

2008

## In Vitro Effects of Emollient Substances on Release of Ketorolac Tromethamine

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IN VITRO EFFECTS OF EMOLLIENT SUBSTANCES ON RELEASE OF  
KETOROLAC TROMETHAMINE

BY

BURCAK ALIOGLU

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE  
REQUIREMENT FOR THE DEGREE OF

MASTER OF SCIENCE

IN

DEPARTMENT OF

BIOMEDICAL AND PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2008

MASTER OF SCIENCE THESIS


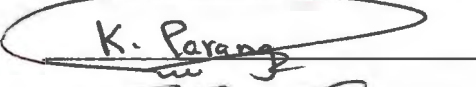
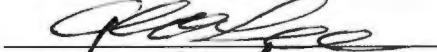
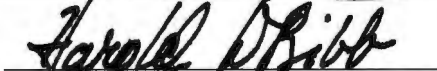
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2008

## Abstract

Ketorolac tromethamine is a non-steroidal drug that has potent analgesic and moderate anti-inflammatory activity. A single dose of ketorolac tromethamine is clinically more effective than that of many drugs in the management of moderate to severe postoperative pain. Transdermal delivery of ketorolac tromethamine seems as a potential method of administration that would be non-invasive and eliminate repeated dosing regimens. Although a transdermal dosage form of ketorolac has not arrived in the market, permeation enhancement of ketorolac tromethamine transdermally and topically has been the subject of several pharmaceutical research studies.

The objective of this study was to evaluate the possible release enhancement effects of several commonly used skin emollient substances on the *in vitro* release of ketorolac tromethamine from topical emulsion formulations. The O/W emulsions containing 1.65% ketorolac tromethamine were prepared as topical formulations. Six different emulsions with three different emollients; sucrose polysoyate, di-ppg-2-myreth-10 adipate, and ppg-3-benzyl myristate at 1 and 5% levels were prepared. The release of ketorolac tromethamine from each emulsion was studied *in vitro* using static Franz diffusion cells. The diffusion studies were conducted across cellulose ester and silicone membranes. A validated HPLC assay method was used to analyze the drug concentration. A linear mixed-effect model was used to test the statistical significance of all the release rates from the six emulsions compared to the control at a significance level of  $p < 0.05$ . The complex viscosity and the thixotropy measurements of the emulsions were determined by using an Advanced Rheometer 2000.

The release experiment results show that sucrose polysoyate significantly increased the release rate of ketorolac tromethamine both at 1 and 5% levels across the silicone membrane, although it increased the release rate of the drug only at 5% ratio across the cellulose ester membrane. According to the rheological analysis results, addition of sucrose polysoyate at 5% level increased the complex viscosity and the thixotropy values. Di-ppg-2-myreth-10 adipate also increased the release rate of the drug both at 1 and 5% levels across the silicone membrane, however it had no effect on the release rate of the drug at 1% and significantly decreased the release rate of the drug at the 5% concentration across the cellulose ester membrane. The addition of di-ppg-2-myreth-10 adipate both at 1 and 5% concentrations showed a decrease in the complex viscosity and the thixotropy values. PPG-3- benzyl myristate increased the release rate of ketorolac tromethamine both at 1 and 5% concentrations across the cellulose ester and the silicone membrane. PPG-3-benzyl myristate, at 1% level increased the complex viscosity and the thixotropy value however it had no effect on the viscosity, and lowered the thixotropy at 5% level.

Our in vitro test results helped us understand how the skin emollients may affect the diffusion rate of ketorolac tromethamine out of topical formulations and as O/W emulsions across two different membranes. It also gave us an idea whether these emollient substances could be studied and evaluated further as potential permeation enhancers for in vivo studies. Further, this research identified the inadvertent effect that emollient excipients may have on the permeation of other components when used for their emollient effect in various skin preparations.

## Acknowledgements

I truly would like to express my gratefulness to my major professor, Dr. Thomas Needham for his endless support and kindness throughout my master's thesis project. I learnt a lot during all those times that I was his student.

I also would like to extend my thankfulness to my committee members, Dr. Keykavous Parang and Dr. Chong Lee, and the chair of defense, Dr. Norma Owens for their time and input.

I would like to acknowledge the support of chemistry department, especially Professors Bill Euler and William Rosen for allowing me to work as a teaching assistant in their departments.

I would like to thank my friend Rajesh Narwal for helping me working on the statistics of my results, and Maryjo Bent for her help with the necessary arrangements in the analytical and the quality control lab.

My many thanks also go to Rahmi Koc, Vehbi Koc Vakfi and Dr. Zikri Altun, Turk Petrol Vakfi for their financial support that initiated my journey to University of Rhode Island.

