured. Secondly, after reviewing existing responsive drug-release technologies, a technique for making a thermal-responsive rate-controlling membrane was adopted for the PGE1 implant. The permeabilities of PGE1 and its model compound, propranolol HCl (PRO), through the thermal-responsive membrane were measured at different temperatures. Finally, based on the results of the stability and permeation experiments, the feasibility of making such a thermal-responsive-

release PGE1 penile implant was assessed.

The hypotheses of this thesis will be presented in section 2.4, after the necessary background material is reviewed.

2.0 Background

2.1 Penile Erectile Dysfunction

Penile erectile dysfunction or impotence is defined as "the inability to achieve and maintain an erection that is sufficient for satisfactory intercourse,"[11] and its prevalence increases with age. The prevalence of erectile dysfunction is 39% among 40 years old and 67% among 70 years old. [12] It was estimated that approximately 30 million men in the United States had difficulty achieving an erection.[13] Impotence is a clinical manifestation, the origin of which can be psychologically, vascular, neurologically, hormonal or drug induced.[13, 14] In some cases, there is no definitive cause or the cause can be multifactorial.

Identifying the cause of impotence can assist the selection of an efficacious therapy. By knowing which part of the erectile function is affected, the physician can select therapeutic intervention that corrects the defect. A diagnostic plan should be carried out before the selection of therapeutic intervention. The diagnostic plan for the patient should be comprehensive and should include: obtaining the patient's sexual and general history, conducting clinical and physical examinations, and measuring laboratory parameters to check for hormonal imbalances.[15] Common physical examinations used to diagnose impotence are: PGE1 pharmacological

test, duplex sonography, dynamic pharmacocavernosography, dynamic pharmacocavernosometry, penile sonography and selective angiography.[15]

2.1.1 Physiology of the Erectile Tissues [16, 17, 18]

The normal function of erectile tissues requires the coherent coordination of many cellular pathways. For instance, the contractile activity of penile arterial smooth muscles is regulated by several factors: adequate levels of agonists, adequate expression of receptors, integrated transduction mechanisms, functional calcium homeostasis, synergistic interaction between contractile proteins, and effective intercellular communication among smooth muscle cells.

Figure 2.1 shows the cross sectional anatomy of a penis. The synergistic engorging effect of three cylindrical cords of erectile tissues - two corpora cavernosa and one corpus spongiosum - causes a penile erection. Under normal circumstances, the smooth muscles around the central arteries circulating inside the penis are in a contractile tone. As a result, there is a limited supply of blood flowing into the corpus cavernosa, and the penis is flaccid. The detumescence is maintained by constant adrenergic stimulation causing vasoconstriction of the penile arteries and contraction of the trabecular muscles, resulting in, respectively, reduction of the arterial inflow and collapse of the lacunar spaces. The maintenance of penile flaccidity has been attributed to the activity of the peptide endothelin and some eicosanoids ($PGF_2\alpha$ and thromboxane A_2).

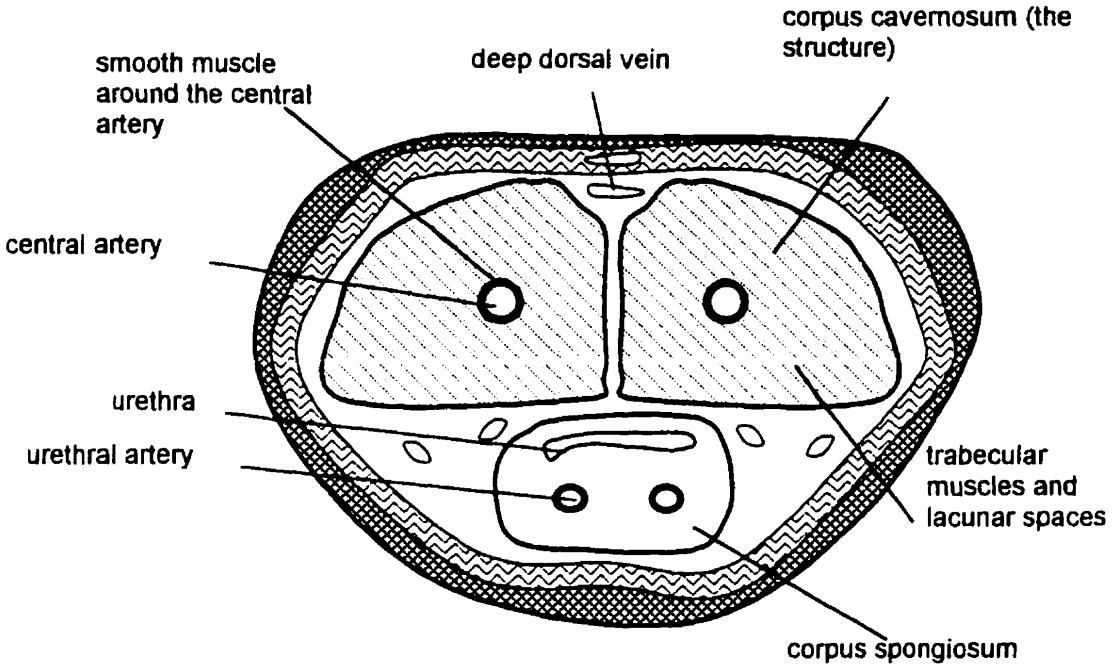

Figure 2.1 Cross section of the body of a penis.

When a man is aroused by sexual stimuli, dilation of penile arteries is the first event in the development of an erection. Nerve signals and chemical messengers direct the relaxation of cavernous arterial smooth muscles. As the tone of the muscles decreases, arterial blood flow to the cavernosal cavities increases from 4 to 12 cm^3/minute,[19] and more blood enters the lacunar spaces of the penis. The increased pressure in the lacunar spaces compresses the veins that drain the cavernosal cavities and facilitates the accumulation of blood; the rigidity of the penis is thus maintained. A similar process occurs in the corpus spongiosum, causing glans penis engorgement. A successful erection involves the coordination of many bodily functions, and any defects aong the pathway can cause impotence.

2.1.2 Current Erectile Dysfunction Therapies

Current erectile dysfunction therapies include oral ingestion of sildenafil,[9] cavernosal injection of vasoactive substances,[6] transurethral prostaglandin,[4, 20] vacuum suction therapy,[21] topical vasodilator, [8] hormonal therapy,[25] vascular surgery,[22] and insertion of mechanical prostheses.[23] The efficacy and side effects of each treatment option are summarized in table 2.1.

There are many limitations in the current treatment of erectile dysfunction. Oral therapy causes systemic side-effects such as hypotension and is contraindicated with co-existing anti-anginal drug therapies.[9] Intracavernous injections are painful and troublesome. Repeated needle puncture of the skin may cause hematoma, leading to penile deformity.[6] Improper injection technique can lead to complications such as infection. Although intraurethral PGE1 therapy is not as invasive as intracavernous injection, significant pain has been associated with the intraurethral use of PGE1.[20] A man using the intraurethral system should use a condom if his sexual partner is pregnant, as PGE1 can cause cervical dilation which may lead to premature labour or an abortion. The vacuum constriction device is not convenient to use and it gives the penis a cold, numb feeling.[21] Topical therapy, such as the nitrates, can lead to undesirable systemic side-effects, e.g. hypotension.[8] Hormonal treatment [7] and vascular surgery [22] are only effective when the specific defect is identified. Surgical insertion of a penile prosthesis is an invasive procedure and many complications can arise. Current erectile dysfunction

Table 2.1 Summary of current erectile dysfunction treatments.

Treatments	Brief Description	Efficacy	Side Effects
sildenafil [9]	• oral drug to be taken one hour prior to sexual activity	• average successful intercourse rate was 60% vs. 20% with placebo	• headache, flushing, indigestion, vision changes • contraindicated in co-administration of organic nitrates
intracavernal injection of vasoactive substances [6] e.g. alprostadil (PGE1), papaverine, papaverine / phentolamine	• inject vasoactive substances into the cavernosal cavity which produces smooth muscle relaxation in the penis • inject just prior to sexual intercourse	• efficacy rate reported to be between 65% to 85%	• penile fibrosis, priapism, painful erection • up to 50% of men who begin this form of treatment eventually discontinue therapy for various reasons (e.g. perceived unnaturalness of the injections, inadequate response, development of complications)
transurethral alprostadil [20]	• administer PGE1 to the urethra using a disposable applicator • insertion just prior to sexual activity	• overall response rate is about 40%	• penile pain, minor urethral trauma
topical agents [8] e.g. nitrate, minoxidil	• topically apply vasodilating drugs	• limited efficacy	• systemic hypotension in patient and partner • cervical dilation in partner

Table 2.1 Summary of erectile dysfunction treatments. (continued)

Treatments	Brief Description	Efficacy	Side Effects
hormonal therapy [7] e.g. testosterone, bromocriptine	• correct hormonal imbalance by administering the deficient hormone	• only useful for patients diagnosed with hormonal induced impotence	• systemic steroid administration can affect the functioning of other organs
vacuum constriction device [21]	• composed of a plastic cylinder, a vacuum pump and an elastic constriction band	• reported success rate between 65% to 90% • if used properly, a reliable and safe method to induce erection	• pain from constricting band, lack of spontaneity • up to 20% of patient may discontinue treatment • gives cold, numb feeling
vascular surgery [22]	• reconstruct damaged vasculature • the damaged site has to be identified before surgery	• only useful for patients diagnosed with vascular impotence	• surgery required • risk involved with surgery
penile prosthesis [23]	• insert mechanical prosthesis surgically	• fully capable of giving an erection	• possible mechanical failure • biocompatability concerns • surgery required • risk involved with surgery • many potential complications (e.g. infection, device malfunction)

therapies, other than the oral drug, sildenafil, lack acceptance by the general public. There is a need to provide improved alternatives in erectile dysfunction treatment.

2.2 Prostaglandin E_1

Prostaglandin E_1, also called alprostadil, has been approved for intracavernous[3] or intraurethral[4] use to treat erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

2.2.1 Pharmacology [16]

Prostaglandin E_1 is synthesized by the trabecular muscles and causes trabecular muscle relaxation. As PGE1 binds to the EP2 and EP4 surface receptors on smooth muscle cells, it causes the intracellular conversion of ATP to cAMP by adenylate cyclase. The intracellular mediator, cAMP, lowers the intracellular Ca^{2+} concentration, resulting in the loss of smooth muscle contractile tone, and thus mediates the smooth muscle relaxation response of PGE1. In addition to the direct muscle action, PGE1 also reduces the adrenergic constrictor tone by inhibiting the release of noradrenaline.

The half-life of PGE1 in plasma is less than 1 minute. Systemically, 60 - 80% of circulating PGE1 is metabolized after first pass through the lungs. Locally, human

cavernous tissues contain 15-hydroxy-dehydrogenase which provides local metabolism (intracavernosal) of PGE1. Endogenous PGE1 plasma concentrations range from 1.2 to 1.8 pg per mL.[24] An intravenous pharmacokinetic study demonstrated that the total body clearance of PGE1 was 104 L per minute.[24] However, the local cavernosal PGE1 clearance could not be accurately determined due to experimental difficulty.[25]

The intracavernous PGE1 dose for treating erectile dysfunction, depending on the underlying etiology, ranges from 5 to 20 μg per injection while some clinical trials used doses up to 60 μg.[10] The dose needs to be titrated, and the patient is taught the injection technique in the physician's office. The optimal dose would give the patient an erection which persists for up to 1 hour.[3] The medical community considers PGE1 as safe and as effective as the other vasoactive substances for intracavernous treatment of impotence.[26] Moreover, PGE1 is less likely to cause priapism than injection of other vasoactive agents.[27] Since PGE1 is approved to be used locally to exert an erectile effect, it was selected as the active ingredient to be incorporated into the proposed thermal-responsive release device. The safety and efficacy of PGE1 use in erectile dysfunction treatment have been established.

2.2.2 Stability

2.2.2.1 Stability Studies

Prostaglandin E_1 readily undergoes a dehydration reaction in an aqueous environment. (see figure 2.2) Previous stability studies of PGE1 in various pharmaceutical vehicles are summarized in table 2.2. The 90% shelf life, the time elapsed when 90% of the original mass of PGE1 remains in a pharmaceutical product, is also included in table 2.2.

Aqueous stability studies demonstrated that the kinetics of PGE1 dehydration to the inactive PGA1 was pH dependent. The shelf lives of PGE1 at 37 °C were 23.4 hours at pH 3 and 4 minutes at pH 11.3.[28] The shelf life of PGE1 in a physiologically compatible solution, 4% alcohol and 0.9% saline solution, was found to be 9.8 days at 25 °C.[29] Attempts to stabilize PGE1 in lipid emulsion[31], gel ointment[33], and aqueous solution in the presence of cyclodextrin[32] yielded no improvement in PGE1 stability.