I am also indebted to Dr. Ahmet Baydar from the Gillette Company, who kindly provided lab and tools for my project.

I would like to thank my parents and my brother, who always supported me from the beginning to the end in every way I took in my life. And, of course my beloved husband, Ertunc, who encouraged me and always believed in me.

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## 1.0 Introduction

### 1.1 Emulsions in Topical Drug Delivery

An emulsion is a thermodynamically unstable system that consist of at least two immiscible liquid phases, one of which is dispersed as globules in the other liquid phase, stabilized by the presence of an emulsifying agent (1). One of the liquid phases in the emulsion is fundamentally polar or aqueous, whereas the other liquid phase is relatively non-polar or oil. In general, there are two types of emulsion systems. When the aqueous phase is dispersed in the oil phase, it is referred to as a water-in-oil (W/O) emulsion, whereas if the oil phase is dispersed in the aqueous phase, the system is called oil-in-water (O/W) emulsion. The particle diameter of the dispersed phase is given generally in the range 0.1 to 100  $\mu\text{m}$ . Dermatologic and cosmetic lotions and creams are O/W emulsions and are acceptable among the patients and physicians because they spread easily and cover the affected area (1).

Emulsions are semi-solid preparations, which are used in pharmacy, medicine and cosmetics, and are for applications externally to the skin or mucous membranes. Mixed emulsifiers of surfactant/amphiphile type are often preferred to make topical O/W creams. An amphiphile is defined as either a long-chain fatty alcohol or fatty acid particularly for cosmetic applications, and these materials are able to stabilize and to give body to the emulsion system. The higher fatty alcohols with a chain length from  $\text{C}_{14}$  to  $\text{C}_{18}$  or fatty acids such as palmitic or stearic acid are usually employed. The water-soluble surfactant could be anionic such as sodium lauryl sulfate, cationic type such as quaternary ammonium salt of bromide or a nonionic

surfactant such as ceteth-20, which is the polyethylene glycol ether of cetyl alcohol (2).

## 1.2 Trans-Epidermal Drug Enhancers

### 1.2.1 Functions and Structure of the Skin

The skin, the heaviest single organ of the body, physically protects the internal organs and restricts the passage of substances into and out of the body. The skin, which covers an area of 1.8 m<sup>2</sup> for an average 70-kg human being, regulates the body temperature and blood pressure with its circulation and evaporation systems (2).

Despite the complex nature of the skin structure, it is composed of three layers the epidermis, dermis and subcutaneous tissue. Skin appendages such as hair, as well as sweat and sebaceous glands are originate in the skin (Figure 1). The epidermis is composed of four individual layers, from the external surface inwards, these layers are called the horny layer (stratum corneum), the granular layer (stratum granulosum), the prickle cell layer (stratum spinosum), the basal layer (stratum germinativum). The cells, which are formed in the basal layer of the epidermis, differentiate as they move outwards, and complete their final stage of differentiation by becoming flattened, anucleic, keratinized, stacked vertically and constitute the outermost epidermal layer of the skin, stratum corneum. The stratum corneum has a key role in controlling the percutaneous absorption of drug molecules. The next layer the dermis is composed of connective tissue. This layer contains the blood vessels, nerves, lymphatic, and skin appendages such as sweat glands, sebaceous glands. Beneath the dermis, the subcutaneous tissue, which is a layer of fat, connects the flexible skin and the underlying structures. It serves as a thermal barrier and a mechanical cushion (2).

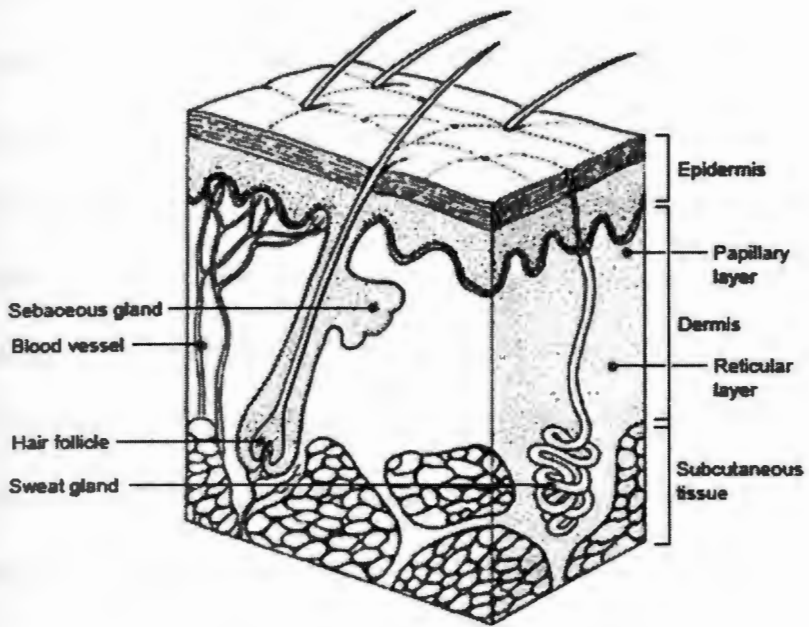


Figure 1. Structure of the skin (3)