On the other hand, the stability of PGE1 was better maintained in oleaginous vehicles. As demonstrated by Yamamura and Yotsuyanagi,[34] PGE1 remained stable for 3 months at 40 °C in white petrolatum. White petrolatum is a purified mixture of semi-solid hydrocarbons obtained from petroleum[35] and is inert when well protected from light and air. The enhanced stability of PGE1 in white petrolatum is probably

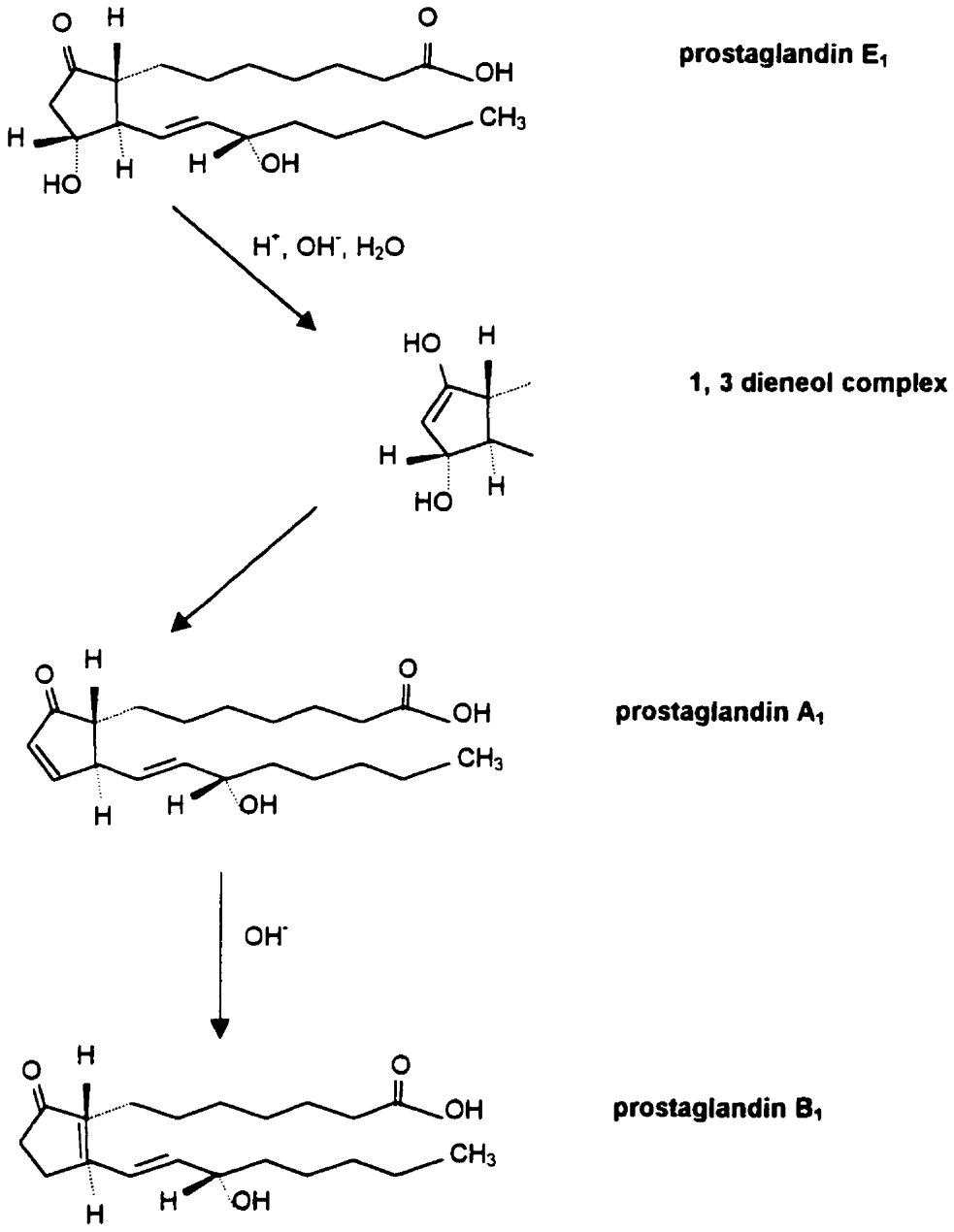

Figure 2.2 Dehydration reaction of prostaglandin E_1 to prostaglandin A_1 and B_1.

Table 2.2 The stability of prostaglandin E_1 in various media.

Researchers	Pharmaceutical Vehicles	Storage conditions	90% shelf lives
Stehle R [28]	citrate buffer, pH 3 pH 11.3, sodium or potassium hydroxide	37 °C 37 °C	23.4 hours 4 minutes
Shulman NH [29]	4% alcohol and 0.9% saline solution	25 °C	9.8 days
Gatti R [30]	"physiological solution"	23 - 25 °C	15 days
Teagarden DL [31]	soybean oil-in-water emulsion, pH 5	35 °C	12 days
Uekama K [32]	aqueous maltosyl-ß-cyclodextrin solution	60 °C	5.5 days
Yamamura K [33]	Gel ointment (carboxyl vinyl polymer, propylene glycol, ethanol, ammonia, water)	25 °C	26 days
Yamamura K [34]	white petrolatum macrogol ointment	40 °C 40 °C	90 days 40 days
Miwa K [36]	tricaprylin filled, sealed hard gelatin capsules	40 °C	> 3 months (99.9% remained at 3 months)

due to the inert, semi-solid, and acid-free environment petrolatum provides. Moreover, Miwa et al.[36] demonstrated that hard gelatin capsules of PGE1 stabilized in tricaprylin remained stable at 40 °C for 3 months. Tricaprylin, see figure 2.3, is an esterified glycerol with low acidity. This finding further confirms that PGE1 can be stabilized in inert, acid-free vehicles. The acid values of some selected oleaginous vehicles are presented in table 2.3

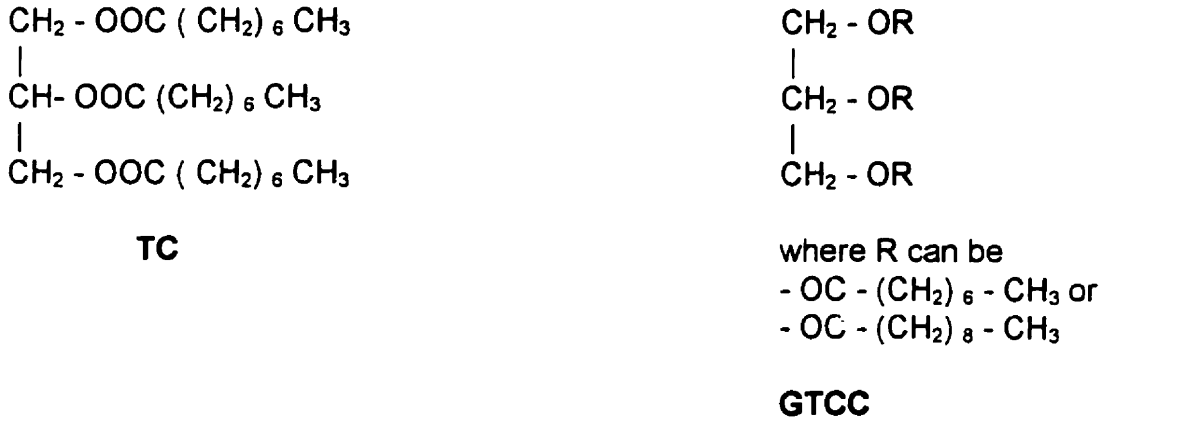

Figure 2.3 Chemical structures of tricaprylin (TC), caprylic / capric triglycerides (GTCC), and ethyl oleate (EO).

Table 2.3 Acid values of selected oleaginous pharmaceutical vehicles suitable for parenteral use. [37]

Pharmaceutical Vehicles	**Acid value (less than or equal to)**
caprylic / capric triglyceride (GTCC)	0.2
sesame oil	0.3
ethyl oleate (EO)	0.5
peanut oil	0.5
soybean oil	0.6
polyoxyethylene castor oil	2
corn oil	2-6
lecithin	36

The inability to stabilize PGE1 prompted researchers to look for compounds which have PGE1's pharmacological action, yet better chemical stability. Delta (8)-9-O-butyryl prostaglandin F-1 butylester (AS013), structure shown in figure 2.4, is a prodrug of PGE1.[38] The prodrug itself has little pharmacological activity, but it can be hydrolyzed by human serum esterase to form PGE1. Acylation at C-9 protects the five-carbon ring from forming the enol complex which leads to the dehydration of PGE1. Esterification at C-1 enhances the solubility of the compound in soybean oil to prevent unwanted liposomal leakage. AS013 was incorporated into lipid microspheres, made of lecithin-emulsified soybean oil. About 90% of the AS013 incorporated in lipid microspheres was recovered unchanged after storage at 40 °C for one week.[39]

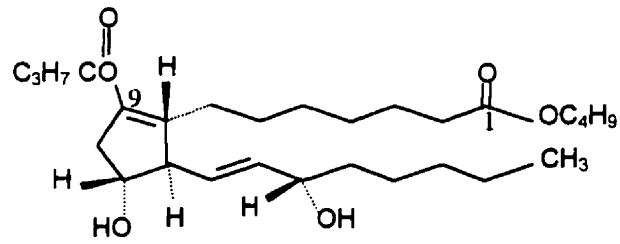

Figure 2.4 Chemical structure of the prostaglandin E_1 prodrug, delta (8)-9-O-butyryl prostaglandin F_1 butyl ester (AS013).

2.2.2.2 Degradation Mechanism

Dehydration of PGE1 can be catalyzed by acids, bases, or water to form PGA1, and PGA1 further isomerizes to PGB1 in a basic environment (see figure 2.2).[28] Studies have been performed to measure the specific rates of PGE1 degradation, and a degradation mechanism has been proposed.[28, 40] The cyclopentanone ring of PGE1 is attacked by acid, base, or water to form a 1, 3-enediol, an enolized complex. The 1,3-enediol complex rearranges to form PGA1, and PGA1 rearranges to PGB1 in a basic environment. If hydrogen ions, hydroxyl ions, and water molecules can be eliminated from the surroundings, it is possible that the rate of PGE1 dehydration reaction can be minimized.

2.3 Responsive Drug Release Technology

2.3.1 Overview

The area of earlier drug delivery research focused on identifying ways to release drug slowly, preferably with a zero-order release profile, to maintain the drug concentration within the therapeutic window. [41] However, in some therapeutic regimens, the drug is not needed continuously; instead, only pulses of drug are needed at specific times. For example, excess insulin is not needed unless the blood sugar concentration raises above a critical level.

In recent years, research has been devoted to the discovery of novel responsive-release mechanisms which respond to small changes in the environment, including changes in pH[42], temperature[42], oscillating magnetic fields[43], ultrasound[44], electrical fields[45] or ionic strength. [46] Although the pulsatility and repeatability of these systems have been demonstrated, there has not been much success utilizing such a technology to make clinically effective responsive drug-release devices.

A common way to regulate the release of drug is by allowing the drug to diffuse through modified pores of a polymer membrane,[47, 48] see figure 2.5. In order for the drug to diffuse from one side of the membrane to the other, drug molecules have to diffuse through the modified pores of the membrane. A solute's permeability

through a membrane can be regulated by the responsive pore-filling materials which respond to environmental changes. The porous membrane acts as an inert physical support for the pore-filling material, which can be absorbed by or covalently attached to the membrane. As the pore-filling material changes properties in response to a specific signal, responsive-release of drug can be achieved. Drug diffusion through the polymer should be insignificant to maximize the responsive effect.

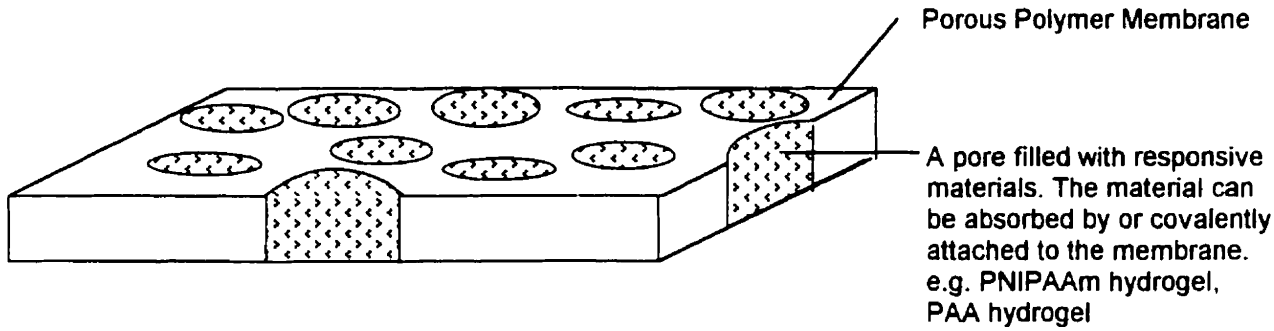

Figure 2.5 Microscopic view of the signal-responsive modified porous polymer membrane.

The intrinsic water solubilities of poly (N-isopropylacrylamide), PNIPAAm, and Poly (acrylic acid), PAA, vary in response to different temperature and pH, respectively. At temperatures below the lower critical solution temperature (LCST), around 32-34 °C,[48] the PNIPAAm chains adopt an extended conformation in water. When the temperature of the polymer solution is raised above its LCST, hydrophobic interactions of the N-isopropyl groups dominate. As a result, the polymer chains collapse, maximizing intramolecular interactions, and precipitate out

of the solution. The PNIPAAm chains can be covalently attached to a porous polymer membrane by UV [42] or plasma [49] surface modification techniques. It was demonstrated that PNIPAAm-modified polymer membranes have different solute permeabilities at temperatures below and above the LCST.[48]

Poly (acrylic acid) has an ionizable side group and responds to pH changes. At pH values above the pKa of PAA, the side group is ionized; as a result, the polymer chains adopt an extended conformation in water. At pH values below the pKa of PAA, the side group is not ionized, and the polymer chains collapse. When PAA chains are attached to the pores of a polymer membrane, solute permeability through such a modified polymer membrane would vary in response to changes in pH.

In addition to covalently attaching responsive polymer chains to porous membranes, porous membrane filled with responsive hydrogels can also regulate solute permeability. Kapur et al.[50] demonstrated that crosslinked polyacrylamide hydrogels embedded in a porous polymer membrane could regulate the diffusion of proteins in response to ionic strength changes. The result shows promise in the development of protein separation by molecular weight and ionic charge.

Hydrogels swell and deswell in response to specific stimuli. However, the slow kinetics of swelling and deswelling imply that it may take a long time for the hydrogel to reach equilibrium dimensions.[51] Moreover, the usual on-off permeability

ratios of hydrogels are small. As a result, a hydrogel-modified membrane would not meet the clinical requirement of fast response for the PGE1 implant. A pore-filling material which would respond sharply to temperature changes is needed.

2.3.2 Thermal-Responsive Drug Release

Poly (L-glutamates) with long n-alkyl side chains are comb-like polymers, see figure 2.6, which melt at specific temperatures depending on the length of the n-alkyl side chain. Landec Corporation (Menlo Park, California, U.S.A.) markets a

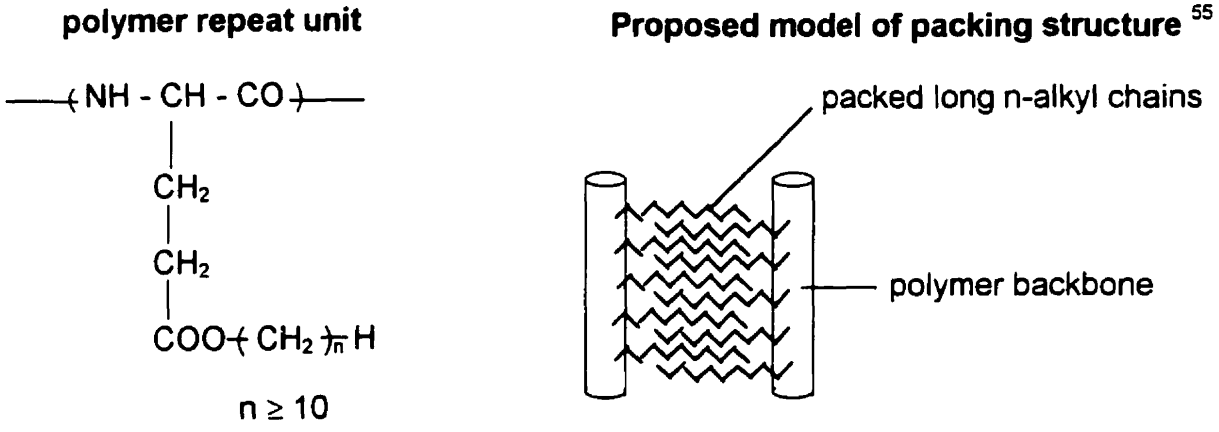

Figure 2.6 Poly (L-glutamates) with long n-alkyl side chains.

thermal-responsive microencapsulated pesticide[52] which is made of these comb-like thermoplastic elastomers.[53, 54] The pesticide microcapsules can be applied to fields

in the Spring and the pesticide is not released until the soil temperature is above the melting point of the thermoplastic elastomers. The rise in soil temperature would correspond to the germination of seeds. However, this form of responsive release is for a single use only.

Nozawa et al.[56, 57, 58] investigated the possibility of modifying polymer membranes using liquid crystals, such as monooxyethylene trimethylolpropane tristearate. Using these liquid-crystal-embedded polymer membranes, they demonstrated sharp and dramatic thermal-responsiveness for the delivery of indomethacin, an anti-inflammatory drug. The drug delivery system was further fabricated into a patch formulation and the thermal-responsiveness was demonstrated in white rabbits.[59] It was shown that the plasma concentrations of indomethacin and ketoprofen were effectively suppressed at 32 °C by the thermo-responsive membrane compared with those at 38 °C. However, more studies are needed to quantify the amount of permeability changes.

2.3.2.1 Extracorporeal Heating Devices

Applying heating to the human body as part of a medical treatment is common. Heating pads are used to alleviate muscle soreness and joint pain. Benign prostatic hyperplasia has been treated with local hyperthermia.[60] Specially designed microwave antenna are used in transurethral hyperthermia treatment in which the tissue underneath is heated and the urethral epithelium is unaffected.

There are two general ways of heating: conductive heating or radiative heating. Conductive heating involves generating a heat gradient from the heat source to the desired site of action. This form of heating is not appropriate for heating an implanted thermal-responsive device because the skin has to be exposed to a much higher temperature than the implant. On the other hand, radiative heating is useful because it can heat the underlying diseased structures or implant without significantly heating up the skin. By adjusting the frequency of the microwave, the depth of maximum heat penetration can be controlled.[61] Moreover, the temperature profile of the surrounding structures can be estimated using a heat transfer model via computer simulation. A better alternative to microwave heating is the use of ultrasound. The additional advantage of using ultrasound is that ultrasonic wave is focusable. [62, 63] When the location of the implant is known, the implant can be selectively heated to trigger drug release. Moreover, if a piezoelectric material, such as polyvinylidene fluoride, were used to encapsulate the implant, more implant-focused ultrasonic heating may be possible.

The value and safety of ultrasound in medical use have been established.[62] In order to make an ultrasonic heater for triggering responsive drug release, the heater should be focusable, be convenient to use, have a low energy requirement, and be of low cost. It appears that technology exists for making such an ultrasonic heater. The actual design and development of this heater, however, is outside the scope of this thesis.

2.4 Research Hypotheses

After reviewing the relevant background, the following hypotheses were articulated and tested in this thesis.

(1) Hydrogen ions, hydroxide ions, and water molecules can promote the formation of PGE1 activated complex. By eliminating such catalytic substances in the pharmaceutical vehicle, the integrity of the β-hydroxycyclopentanone ring of PGE1 can be maintained, thus, limiting PGE1 degradation.

Since PGE1 is known to degrade rapidly in aqueous solution via acid-catalyzed or base-catalyzed reactions, oleaginous pharmaceutical vehicles with low acidity (see table 2.3) are possible candidates to maintain the integrity of PGE1.

(2) By adding an antioxidant to the oleaginous pharmaceutical vehicle, stability of PGE1 in the vehicle can be prolonged.

Oleaginous vehicles can undergo oxidation, forming acidic species which can catalyze the degradation of PGE1. We hypothesize that the addition of an antioxidant to scavenge free radicals in the oleaginous pharmaceutical vehicle would delay oxidation of the vehicle, hence prolonging the stability of PGE1 in such a vehicle.

(3) The melting and crystallization properties of alkanes can be used as a temperature on-off switch to regulate solute permeability.

In dilute aqueous solution, the diffusion coefficient of a low molecular weight (<800) solute is on the order of 10^{-5} to 10^{-6} cm^2/s. Depending on the properties of the solid, the same solute diffuses more slowly in a solid phase, with a diffusion coefficient ranging from 10^{-6} to 10^{-11} cm^2/s.[64] If a membrane were mainly composed of liquid, a solute would easily diffuse through the membrane down its concentration gradient. On the other hand, if the membrane were composed of a crystalline solid, the solute would take a longer time to diffuse from one side to the other. By selectively controlling the phase of the solute's diffusion media, inducing a change in the physical properties of the diffusion media can be used as an on-off switch to regulate drug release.

The chains of aliphatic hydrocarbons, such as alkanes, lie in a parallel arrangement after crystallization, but appear as an amorphous liquid when melted.[65] If the pores of a polymer membrane are filled with alkanes, solute diffusion through such a membrane can be thermally controlled by alternating the phase of the alkanes embedded in the porous membrane. Solute can only diffuse through the alkane-filled channels. Such an alkane-absorbed polymer membrane can be used as the thermal-responsive membrane of the PGE1 implant.

A suitable alkane is needed, so that at body temperature, the alkane would remain crystalline, limiting the permeability of PGE1. However, upon heating the membrane to temperatures above the melting point of the alkane, the alkane would melt and allow PGE1 to quickly diffuse through. Due to hydrophobic attraction, alkanes would prefer to be retained within the hydrophobic polymer membrane rather than mixing with the surrounding aqueous medium. The heating and cooling cycles of absorbed hydrocarbons are reversible, so that the membrane can be turned on or off as required.

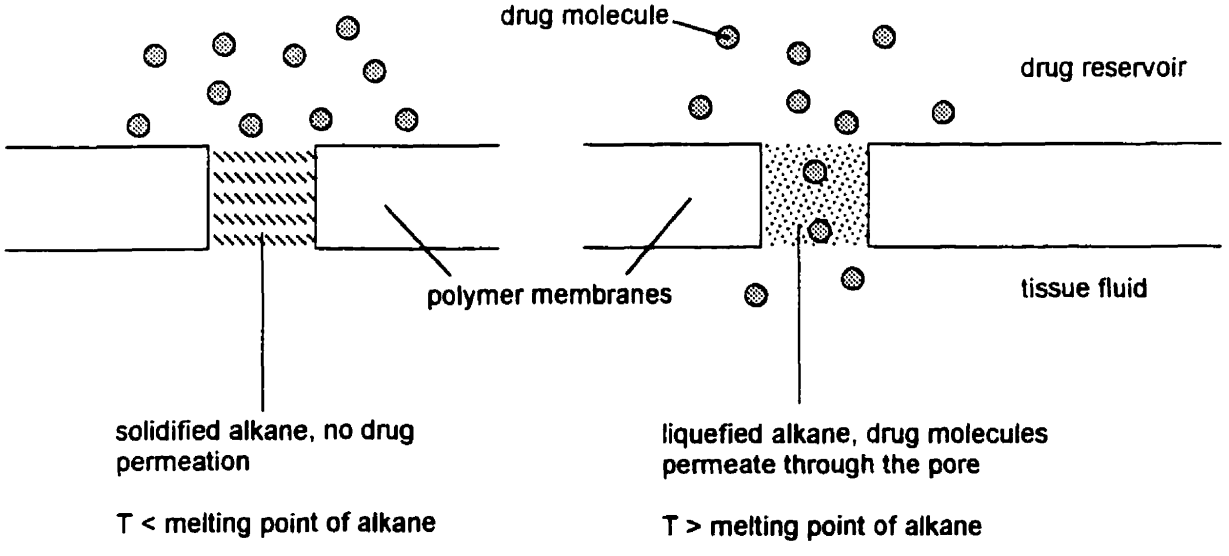

Figure 2.7 Thermal-responsive concept of the alkane-absorbed porous polymer membrane.

(4) By varying the choice of pore-filling material, one can customize the thermal-trigger temperature of the membrane.

The melting point of a molecular solution of two alkanes depends on the relative proportion of each alkane in the mixture. Therefore, control over the trigger temperature of the thermal-responsive membrane can be exerted by varying the alkane mixture composition.

3.0 Methods

3.1 Materials

Ethyl oleate (EO, Crodamol EO™) and caprylic/capric triglyceride (GTCC, Crodamol GTCC™) samples were provided by Croda Canada and were used as the stability vehicles for PGE1. Vitamin E 400 IU, containing 100% d-alpha tocopheryl acetate, made by Webber was purchased from a local pharmacy and used as an antioxidant. DL-propranolol hydrochloride salt (PRO), n-docosane and n-eicosane were purchased from Sigma-Aldrich Canada. Temazepam, the internal standard for the PGE1 HPLC assay, was provided by Novartis Canada. Prostaglandin E_1 (PGE1) was either purchased from Sigma-Aldrich Canada or received as a sample from Pharmacia & UpJohn, Kalamazoo, Michigan, U.S.A. The porous polyethylene (PE) membrane made by 3M was supplied as a flat sheet with 50 μm thickness, 70% porosity and an average pore size of 0.2 μm. Porous polypropylene (PP) filtration membrane (Metricel™) with 0.1 μm pore size and 70% porosity was purchased from Gelman Sciences. Flat sheet polyvinylidene fluoride (PVDF) (Westran™) with a 0.45 μm pore size was received as a sample from Schleicher & Schuell. HPLC grade acetonitrile and methanol were obtained from Caledon Laboratories. Deionized water, collected from a Milli-Q water filtration system made by Millipore, was used to prepare the HPLC mobile phase. All other reagents used were of reagent grade.

3.2 Drug Assays

3.2.1 Prostaglandin E_1

A prostaglandin E_1 high-performance liquid chromatography (HPLC) assay similar to the one reported by Lee and DeLuca[66] was used to determine the PGE1 concentration in an aqueous sample. An HPLC system made by Shimadzu of Japan was used to analyze the PGE1 samples. The HPLC system was composed of: SCL-6B system controller, SIL-6B autoinjector, LC-600 solvent pump, SPD-M6A photodiode array UV-VIS detector connected to an NEC 386/25 computer running the SPD-M6A Operating Software version 2.24. The analytical column used was a reverse phase Supelco LC-8 with 3 micron packing, and had dimensions of 15.0 cm (length) by 4.6 mm (inner diameter). The mobile phase was composed of acetonitrile and 0.002 M, pH 3.5 H_3PO_4 / NaH_2PO_4 buffer in a 35:65 (v/v) ratio. During the isocratic HPLC analysis, the temperature of the column was ambient and the flow rate of the mobile phase was 1.4 mL per minute. Temazepam dissolved in methanol with a concentration between 80 and 120 µg/mL was used as the internal standard. Six hundred microlitres of an aqueous sample was mixed with 50 µL of the temazepam standard solution prior to injection to the analytical column. PGE1 in pH 3.5 buffer absorbs UV light at 197 nm strongly. When the concentration of PGE1 in the aqueous sample was between 5 and 60 µg/mL, the absorbance area ratio of the PGE1 and temazepam peaks at 197 nm was linearly related. The detection limit of this assay was 2 µg/mL of PGE1. The PGE1 standard curve, intra-sample

variability, intra-day variability, PGE1 absorption spectrum, and retention time are summarized in section 8.1. A sample chromatogram was also included.

3.2.2 Propranolol HCl

The absorbance of propranolol HCl aqueous samples at 290 nm was measured by a UV spectrophotometer. By generating a standard curve, the absorbance value was linearly related to PRO concentration between 5 and 60 µg/mL. As a result, the concentration of PRO in the sample could be determined by measuring the sample's UV absorbance. The details of the PRO UV assay are summarized in section 8.2.

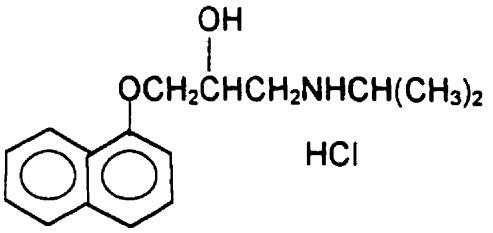

Figure 3.1 The structure of propranolol HCl.

3.3 Stability Studies of Prostaglandin E_1 in Oleaginous Vehicles

Stability samples of PGE1 in oleaginous vehicles were prepared by dissolving a known amount (60-255 µg/mL) of PGE1 in vehicles such as EO, GTCC,

or GTCC with 0.02% (w/w) vitamin E. The preparations were bottled into glass scintillation vials (25 mL), purged with nitrogen gas and stored at either room temperature (~23 °C), 40 °C or 60 °C. For analysis, the vials were left to cool to room temperature and 1 mL samples were pipetted into a test tube. Another 1 mL of solvent was added to the test tube to extract PGE1 from the oleaginous vehicle. For EO and GTCC containing samples, mobile phase and methanol were used, respectively, as the extracting solvent. The extraction efficiency remained constant at 60% for the concentration range between 10 and 60 μg of PGE1 per mL of the oleaginous vehicle. The aqueous phase was aspirated from the test tube and assayed for its PGE1 concentration. The sample vial was purged with nitrogen again prior to further storage.

The rate of PGE1's β-hydroxycyclopentanone ring dehydration is known to depend upon the hydrogen ion and hydroxyl ion concentration.[28, 67] For many pharmaceutical solution systems, first order degradation kinetics was observed.[68] That is,

$$[PGE1]_t = [PGE1]_o e^{-kt} \quad \text{.....(1)}$$

where, $[PGE1]_t$: concentration of PGE1 in the vehicle at time t

$[PGE1]_o$: initial concentration of PGE1 in the vehicle

k: first order degradation rate constant

Rearranging equation (1) gives

$$\ln [PGE1]_t = \ln [PGE1]_o - kt \qquad \ldots\ldots(2)$$

By plotting the concentration of PGE1 remaining in GTCC and EO against time on a semi-log scale, the slope of the line would represent the apparent first order degradation rate constant, k. The degradation rate constants at different temperatures could be related by the Arrhenius equation.[68]

$$k = A\, e^{-Ea/RT} \qquad \ldots\ldots(3)$$

where, Ea: energy of activation

R: gas constant (8.314 J K^{-1} $mole^{-1}$)

T: temperature

A: Arrhenius factor

Rearranging (3) gives,

$$\ln k = \frac{E_a}{R} \times \frac{1}{T} + \ln A \qquad \ldots\ldots(4)$$

By measuring the degradation rate constants of PGE1 in a pharmaceutical vehicle at various temperatures, the shelf life of PGE1 in that vehicle at body

temperature could be estimated. The shelf life of PGE1 in EO, GTCC, GTCC with 0.02% (w/w) vitamin E at 23 °C, 40 °C, and 60 °C was determined.

3.4 Alkane-Absorbed Membranes

3.4.1 Melting Point Determination of the Mixture of Alkanes

N-docosane and n-eicosane were mixed in different mole fractions ranging from 0% docosane to 100% docosane. The mixture was then heated and stirred on a hot plate to ensure uniform mixing. The melting point of a small sample of the mixture was determined using the Gallenkamp Melting Point Apparatus.