### 1.2.2 Percutaneous Absorption and Penetration Enhancers

Percutaneous absorption of a drug starts with diffusion out of its vehicle to the stratum corneum of the skin. The stratum corneum, which has a thickness of around 15-20  $\mu\text{m}$  over the human body, and is made up with blocks of keratin embedded in extra cellular lipid, constitutes the primary permeation barrier for the drug molecule (4). This barrier presented by the stratum corneum structure is explained as “brick and mortar” structure, which is analogous to a wall. The corneocytes of hydrated keratin constitute the bricks, which is surrounded in the mortar that is multiple lipid bilayers, which are composed of ceramides, fatty acids, cholesterol and cholesterol esters. If this stratum corneum were absent, the passage of most of the small water-soluble non-electrolytes would be a thousand times more rapidly (5). One of the solutions to increase the permeability of the stratum corneum has been the use of penetration enhancers in transdermal drug delivery. Penetration enhancers are the chemicals, which penetrate into skin to decrease the barrier resistance of the skin. Penetration enhancers promote drug flux by one or more of the mechanisms described below i.e. making alterations at the molecular level such as: disrupting the lipid structures of the stratum corneum, solvating the keratins and reducing the drug/tissue binding, increasing the fluidity of the lipid region in the stratum corneum, interacting with the proteins and enhancing drug partitioning into the skin (6).

### 1.2.3 Penetration Enhancement by Hydration of Stratum Corneum

Water has long been considered to increase the transdermal and topical delivery of drugs. The human stratum corneum has water content of around 15-20% of the

tissue dry weight depending on the humidity of the environment. This water content can come in equilibrium with that of the dermal layer if the skin is immersed in water, exposed to high humidity environments, or is occluded so that the transepidermal water loss is not permitted (7). Mechanisms of action by which hydration of stratum corneum facilitates transdermal absorption is not clearly known, however there are several theories that partially explain this phenomenon. One of the theories is that the free water in the tissue could change the solubility of the drug molecule in the stratum corneum, however this mechanism does not explain the hydration-enhanced delivery of lipophilic molecules such as steroids. Another theory is a "pore pathway" formation in the stratum corneum that would enhance the drug penetration. According to the theory, under extensive hydration, the lacunae will expand and interconnect. The lacunar domain is defined as the sites of corneodesmosome degradations, which lie within the lipid bilayers of the stratum corneum (7).

Based on the principle of hydration of the stratum corneum, transdermal drug bioavailability can be improved by hydrophobic ointments, moisturizers, occlusive films and transdermal patches (8). Although in general skin hydration leads to an increase in transdermal delivery of both hydrophilic and lipophilic molecules, there are some studies that show occlusion does not always lead to percutaneous absorption enhancement (9).

### 1.3. Classic Approaches to Hydrate the Stratum Corneum

There are three classic approaches used in the pharmaceuticals, cosmetics and personal care area to hydrate the stratum corneum:

(a) Using Humectants.

Humectants, which are used in skin preparations, are water-soluble organic compounds that can absorb water. Humectants hydrate the stratum corneum by holding water that would normally be free and result in trans-epidermal water loss. Under high humidity conditions, these substances are also able to pull water from the exterior to the skin (10). Glycerol, sorbitol, propylene glycol, butylenes glycol, urea, sodium lactate and sodium pyrrolidone carboxylic acids are among the widely used humectants.

(b) Using Occlusives.

Occlusives are used to occlude the skin, and to reduce the transepidermal water loss. Non-water permeable substances are utilized in most of the moisturizer preparations. Mineral and vegetable oils, lanolin and silicones are the primarily used to occlude the skin (11).

(c) Using Emollients.

An emollient is a substance, which gives a smooth feel and a general sense of well being to the skin. An emollient will even out the lines on the surface of the skin and make the individual corneocytes rounded (11). The mechanism of action of emollients is attributed to the hydration caused by their occlusive nature/ effect. Because any liquid, semi-solid or a solid that has a low-melting point along with a cosmetic quality could be utilized as an emollient, a complete list of emollients will be almost impossible to list here.