3.4.2 Preparation

To prepare alkane-absorbed membranes, the desired alkane or alkane mixture was heated in an oven maintained at a temperature above the melting point of the alkane. Preweighed polymer membrane (PE, PP or PVDF) was soaked in the melted alkane for 30 minutes to 1 hour in the oven. After removal of the membrane from the alkane solution, the membrane was washed repeatedly in a 60 °C water bath and blotted dry with tissue paper until the weight of the membrane was constant.

3.4.3 Characterization

3.4.3.1 Percent Weight Gain

The weight of alkane absorbed on the polymer membrane was determined from the weight changes of the polymer membrane before and after the alkane addition.

3.4.3.2 Thermal-responsiveness

Thermal-responsiveness of the membrane was characterized by measuring the change in drug permeability across the membrane at different temperatures. Only the thermal-responsiveness of the alkane-absorbed PE membrane was investigated. Since PGE1 is not stable, PRO, which has a similar octanol/water partition coefficient and molecular weight, was used initially as a model compound to characterize the thermal-responsiveness of the membrane. Unmodified PE polymer membranes were first wetted with methanol, then left in pH 7.4 buffer for at least 8 hours. The exchange of methanol with buffer was carried out so that the pores of unmodified membranes were filled with buffer. Permeabilities of solute through the unmodified PE membranes were compared with those through the alkane-absorbed PE membranes.

To determine the solute's permeability, the test membrane was clamped between two classical diffusion cells, each with a cross sectional area for transport of 2.01 cm^2. The setup, illustrated in figure 3.1, was immersed in a 37 °C, 42.5 °C or 45 °C water bath. The receptor cell was filled with 7 mL of pH 7.4, 0.15 M phosphate buffer while the donor cell was filled with an equal volume of either PRO solution, of 500-800 µg/mL concentration, or PGE1 dispersion, of 500 µg/mL concentration, in pH 7.4, 0.15 M phosphate buffer. The appearance of solute in the receptor cell was monitored over time. The permeability of PRO through the membrane was determined using the following equation derived from Fick's Law[69]:

$$\ln (C_o - 2 C_r) = \frac{P A t}{V} \qquad \text{.....(5)}$$

where,

C_o : initial drug concentration in the donor cell;

C_r : drug concentration in the receptor cell at time, t;

P : DK = diffusion coefficient × partition coefficient = permeability;

A : area of the membrane;

V : volume of solution in one side of the diffusion cell.

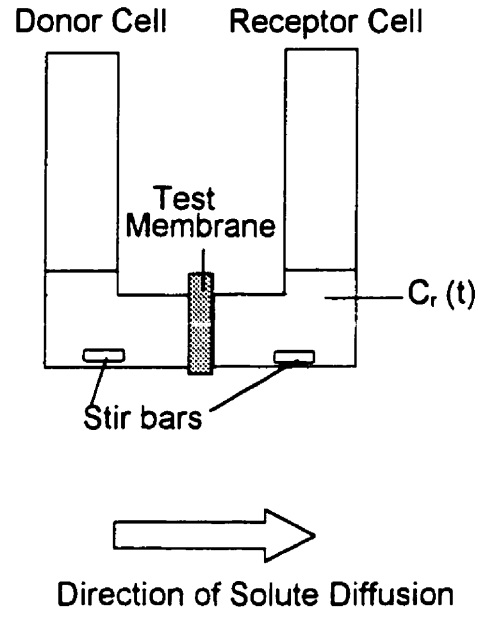

Figure 3.2 Diffusion cell for the determination of membrane permeability. Concentration of solute in the receptor cell (C_r) was monitored over a period of time.

The permeabilities of PRO through 3 independent batches of alkane-absorbed PE membrane, each with 5 cycles of temperature oscillation, were recorded.

3.5 Determination of Solubilities and Distribution Coefficients

Different masses of PGE1 were weighed into scintillation vials. To the vials, an accurate volume of 0.15M, pH 7.4 phosphate buffer was added and the vials

were left on a shaker for 2 hours at room temperature. The appearance of precipitate at the end of the 2 hours was recorded. The experiment was repeated at 45 °C with pH 7.4 buffer and at 45 °C with melted docosane. Solubility was reported as the average concentration of PGE1 in the vial containing the largest amount of totally dissolved PGE1 and the PGE1-saturated vial containing the least amount of undissolved PGE1.

To determine the distribution coefficient (DC) of PRO, 1 mL of a known concentration of PRO solution was mixed with 1 mL of melted docosane in a small bottle. The bottle was sealed and maintained at 45 °C in an oven for 4 hours. The concentration of the PRO in the aqueous solution was measured before and after mixing with melted docosane. Since the volume of both phases was 1 mL and PRO was not known to be surface active, the difference between the initial and final aqueous concentration was the amount of PRO that had partitioned into the docosane phase.

$$DC_{45\,^{\circ}C}(PRO) = \left(\frac{[PRO]_D}{[PRO]_B}\right) \text{ at } 45^{\circ}C = \frac{[PRO]_{B\ initial} - [PRO]_{B\ final}}{[PRO]_{B\ final}} \quad \ldots\ldots(6)$$

where , B: pH 7.4 buffer;

D: docosane.

For PGE1, the distribution coefficient was hard to measure directly due to the surface active properties of PGE1. Therefore, the ratio of solubilities of PGE1 in docosane and PGE1 in pH 7.4 buffer was used to estimate the distribution coefficient. The partition coefficient (PC) is defined as the ratio of a species' activity in the top phase over the activity in the denser, immiscible, bottom phase.[70] For an aqueous solution of a small molecule in low concentration, the solute mole fraction is a product of the solute molar concentration and the solvent molar volume. Therefore, the docosane/water distribution coefficient was determined by the ratio of the concentration of PGE1 in docosane over the concentration in pH 7.4 buffer. The partition coefficient indicates the relative distribution of unionized PGE1 in the two phases. The distribution coefficient (DC) indicates the ratio of unionized PGE1 in the lipophilic phase over the sum of ionized and unionized PGE1 in the aqueous phase. The distribution coefficient (DC) of a weak electrolyte is related to the partition coefficient (PC) by its pKa as illustrated in equation 8.

$$DC_{45\,^{\circ}C}\,(PGE1) = \frac{[PGE1]_{SD}}{[PGE1]_{SB}} = \frac{[PGE1]_{D}}{[PGE1]_{B} + [PGE1^{-}]_{B}} \qquad \ldots\ldots(7)$$

where,

$[PGE1]_{SD}$: saturated solubility of PGE1 in docosane;

$[PGE1]_{SB}$: saturated solubility (unionized and ionized form) of PGE1 in pH 7.4, 0.15M phosphate buffer.

$$\log DC = \log PC - \log (1 + 10^{pH-pKa}) \qquad \ldots\ldots(8)$$

4.0 Results and Discussion

4.1 Stability Studies of Prostaglandin E_1

4.1.1 Effect of Temperature

The degradation kinetics of PGE1 in caprylic / capric triglycerides (GTCC) and ethyl oleate (EO) at different storage temperatures are shown in figures 4.1 and 4.2, respectively. The first order degradation rate constants, k, for GTCC and EO at different temperatures, are summarized in table 4.1. The reported standard errors of mean (SEM) in table 4.1 are the errors of the fitted lines. The apparent energies of activation, E_a, and frequency factors, A, are estimated and summarized in table 4.2. The shelf life was measured in terms of the $t_{90\%}$, or the time elapsed when 90% of the original amount of substance remained, at 4 °C and 37 °C and values are summarized in table 4.2.

By eliminating water and minimizing available protons, the stability of PGE1 was prolonged in oleaginous vehicles with low acidity. Prior PGE1 stability studies, as summarized in 2.5.1, had shown that PGE1 dehydrated rapidly in an aqueous vehicle with a shelf life of 2.9 days at 37 °C.[29] The nonaqueous vehicles used in this thesis, GTCC and EO, stabilized PGE1, leading to a shelf life between 12.4 to 19.7 days in GTCC and 24 to 47 days in EO at 37 °C. The degradation reaction of PGE1

in these vehicles is characterized by a similar activation energy: 4.6 (±1.1) × 10^4 J/mole in GTCC and 2.7 (±1.6) × 10^4 J/mole in EO. Due to the large scatter in EO stability data, no difference could be found in the activation energy of PGE1 degradation in the tested oleaginous vehicles. The large scatter may be related to the inability to precisely aspirate the bottom phase for assay during the extraction procedure.

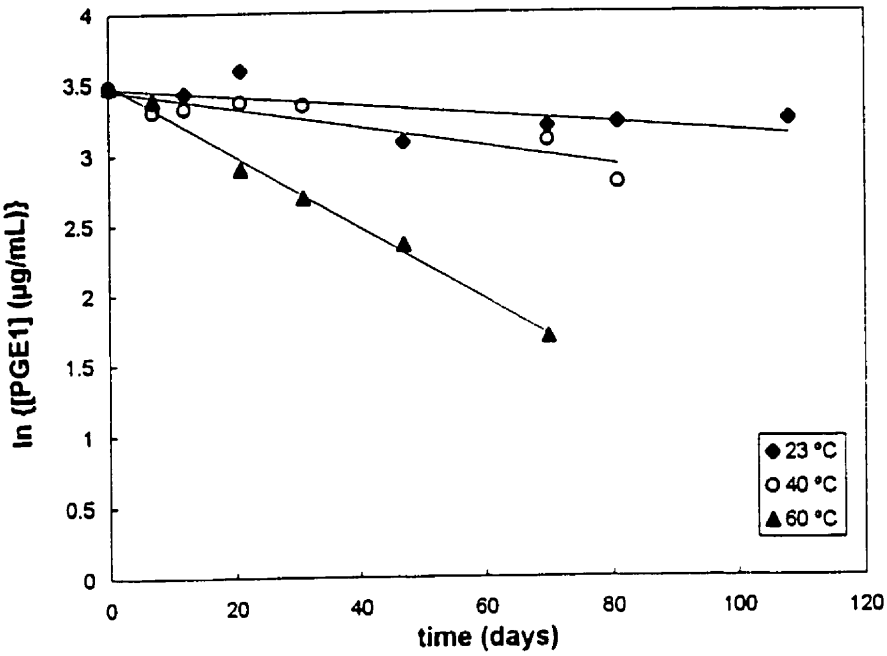

Figure 4.1 Degradation of prostaglandin E_1 (PGE1) in GTCC. (n=1)

Table 4.1 Degradation rate constants, k, of prostaglandin E_1 in GTCC, GTCC with 0.02% (w/w) vitamin E, and EO. (mean ± SEM of the fitted line)

Storage Temperature	k (day $^{-1}$)		
	GTCC	GTCC with 0.02% vitamin E	EO
23 °C	0.0032 ± 0.0038	0.0020 ± 0.00078	0.0022 ± 0.0080
40 °C	0.0066 ± 0.0033	0.0057 ± 0.0024	0.0026 ± 0.0017
60 °C	0.026 ± 0.0026	0.015 ± 0.0021	0.0073 ± 0.0048

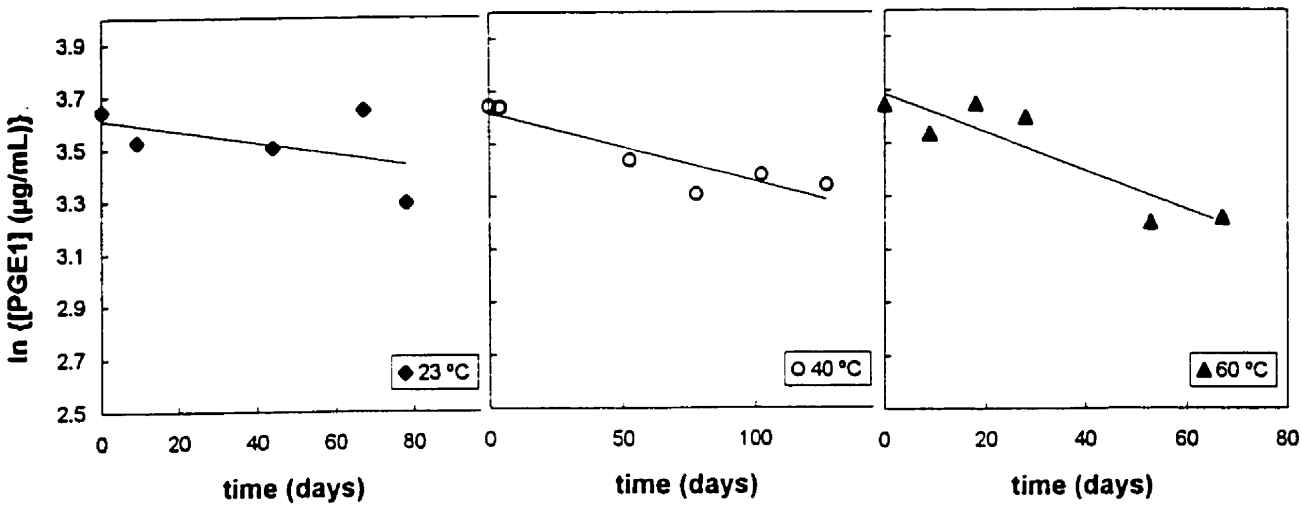

Figure 4.2 Degradation of prostaglandin E_1 (PGE1) in EO. (n=1)

Table 4.2 Activation energy (E_a), frequency factor (A), and the predicted 90% shelf life ($t_{90\%}$)of prostaglandin E_1 at different temperatures in GTCC, GTCC with 0.02% (w/w) vitamin E, and EO.

Parameters	GTCC	GTCC with 0.02% vitamin E	EO
E_a (J/mole) (mean ± SEM)	4.6 (± 1.1) × 10^4	4.4 (± 0.28) × 10^4	2.7 (± 1.6) × 10^4
ln A (ln day^{-1}) (mean ± SEM)	13.0 (± 2.9)	11.8 (± 0.75)	6.26 (± 4.3)
$t_{90\%}$, 4 °C (days) mean (95% C.I.)	134 (107, 169)	176 (166, 187)	124 (83, 164)
$t_{90\%}$, 37 °C (days) mean (95% C.I.)	16 (12.4, 19.7)	23 (21.6, 24)	30 (24, 47)

The degradation reaction of PGE1 in EO has a smaller frequency factor compared with PGE1 in GTCC, which indicates that PGE1 has less intrinsic reactivity when contained in EO. This result contradicts our prediction that GTCC, which has a smaller acid value and a closer resemblance to tricaprylin, should be able to stabilize PGE1 for a longer duration. This inconsistency is probably caused by the large scatter in PGE1 stability data in EO, which results in an imprecise measure of PGE1 stability in EO.

The selection of drug reservoir was limited to materials previously used for subcutaneous, intramuscular, or intravenous administration to minimize tissue irritation by the reservoir vehicle should the thermal-responsive membrane break while the implant is inside the body. Some oleaginous pharmaceutical vehicles suitable for parenteral use are listed in table 2.3. The vehicles selected, EO and GTCC, are of low acidity, as reflected by their low acid values. The acid value is defined as the number of milligrams of potassium hydroxide needed to neutralize the free acids in 1.0 g of oily sample.[71] Most of the oleaginous vehicles are derived from naturally occurring fatty acids and thus, have high acid values. Free fatty acids in the vehicle can catalyze PGE1 degradation, making the vehicle unsuitable as the reservoir material.

Although the reported shelf lives of PGE1 in GTCC and EO are longer than that of PGE1 in an aqueous vehicle, the t_{90} in these vehicles is still shorter than that of PGE1 encapsulated with tricaprylin in sealed hard gelatin capsules. PGE1 in

such capsules was shown to remain stable for longer than 3 months at 40°C.[36] GTCC closely resembles tricaprylin structurally, see figure 2.3, and should have a similar ability to prevent PGE1 degradation. The difference may be attributed to the design of the stability experiment. Samples were taken from the same sample bottle at different time points; introduction of contaminants may occur and accelerate the degradation reaction of PGE1. Moreover, the sample bottle may not be as air-tight as the gelatin sealed hard capsules. Since only one stability batch for each sample was tested, further studies with more stability batches are required to accurately quantify the shelf life of PGE1 in these oleaginous vehicles.

4.1.2 Effect of the Addition of an Antioxidant

The addition of 0.2% w/w vitamin E to GTCC prolonged PGE1 stability. The shelf life of PGE1 in vitamin E added GTCC was between 21.6 to 24 days at 37°C compared with 12.4 to 19.7 days of PGE1 in GTCC alone. The degradation of PGE1 in vitamin E-added GTCC is plotted in figure 4.3. The degradation rate constants and other parameters are summarized in tables 4.1 and table 4.2.

GTCC and EO are esters which can undergo oxidation and release free fatty acids. The fatty acid acts as a catalyst to promote the degradation of PGE1. With the addition of an antioxidant, oxidation of the oleaginous vehicle can be suppressed, and the shelf life of PGE1 in such a vehicle is prolonged. Alpha tocopherol, vitamin E, was used as the antioxidant in this study because it was easy

to obtain and was compatibile with oleaginous vehicles. Vitamin E has an established effective antioxidant concentration between 0.001 and 0.05%.[72] Vitamin E in 0.02% (w/w) concentration was added to GTCC. It was observed that the shelf life of PGE1 at 37 °C was longer than that of PGE1 in GTCC alone. The antioxidant works by scavenging free radicals, and thus, prevents oxidization of the esters. Minimal free fatty acid is formed all vitamin E is consumed. However, adding too much vitamin E to an oleaginous vehicle can counteract the stabilizing effect because vitamin E itself can be catalyzed by oxygen, ferric and silver salts to form acidic products.[71] To effectively stabilize PGE1 in an antioxidant-added oleaginous vehicle, an optimal amount of antioxidant is needed in the system. Since only one batch of vitamin E added GTCC was tested, further PGE1 stability enhancement may be possible by optimizing the concentration of vitamin E in the pharmaceutical vehicle.

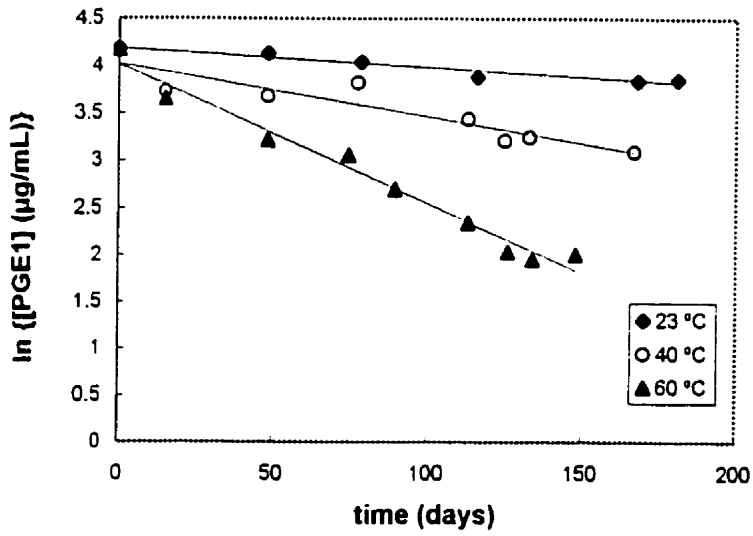

Figure 4.3 Degradation of prostaglandin E_1 (PGE1) in GTCC with 0.02% (w/w) vitamin E added. (n=1)

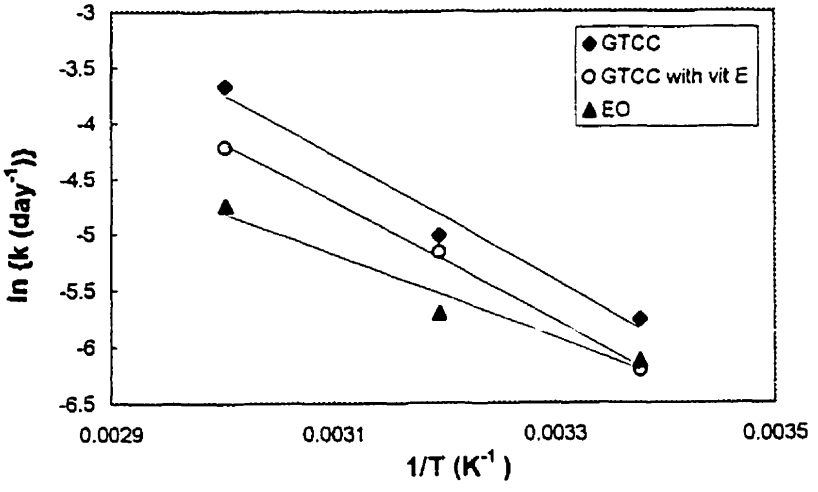

Figure 4.4 First order Arrhenius plot of the rate constants, k, of prostaglandin E_1 in GTCC, GTCC with 0.02% (w/w) vitamin E and EO.

4.2 Characterization of the Alkane-Absorbed Membranes

Polypropylene (PP), polyethylene (PE), and polyvinylidene fluoride (PVDF) porous polymer membranes were modified with docosane. Using the density of docosane, and the membrane porosity reported by the manufacturer and measured thickness, the theoretical weight gain of the membrane after alkane-modification was calculated, as shown in table 4.3.

The value of the experimentally measured weight-gain is comparable to the value of theoretical weight-gain of the 3 different types of docosane-absorbed porous polymer membranes. The correspondence between actual and theoretical

weight-gain suggested that docosane was only filling the pores and not affecting the solid polymer.

Table 4.3 Theoretical weight gain versus actual weight gain of docosane-absorbed polymer membranes. (mean ± SEM)

Polymer Membrane, Pore Size	**Predicted Weight Gain (%)**	**Actual Weight Gain (%)**
Polypropylene, 0.1 μm	186	180 ± 1.7
Polyethylene, 0.2 μm	252	227 ± 19
Polyvinylidene fluoride, 0.45 μm	104	90 ± 10

The weight of alkane-absorbed PE membrane was monitored during the washing cycles. The membranes achieved constant weight after about 10 cycles of washing and drying, as shown in figure 4.5. The washing was intended to remove excess alkane on the surface of the membrane, while leaving the alkane inside the pores untouched. Since, after 10 cycles of washing, the membrane achieved a constant weight and the weight corresponded to the predicted weight-gain, this suggested that only docosane on the surface was removed by the washing procedure.

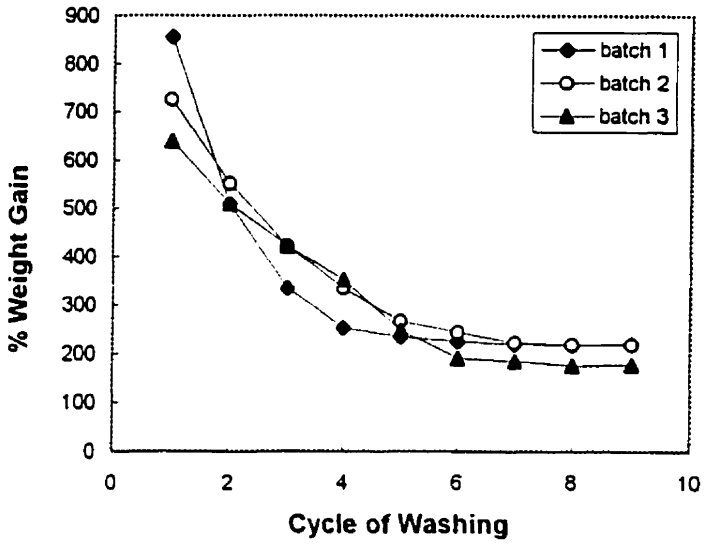

Figure 4.5 Weight of docosane-absorbed polyethylene membrane after cycles of washing and blot drying.

Functional properties of docosane-absorbed polymer membranes were examined. Modified PP membranes were too brittle to be used for further permeation studies. The brittleness may be related to the PP crystallinity, although its exact value was not known. PVDF is a piezo-electric material, which may be selectively targeted by an ultrasonic heater. However, the docosane-absorbed PVDF membrane had a patchy appearance, suggesting that docosane was not uniformly absorbed. Further investigation of the membrane modification technique is needed before such an alkane-absorbed PVDF membrane can be useful. The PE membranes were not brittle after docosane modification and the docosane appeared to be uniformly absorbed.

In addition to the desired physical properties of the docosane-absorbed PE membrane, low density PE has been known to have a low incidence of tissue reactivity [73] and has been used as woven fabric for penile prostheses.[74] As a result, porous PE membranes were selected to be studied further.

4.2.1 Modification of the Membrane Transition Temperature

The thermal-responsive alkane-absorbed PE membrane consists of two components. The porous hydrophobic polymer membrane is a mechanical support for the pore-filling material. The solid phase of the polymer membrane should be impermeable to solute in order to maximize the membrane's on/off response. The solute should only diffuse through the pore-filling material, which changes phase in response to a temperature change. The pore-filling material used in the current design of thermal-responsive membrane is the alkane series. The alkane fills the pores, acts as a nonmechanical valve to control solute permeability through the modified polymer membrane.

The desired release-trigger temperature for the penile implant is between 42 and 43 °C. Initially, docosane, which has a melting point at 44.4 °C, was used as the pore-filling material to demonstrate the concept of membrane thermal-responsiveness. Docosane is chemically similar to polyolefins. Due to its hydrophobicity, docosane would prefer to stay within the hydrophobic polymer

membrane even in its liquid state. This is consistent with the observation that no significant reduction in membrane weight occurred after permeation experiments.

The trigger temperature of the thermal-responsive membrane is determined by the melting point of the pore-filling material. Thus, by the appropriate choice of pore-filling material, the trigger temperature of the device can be set to meet the clinical requirements. The thermo-pain threshold of skin is between 45 and 50 °C.[2] If heating is continued after pain is felt, blood vessels in the area would dilate, and eventually, a skin burn would result.[2] Therefore, 45 °C, a temperature just above the melting point of docosane, is too high a temperature to serve as an on-signal for the penile implant. Two branched alkanes, 1-phenyl-eicosane and 1-cyclopentyl uneicosane, have melting points at 42 °C.[75] They could be used as the pore-filling materials so that the trigger temperature of the device would be between 42 and 43 °C. However, these branched alkanes are not commercially available. Lengthy synthesis and characterization of these branched alkanes are needed before they can be used. An alternative way to adjust the melting point of an alkane is by mixing docosane with another shorter alkane. With the right proportion of each alkane, the desired trigger temperature can be obtained (see tables 4.4 and 4.5). The 90:10 (mole%) docosane:eicosane mixture melted at 42.5 °C, which is the desired device-trigger temperature.

During the melting point determination of the mixture, only a single melt transition was observed. However, it is possible that detailed thermal analysis may

reveal more complex phase behaviour of the alkane mixture. If the mixture existed as a single phase, the melting transition would be reversible. As a result, the thermal-responsive membrane would be "turned on" at the same temperature for every heating cycle. On the other hand, if the mixture existed as a two-phase mixture, each phase would tend to aggregate with itself and to phase-separate from each other. In that case, after many cycles of heating, the composition of the pore-material would become two phases, and the trigger temperature of the membrane may change. This time-dependent change in trigger temperature would adversely affect the reproducibility and reversibility in drug permeation rate of the thermal-responsive delivery device.

Using the melting point apparatus, only one melting point was observed in the docosane-eicosane mixture. Since the main chain of eicosane and docosane differ only by 2 carbons, they are structurally and chemically similar and their mixture is likely to be of one-phase. Moreover, the pore size of the membrane is about 0.2 μm (2000A) which is relatively large compare with the size of an alkane molecule. Therefore, the alkane composition in the pores should be the same as that in the bulk mixture. The docosane-eicosane mixture was used as the pore-filling material to prepare more batches of alkane-absorbed PE membrane. Propranolol HCl permeability through these membranes was measured.

Table 4.4 Melting points of some straight chain alkanes. [79, 80]

n-Alkane	Chemical Formula	Melting Point (°C)
octadecane	$C_{18}H_{38}$	28.2
nonadecane	$C_{19}H_{40}$	32.1
eicosane	$C_{20}H_{42}$	36.8
heneicosane	$C_{21}H_{44}$	40.5
docosane	$C_{22}H_{46}$	44.4
tricosane	$C_{23}H_{48}$	47.6
tetracosane	$C_{24}H_{50}$	50.9

Table 4.5 Melting points of n-docosane and n-eicosane mixtures in different mole fractions. (n=1)

Mole % n-Docosane	Mole % n-Eicosane	Melting Point (± 0.5°C)
0	100	37
49.2	50.8	39.5
59.6	40.4	40
70.0	30.0	41
73.4	26.6	41.5
80.0	20.0	42
89.9	10.1	42.5
100	0	44.5

4.3 Permeation Studies Using the Alkane-Absorbed Polyethylene Membranes

4.3.1 Propranolol HCl Permeation

Results of the permeation experiments of PRO are presented in figures 4.6, 4.7, 4.8 and 4.9. Figure 4.6 shows the dynamic permeation of PRO through docosane-absorbed PE membrane for 5 cycles of temperature oscillation between

37 and 45 °C. The data shows reproducible and reversible permeation behaviour between the two temperatures. The inset illustrates the membrane's rapid response to temperature changes. The slope of the line connecting points of the same temperature is related to the permeability of the membrane. Sufficient time was allowed for the solution in the diffusion cell to reach equilibrium temperature with the water bath. Eight or five minutes after the immersion of the diffusion cell in a 45°C or 37 °C water bath, respectively, the first sample was taken. Within eight minutes of placing the diffusion cell setup in the higher temperature water-bath, there was a noticeable increase in membrane permeability. Similarly, within five minutes of lowering the membrane temperature, no additional PRO was detected in the receiver side. The total amount of PRO permeated for each 45 °C cycle was dependent on the duration of heating. The longer the setup was placed in a 45 °C water bath, the more PRO permeated across the membrane. In the first cycle of figure 4.6, the setup was placed in a 45 °C water bath longer than the remaining four cycles, and more PRO had permeated through, as illustrated by a larger change in the cumulative amount of PRO after the first cycle. Figure 4.7 shows the steady state average permeability of the membranes in each temperature cycle. It can be seen that the on/off permeabilities are reproducible among the 5 cycles. Figures 4.8 and 4.9 show similar PRO permeation behaviour using the eicosane-docosane PE membrane with oscillating temperature cycles between 37 and 42.5°C.

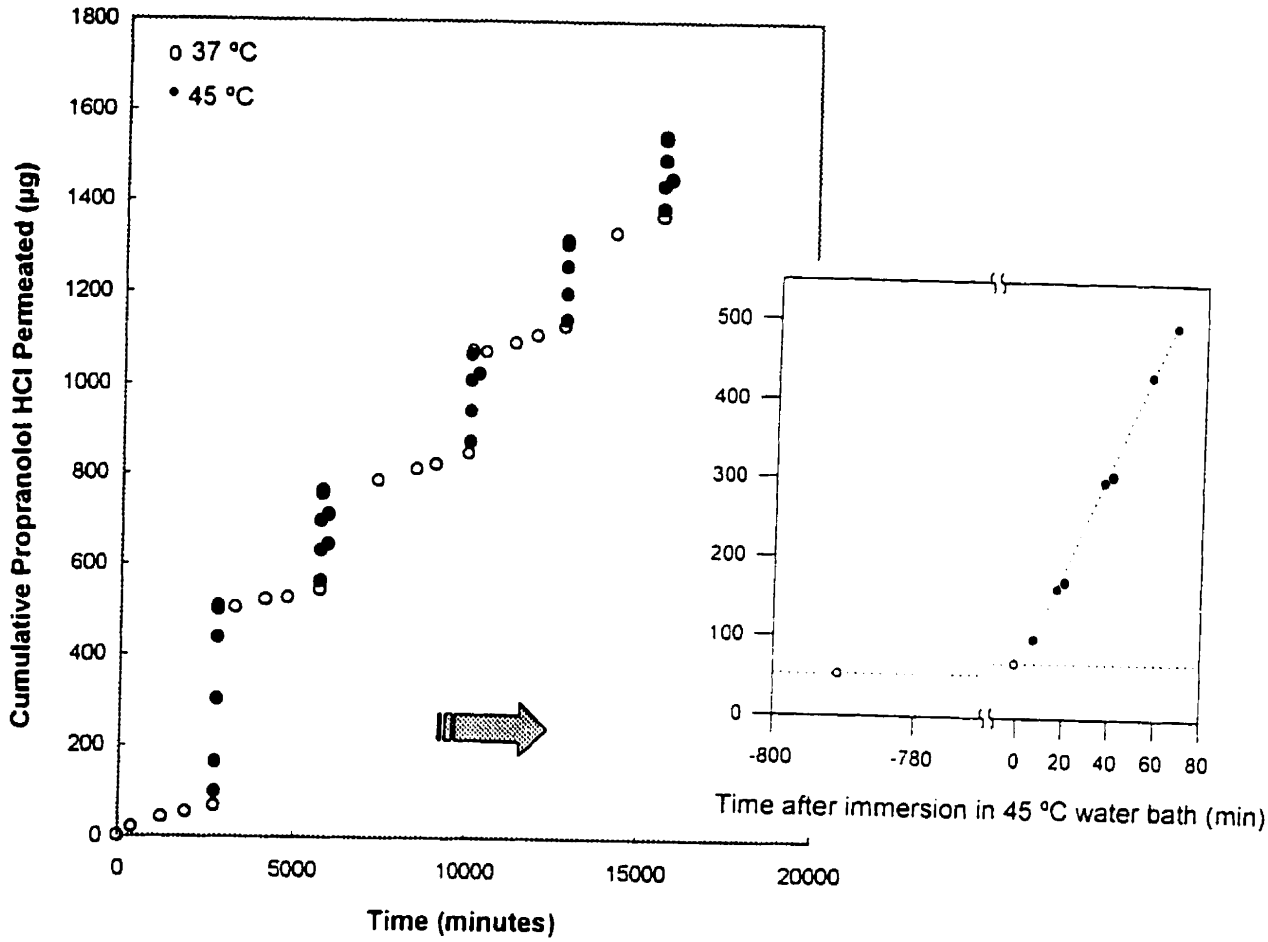

Figure 4.6 Cumulative propranolol HCl permeated through a typical docosane-absorbed polyethylene membrane at 37 °C and 45 °C.

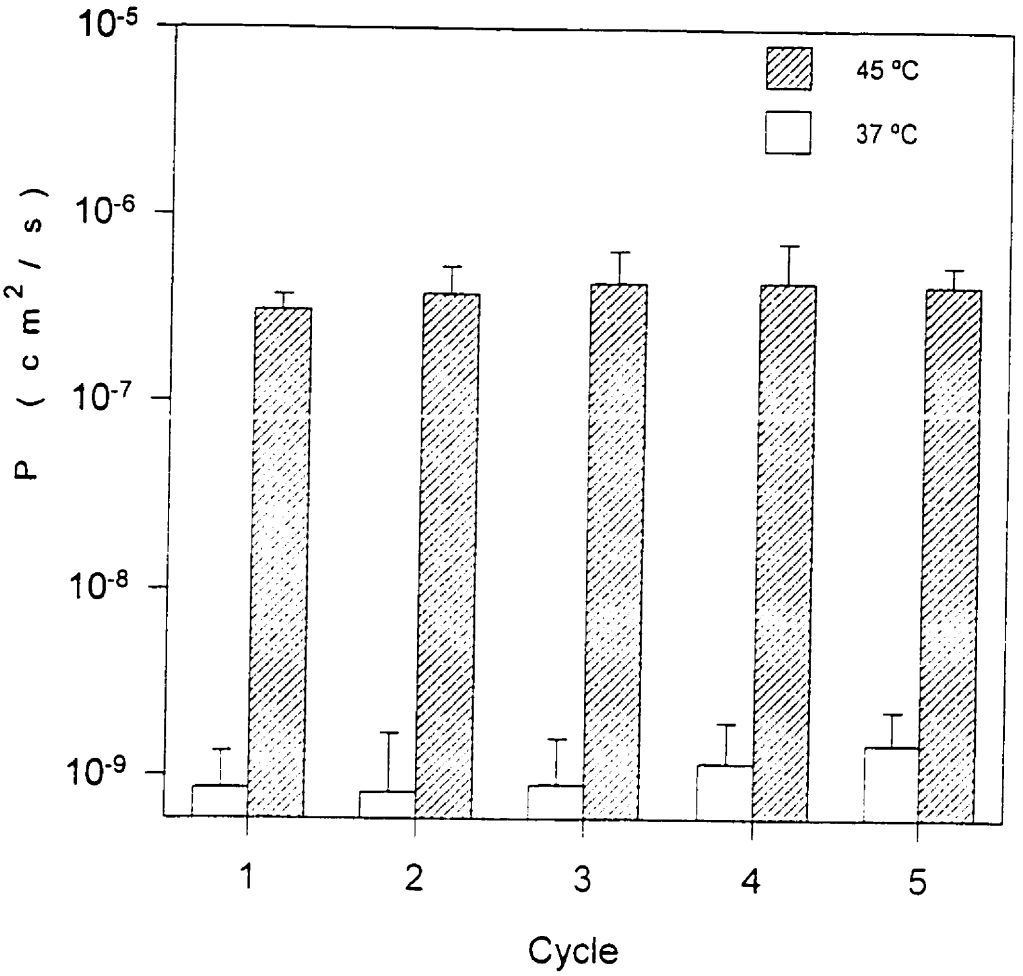

Figure 4.7 Permeabilities of propranolol HCl through the docosane-absorbed polyethylene membranes for 5 cycles of temperature oscillation between 37 °C and 45 °C. (n=3, I-bars indicate the 95% confidence intervals)

Permeabilities of PRO through the unmodified PE membrane and the alkane-absorbed membranes at different temperatures are summarized in tables 4.6 and 4.7. The trigger temperature of docosane-absorbed PE membrane was 45 °C, while that of the 90% docosane-10% eicosane-absorbed PE membrane was 42.5 °C. At the trigger temperature, the membrane is switched "on", allowing solute to diffuse through. At body temperature, however, the membrane is switched "off", and

minimal solute can diffuse through the membrane. The on-off ratio, P_{on}/P_{off}, is defined as the permeability of solute at the on-state of the membrane divided by the permeability at the off-state. The mean on-off ratios of the docosane-absorbed membranes and docosane-eicosane-absorbed membranes were 378 (±65) and 235 (±56), respectively. The "on" and "off" permeabilities were reproducible among 5 cycles of temperature oscillation.

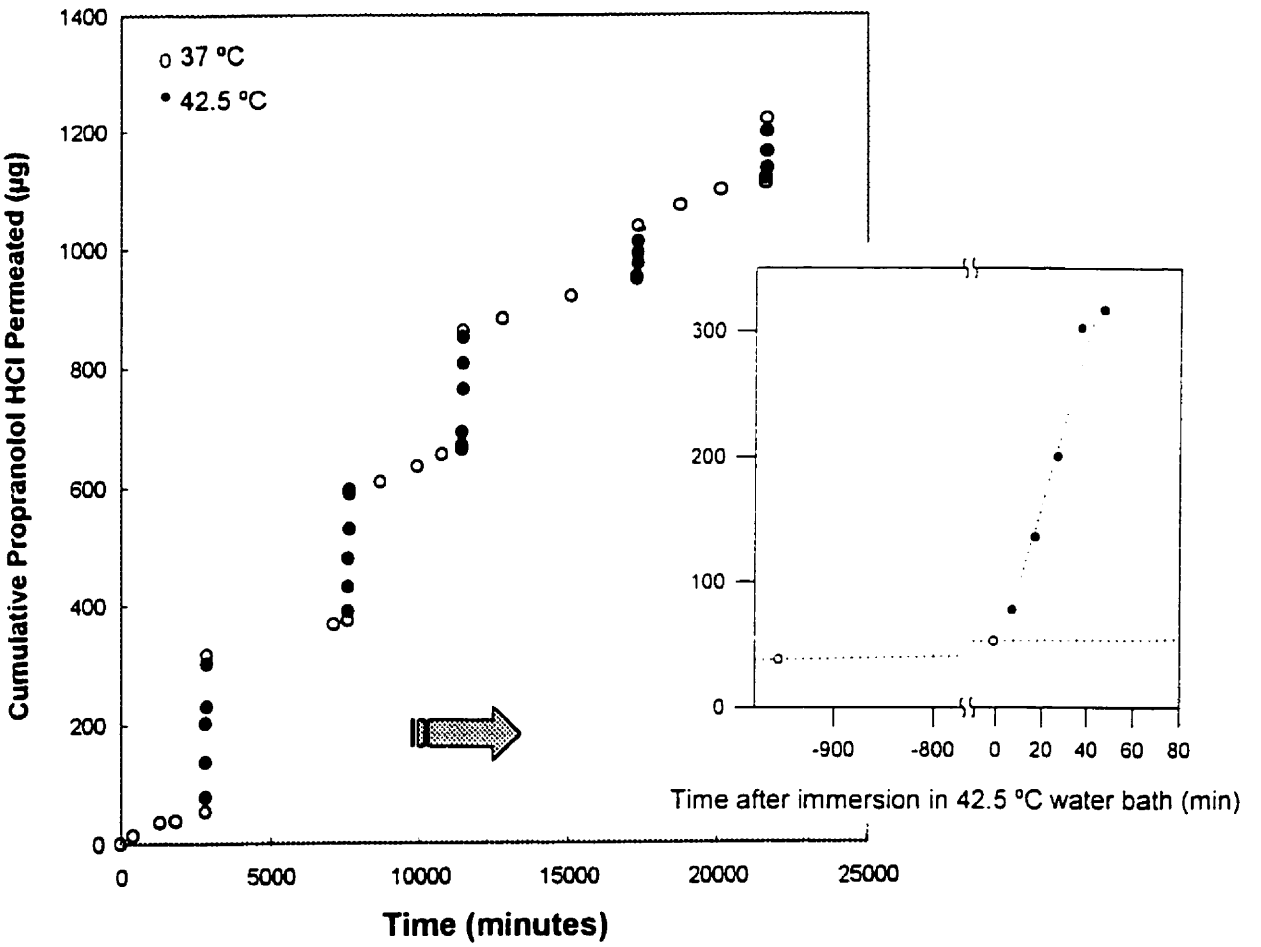

Figure 4.8 Cumulative propranolol HCl permeated through a typical 90% docosane-10% eicosane-absorbed polyethylene membrane at 37 °C and 42.5 °C.

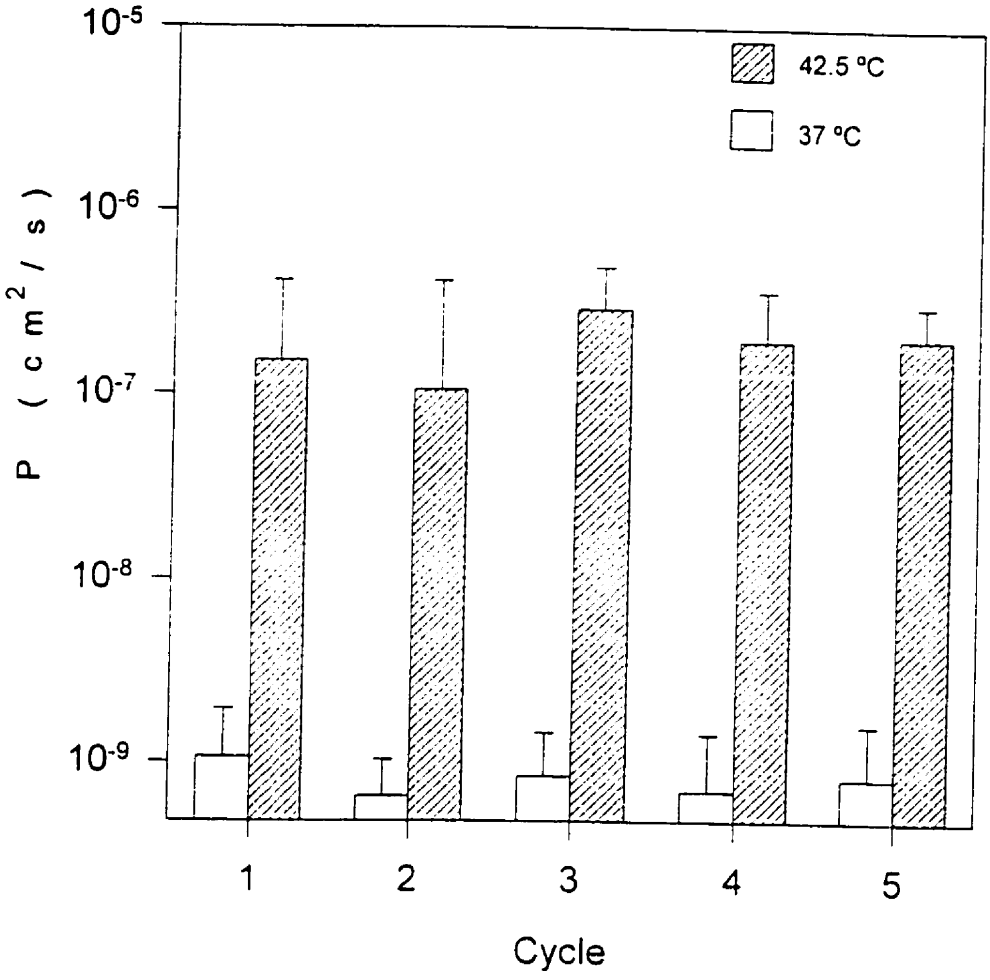

Figure 4.9 Permeabilites of propranolol HCl through the 90% docosane-10% eicosane-absorbed polyethylene membrane for 5 cycles of temperature oscillation between 37 °C and 42.5 °C.

Table 4.6 Permeabilities of propranolol HCl (PRO) and prostaglandin E_1 (PGE1) through unmodified polyethylene membranes at various temperatures. (n=3)

Temperature (°C)	**Permeabilities (cm^2/s)** (mean ± SEM)	
	PRO	**PGE1**
37	1.59 (± 0.37) × 10^{-6}	1.43 (± 1.04) × 10^{-6}
42.5	1.67 (± 0.87) × 10^{-6}	1.66 (± 0.42) × 10^{-6}
45	2.19 (± 0.75) × 10^{-6}	1.81 (± 0.15) × 10^{-6}

Table 4.7 Summary of permeabilities of propranolol HCl through alkane-absorbed polyethylene (PE) membranes. (mean ± SEM) (P_u: permeability of PRO through unmodified PE membrane; P_m: permeability of PRO through alkane absorbed membrane.)

	Docosane-Absorbed PE Membrane	**90% Docosane - 10% Eicosane Absorbed PE Membrane**
P_{off}	1.04 (± 0.16) × 10^{-9}	7.87 (± 0.66) × 10^{-10}
P_{on}	3.93 (± 0.30) × 10^{-7}	1.85 (± 0.41) × 10^{-7}
P_{on} / P_{off}	378 (± 65)	235 (± 56)
Off, P_u / P_m	1529 (± 427)	2020 (± 500)
On, P_u / P_m	5.6 (± 1.9)	9.0 (± 5.1)

The docosane-absorbed membrane has a higher on-off ratio than the mixed-alkane-absorbed membrane. Standard errors of mean PRO permeabilities in the on-state of the docosane-absorbed membranes were smaller, probably due to a narrower melt transition than in the docosane-eicosane mixture. The point, however, was to illustrate that by changing the pore-filling material, the trigger temperature of the membrane can be modified.

There is a large difference in PRO permeabilities through the alkane-absorbed membranes in the off-state and PRO permeabilities through the unmodified membrane at 37 °C. In the off-state, the ratio of unmodified membrane permeability over modified membrane permeability, P_u/P_m, is 1529 (±427) for the docosane-absorbed membrane. However, in the on-state, the P_u/P_m ratio is only 5.6 (±1.9). This difference is attributed to the large magnitude of change in diffusion

coefficients of a solute diffusing through solid and liquid. Moreover, the PRO permeability through the modified membranes during the on-state is only slightly smaller than the PRO permeability through unmodified membrane. This observation indicates that the rate of PRO diffusion through liquefied alkane is similar to that of PRO diffusion through water-filled channels.

The diffusion setup was heated up via conduction by immersion in the higher temperature bath. However, when the thermal-responsive device is in clinical use, radiative heating would be used to heat up the implant. It was shown in the permeation experiments that the drug release was triggered within 8 minutes of conductive heating. When designing the radiative heater, care should be taken to ensure that heating of the implant is fast enough so that drug release can occur within a clinically acceptable time frame.

Cooling of the membrane was achieved by removing the heat source and putting the setup into a 37 °C water bath wherein conductive cooling occurs. This kind of cooling mimics the clinical scenario where the implant is cooled conductively by the circulating blood and the surrounding tissues. It can be inferred from the available data that the thermal-responsive implant would stop releasing drug within 5 minutes of heat removal.

4.3.2 Prostaglandin E_1 Permeation

Success in thermally regulating the permeation of propranolol HCl using the docosane-absorbed and docosane-eicosane-absorbed PE membranes encouraged us to continue using the same membrane for PGE1 permeation experiments. However, permeation experiments using PGE1 as the solute were unsuccessful. No PGE1 was detected in the receptor cell in the membrane's on-state, 45 °C, after 4 hours.

Prostaglandin E_1 permeation experiments using an unmodified PE membrane showed that PGE1 had no difficulty diffusing through the unmodified polymer membrane, see table 4.6. Since PGE1 and PRO have similar molecular weights, their permeabilities across the water-filled channels of the unmodified polymer membrane were predicted to be similar. Experimentally, it was shown that the permeability coefficients of PGE1 and PRO through the unmodified membrane are not significantly different. The initial rationale for the selection of PRO to model PGE1 is that the two molecules have a similar molecular weight and similar reported octanol-water partition coefficients. Based on the similarity of these two physical properties, it was predicted that PGE1 and PRO would have similar permeabilities when diffusing through the alkane-absorbed PE membrane. However, the inability of PGE1 to diffuse through the alkane-absorbed membrane suggests that one of the above assumptions has been violated.

PGE1 is known to be surface-active, thereby adhering to glass and plastic surfaces. If PGE1 adheres to the PE / H_2O, or docosane / H_2O interface, it would not be detected in the receptor cell. However, there was no difficulty in detecting PGE1 in the receptor cell using unmodified PE membranes. Moreover, docosane and PE have similar hydrophobicity; therefore, even though PGE1 may adhere to surfaces, its surface-active properties had minimal effect in the permeation system used here.

Since PGE1 and docosane both contain a long chain of hydrocarbons, their structural similarity may hinder the ability of PGE1 to diffuse through docosane, even when docosane is melted. Based on the lag time from the diffusion experiments, the diffusion coefficient of PGE1 and PRO were estimated. The diffusion coefficient of PRO was found to be greater than 8.7×10^{-9} cm^2/s. No PGE1 was detected in the receptor compartment in the experiments conducted. However, based on the latest sampling time point, a value for the maximum diffusion coefficient of PGE1 could be determined. Using this procedure, PGE1 diffusion coefficient through docosane-absorbed PE membranes were estimated to be less than 8.0×10^{-12} cm^2/s. The difference in diffusion coefficients of PGE1 and PRO may possibly account for the observed difference in permeation behaviour for the two compounds.

There are two more possible reasons which can explain the lack of PGE1 transfer through the docosane-absorbed membrane. If PGE1 had a small docosane/

water distribution coefficient, then PGE1 in the donor cell would have difficulty partitioning into the alkane-absorbed membrane. Alternatively, if PGE1 had a large docosane-water distribution coefficient, it would partition into the membrane, yet have difficulty partitioning out of the membrane into the aqueous phase on the receptor side. However, after a lag period, the duration of which depends on the diffusion coefficient of PGE1 in docosane, PGE1 would appear in the receptor cell. To assess whether either of these possibilities apply, the distribution coefficient of PGE1 between docosane and water at 45 °C was determined.

4.3.2.1 Docosane / Water Distribution Coefficients of Prostaglandin E_1 and Propranolol HCl

Experiments were performed to measure the solubility of PGE1 in pH 7.4 buffer and in docosane at 45 °C. The solubility of PGE1 in pH 7.4 buffer at 45 °C was between 100 and 115 µg/mL. The solubility of PGE1 in docosane at 45 °C was less than 7 µg/mL. Therefore, the distribution coefficient of PGE1 in docosane-pH 7.4 buffer system can be no greater than 7/107, which is 0.065. The assumption that PRO and PGE1 have a similar membrane distribution coefficient is thus incorrect.

Other literature studies provided an explanation for the big difference in the reported octanol-water and the measured docosane-water partition coefficients. Prostaglandin E_1, due to its surface active and ion-pair formation properties, prefers

to partition into octanol from the aqueous phase.[77] Octanol has a hydroxyl group to which PGE1 may adhere. On the other hand, docosane has no such surfactant groups and as a result, partitioning into docosane is not favourable. Yamaguchi [78] reported that the apparent partition coefficient of PGE1 between soybean oil and pH 7.4 buffer at 37 °C was 0.02. Soybean oil is a mixture of long chain fatty acids and is more hydrophobic than octanol. Based on the number of polar groups in the vehicle, PGE1 is likely to have the highest partition coefficient in the octanol / water system, followed by the soybean / water system, and has the smallest partition coefficient in the docosane / water system.

Table 4.8 Properties of prostaglandin E_1 and propranolol HCl. [76, 81, 82]

Properties	**Prostaglandin E_1**	**Propranolol HCl**
Chemical Formula	$C_{20}H_{34}O_5$	$C_{16}H_{21}NO_2 \cdot HCl$
Molecular Weight	354.49	295.81
Water solubilities	80 µg/mL	1 in 20 (~50000 µg/mL)
pKa	4.96	9.5
log PC_{ow} [a]	1.08	1.2
PC_{ow}	12.0	15.8
DC_{ow} [b]	0.0039	0.11
log DC_{DW} [c]	< -1.2	0.2
DC_{DW}	< 0.063	1.6
Diffusion coefficient [d]	$< 8.0 \times 10^{-12}$ cm^2/s	$> 8.7 \times 10^{-9}$ cm^2/s

[a] PC_{ow}: octanol / pH 7.4 buffer partition coefficient [78]

[b] DC_{ow}: octanol / pH 7.4 buffer distribution coefficient, calculated by
$\log DC = \log PC - \log (1 + 10^{pH-pKa})$

[c] DC_{DW}: measured docosane / pH 7.4 buffer distribution coefficient at 45 °C

[d] estimated by latest sampling lag time

For comparison, the distribution coefficient of PRO in a docosane-pH 7.4 buffer system was found to be 1.6 (± 0.2), a value much higher than that for PGE1. Therefore, PRO had no difficulty partitioning into the alkane-absorbed membrane, unlike PGE1. Thus, it is likely that the combination of PGE1's small diffusion coefficient in docosane and its small docosane / buffer distribution coefficient hinder the ability of PGE1 to permeate through the alkane-absorbed PE membrane. As a result, the alkane-absorbed PE membrane is not suitable for use with the PGE1-containing thermal-responsive implant.

4.4 Overall Assessment of the Prostaglandin E_1 Penile Implant

A primary challenge in the development of a PGE1 implant is to maintain the stability of PGE1. This challenge can be overcome by dispersing PGE1 in inert substances such as oleaginous pharmaceutical vehicles with low acid values. It is essential that the drug reservoir has minimal acidity; as demonstrated by the addition of an antioxidant to the oleaginous vehicle, the shelf life of PGE1 can be prolonged. It is likely that hydrocarbons such as long chain alkanes which lack reactive groups could maintain PGE1 chemical stability. Although docosane may effectively prevent the degradation of PGE1, the solubility of PGE1 in docosane is so small that PGE1 cannot partition into the docosane-absorbed membrane. A material which can stabilize PGE1, allows effective transport of PGE1, and has a melting point between 42-43 °C is needed for further development of the thermal-

responsive PGE1 implant. However, the combination of these stringent requirements eliminates almost all reservoir candidates.

The phase change of the pore-filling material regulates solute permeability through the modified membrane. As long as the pore-filling material solidifies below and melts at the desired trigger temperature, a thermal-responsive membrane can be made. By choosing the appropriate pore-filling material, the trigger temperature of the membrane can be customized, as clearly demonstrated using propranolol HCl in this study.

A special feature of the current delivery device is that the pore-filling material, an alkane, not only acts as a rate-controlling barrier for the membrane, but also serves to stabilize PGE1. The permeation experiments described in this thesis used an aqueous solution in the donor cell to model the drug reservoir. If the alkane were also used as the reservoir material, the "off-state" permeability would be very small because the drug reservoir is solidified during the "off-state", hence further limiting the diffusion of PGE1 out of the implant. Conceptually, such a device design meets several of the requirements of the PGE1 implant.

There are deep-heating ultrasonic devices in development for local hyperthermia treatment. These ultrasonic heaters use either a single or multiple acoustic beams to focus the heating to the target site, e.g. a tumour. It was also shown that using a 1.8 MHz single circular trajectory transducer, a tissue of 2 cm

width and 1 cm deep in a dog's leg could reach a temperature of 45 °C.[83] It appears that the same technology can be applied to make a heater which can selectively heat the thermal-responsive drug delivery system to trigger drug release.

The polymer used in this drug-delivery device development, low density PE, has established biocompatibility with tissues. Low density PE is known to elicit minimal tissue reaction, and has been used to fabricate parts of a penile prosthesis.[73] Long chain alkanes have a similar chemical structure to that of PE, so a similar (i.e., negligible) tissue reaction is expected. With PE selected as the membrane material for the implant, undesirable immunogenic reactions can be avoided.

The required pharmacological dose of PGE1 is about 20 μg.[10] If the pore material were miscible with the drug reservoir, there would be significant exchange of materials during the "on-state" of the device. On the other hand, if the reservoir were aqueous in nature, such mixing would not occur. However, due to the instability of PGE1, selection of the reservoir is limited to oleaginous agents, hydrophobic in nature. As a result, every time the device is heated to temperatures above its trigger temperature, mixing would occur with the hydrophobic pore-filling material and the hydrophobic drug reservoir. Alteration of the pore-filling material would lead to an irreversible change in membrane permeabilities. To prevent the loss of membrane thermal-responsiveness, the pore-filling material should either be

the same as the reservoir material, or should be covalently attached to the pores of the polymer membrane.

Due to PGE1's small partition coefficient between docosane and buffer system, this particular alkane-absorbed membrane is not suitable as the encapsulating membrane for the PGE1 thermal-responsive implant. An alternative pore-filling material with a PGE1 partition coefficient larger than that in docosane should be used to modify the polymer membrane so that PGE1 can partition across the membrane during the "on-state" of the device. Alternatively, a thermal-responsive penile implant can be developed using another vasoactive substance such as sildenafil. The selected drug should have a better aqueous stability and a similar docosane-buffer partition coefficient to that of propranolol HCl in order to make use of this thermal-responsive alkane-absorbed membrane.

5.0 Conclusions

1. The shelf life of prostaglandin E_1 was found to be prolonged by dispersing it in low acidity vehicles ethyl oleate and capric/caprylic triglycerides.

2. Oxidation of an oleaginous pharmaceutical vehicle is known to be minimized by the addition of an antioxidant. The antioxidant may work by delaying the release of free fatty acids from the oleaginous vehicle and thus, prolonging the shelf life of PGE1 in such an oleaginous vehicle.

3. Due to the large difference in the rates of solute diffusion through solids and liquids, phase change in the membrane material can be used as a rate-controlling mechanism for responsive drug release.

4. By selecting a pore-filling material which has a melting point close to the desired trigger temperature, the trigger temperature of the thermal-responsive membrane can be customized.

5. PGE1 is not suitable for use with the current thermal-responsive delivery system. The chemical instability of PGE1 requires the reservoir material to be hydrophobic and of low acidity, such as the alkane series. However, PGE1's small docosane/water partition coefficient prevents PGE1 from diffusing through the membrane at a therapeutically useful rate.

6. Although PGE1 does not work with the current alkane-absorbed thermal-responsive membrane, the concept of the thermal-responsive drug delivery system can be applied to other drugs for penile erectile dysfunction and to the treatment of other diseases.

A suitable thermal-responsive implant can be made by encapsulating the drug of interest with a porous polymer membrane filled with a material which melts at the desired trigger temperature. The implant can be activated using an extracorporeal heating trigger, such as heating by an ultrasonic heater, thereby not damaging the surrounding tissue. The drug's permeation coefficient in the solid polymer material should be small so that the rate of diffusion is only governed by the phase of the pore-filling material. When the pore material is melted, the rate of drug diffusion is fast and the implant releases a bolus of drug; when the pore material is solidified, the rate of drug diffusion is insignificant, and no drug is released.

6.0 Recommendations for Future Work

1. Further studies are needed to fully quantify the effect of the oleaginous pharmaceutical vehicle and antioxidant on PGE1 stability.

2. While searching for another potential candidate for the present thermal-responsive delivery system, one should pay attention to the drug's pore-material/buffer partition coefficient. The drug of interest has to have a moderate partition coefficient in order to partition into the filled-pores and partition out of the membrane on the receptor side. The selection of the pore-material will depend on the chemical environment needed to maintain the stability of drug.

3. Drugs which have a similar docosane/water partition coefficient to that of propranolol HCl are potential candidates for use in this thermal-responsive release delivery system. Sildenafil, another erectile dysfunction drug, structurally more hydrophobic than PGE1 and available in a salt form, may be suitable for use with this thermal-responsive delivery system. Further permeation studies with sildenafil can be carried out.

4. The concepts of thermal-responsive and extracorporeally- triggered drug release utilized in this thesis can be adapted and applied to other clinical situations. Further exploration using the current drug delivery concepts can be carried out.

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8.0 Appendices

8.1 Prostaglandin E_1 HPLC Assay

The standard curve:

$$\frac{\text{area of PGE1 peak at 197nm}}{\text{area of temazepam peak at 197nm}} = 0.0343\ [\text{PGE1}]\ (\mu g/mL) + 0.041$$

$R^2 = 0.9941$, n = 7, [PGE1] between 4.75 and 57 µg/mL

$$[\text{PGE1}]\ (\mu g/mL) = \frac{\text{area PGE1}}{\text{area temazepam}} \times \frac{[\text{temazepam standard}]}{3.704} - 1.39$$

Internal standard: [temazepam] = 108 µg/mL

Detection limit: 2 µg/mL

Intra-sample average coefficient of variation: 3.2%

Inter-day variability: 5%

Substance	Retention time (minutes)
PGE1	5 - 6.5
Temazepam	6.5 - 7.5
PGA1	10 - 11
PGB1	12 - 13

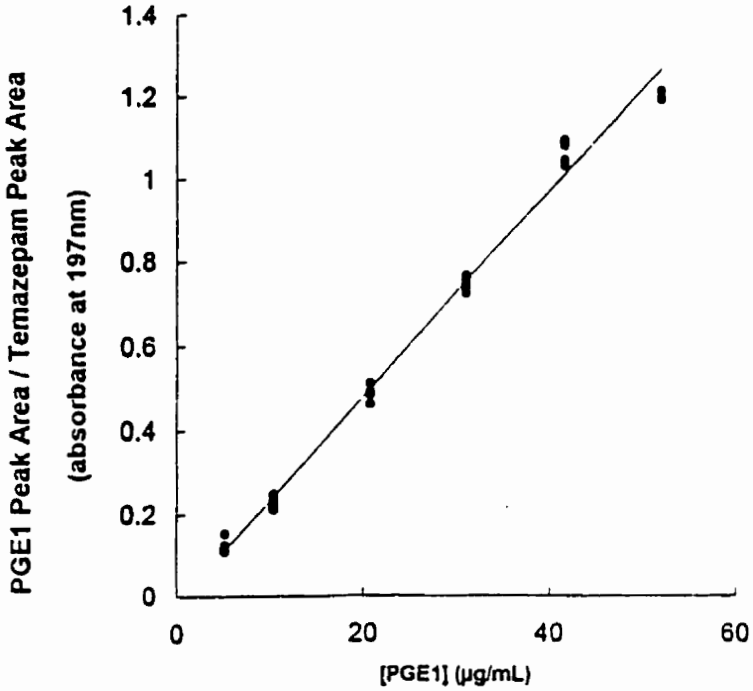

Figure 8.1 Standard curve of the prostaglandin E_1 HPLC assay.

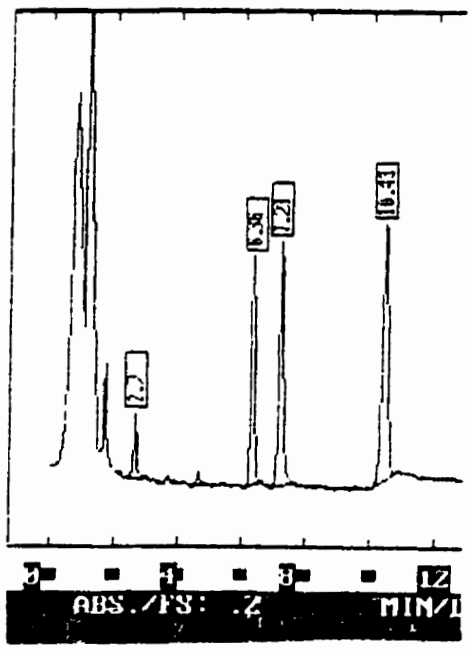

Figure 8.2 A typical chromatogram of the PGE1 HPLC assay.

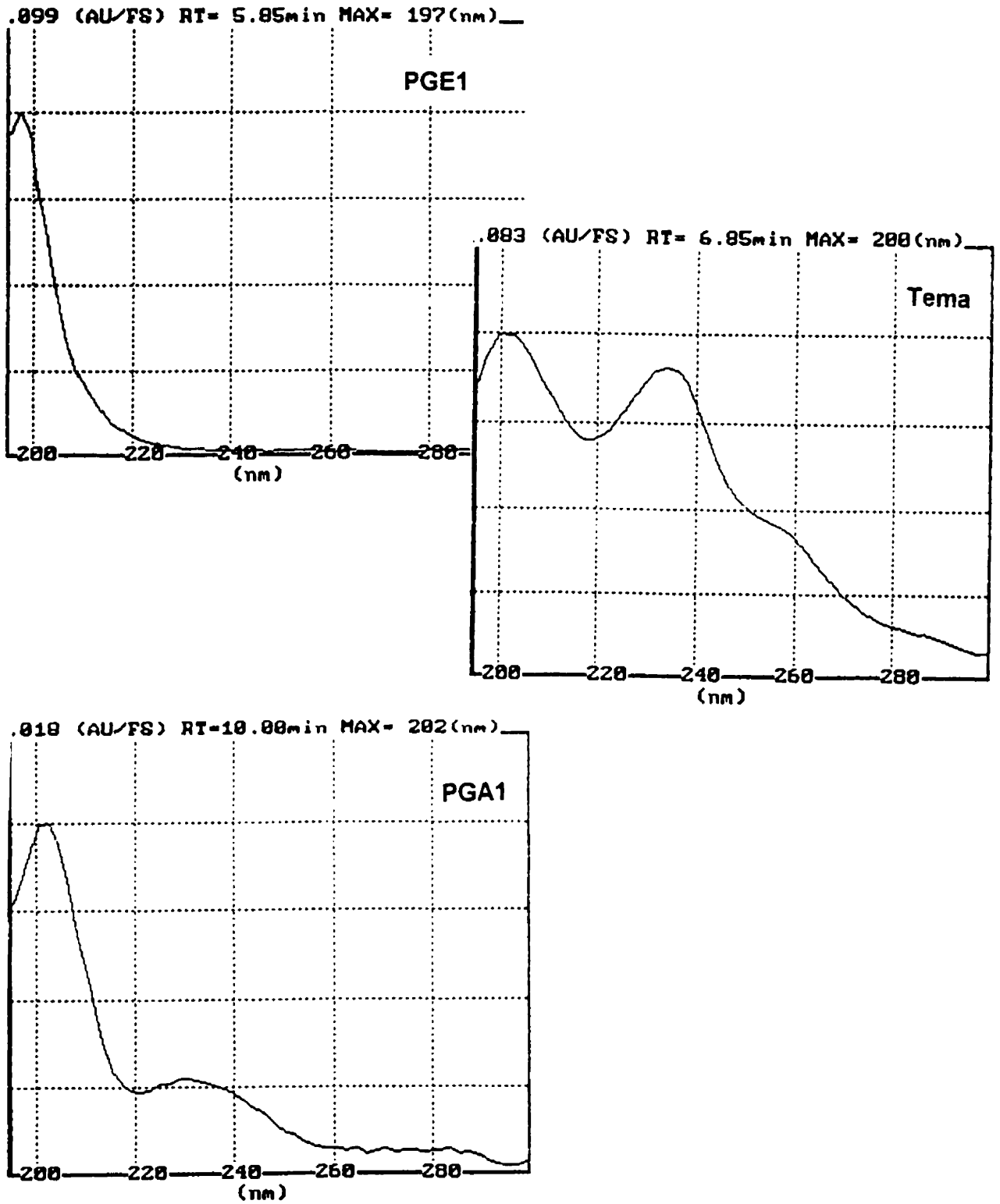

Figure 8.3 The UV absorption spectrum of prostaglandin E_1 (PGE1), temazepam (Tema), and prostaglandin A_1 (PGA1) in pH 3.5 buffer.

8.2 Propranolol HCl UV Assay

PRO absorbance at 290nm = 0.0195 × [PRO] + 0.0089

R^2 = 0.9988, n = 5, [PRO] between 6 and 61 µg/mL

$$[PRO]\ (\mu g/mL) = \frac{PRO\ absorbance - 0.0089}{0.0195}$$

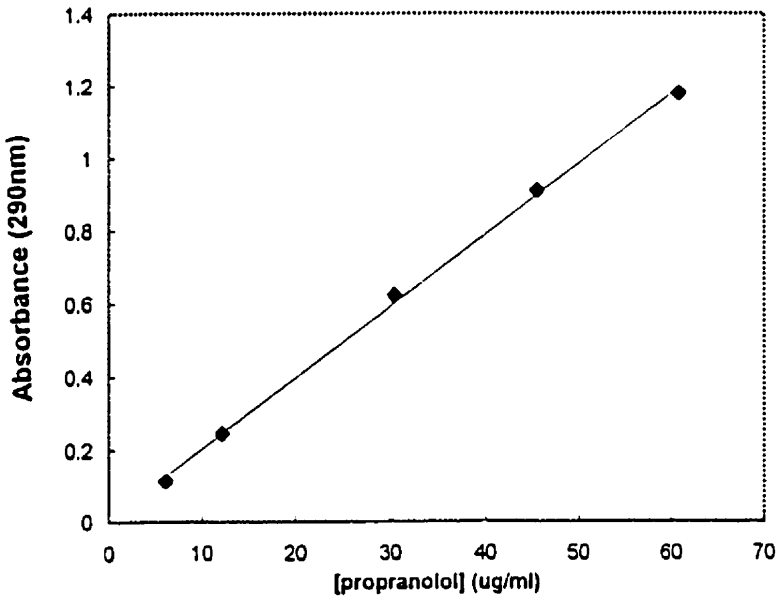

Figure 8.4 Standard curve of propranolol HCl UV spectrophotometric assay.

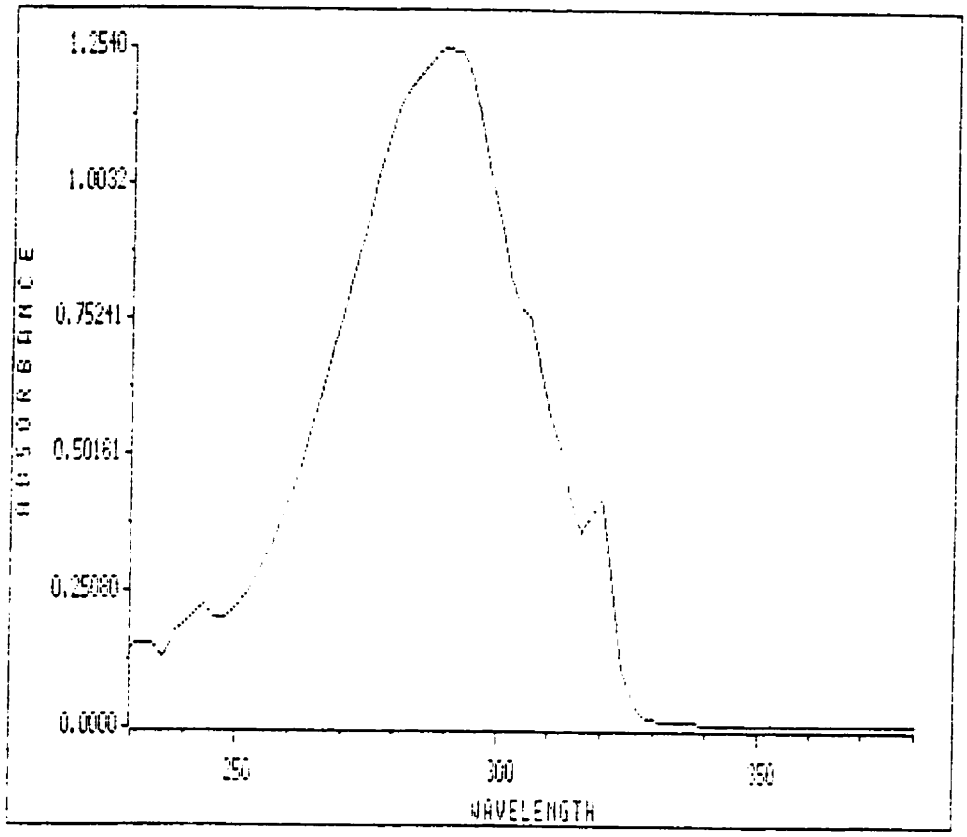

Figure 8.5 The UV absorption spectrum of propranolol HCl in pH 7.4 buffer.