Emollient substances are mainly divided into two groups: water-soluble and oil-soluble. The polyhydric alcohols such as glycerine, propylene glycol, sorbitol, and ethoxylated lipids are the water-soluble emollient substances. Glycerine and

propylene glycol are used both as a humectants and emollients between 15-30% in topical pharmaceutical formulations and cosmetics (12). The oil-soluble emollients comprise a longer list of substances that could be classified into several chemical groups such as hydrocarbon oils and waxes, silicone oils, vegetable oils, fats, alkyl esters, fatty acids and alcohols, and ethers of fatty alcohols. Hydrocarbon oils, waxes and silicone oils are very occlusive substances in nature. They are able to form a hydrocarbon barrier on the skin and are very efficient in preventing the evaporation of water that is supplied by the underlying tissues of the stratum corneum. The silicone oils such as dimethyl polysiloxanes and mixed methyl phenyl polysiloxanes are non-polar, chemically inert, and skin protectant substances. Silicone oils are less occlusive than mineral oil, and by being a skin protectant they do not remove the sebum from the skin, and present a good barrier to chemical irritants (13). Because the fatty acid glycerides make the 50% of human sebum, and 5.5 to 37.5% of the skin surface lipids, the vegetable, animal oils and fats are included in the emulsions as emollient substances. Examples of vegetable oils are peanut, safflower, olive, avocado, corn, and castor oils. Animal oils and fats are mink oil, turtle oil, tallow and hydrogenated tallow (13). Alkyl esters are light, easily spreadable oily substances such as isopropyl myristate and isopropyl palmitate. Today, there is an ever-increasing range of synthetic esters that have unique and multifunctional properties. Alkyl ester type emollients give a smooth and non-greasy film on the skin when applied, and alkyl esters have properties such as pigment wetting, hydroalcohol solubility, emulsification (13). Fatty acids such as lauric, myristic and stearic acid are also used as emollient substances for their slip properties and mild occlusive

properties. Lauryl, myristyl, cetyl, stearyl alcohols are among the examples of fatty alcohols; and ethoxylated lauryl, cetyl, stearyl, isostearyl are few examples for fatty alcohol ethers that are used as emollient substances.

#### 1.4. Emollients Used in this Study

##### 1.4.1 Sucrose Polysoyate

Sucrose polysoyate is a mixture of esters of glycine soja (soy) acid and sucrose. This material is defined as a skin conditioning agent- emollient and as a surfactant-emulsifying agent (14). Sucrose polysoyate is chemically composed of a sucrose backbone esterified with six to eight soybean fatty acid chains. Figure 2 shows the chemical structure of a sucrose backbone, which has eight hydroxyl groups that are available for esterification. Table 1 displays the composition of soybean oil fatty acids. Esterification of lipophilic fatty acids to hydrophilic sucrose moiety gives a structure that has lipophilic and hydrophilic surface active functionality. The number of mono-, di-, tri-,..., hepta- or octaesters of fatty acid esters of sucrose in the mixture establish the lipophilic or hydrophilic character of the mixture. The degree of esterification of the sucrose backbone is the number of sucrose hydroxyl groups, which are esterified with the fatty acids (15). The functional properties of sucrose fatty acid polyesters are described by their hydrophilic-lipophilic balance (HLB) numbers that are controlled their degree of esterification. Sucrose esters may be manufactured at many different HLB values (HLB number between 5-16 would be accepted as high, whereas HLB number between 2-6 would be accepted as a low

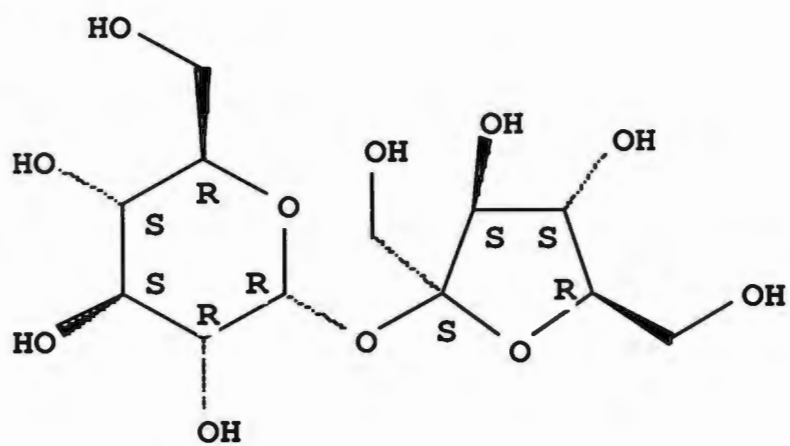


Figure 2. Structure of the sucrose backbone (16)

Table 1.

*Composition of Soybean Oil Fatty Acids (17)*

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Fatty acid	Percent of total (%)
<i>Saturated fatty acids</i>	
Palmitic (C16:0)	11
Stearic (C18:0)	4
<i>Unsaturated fatty acids</i>	
Oleic (C18:1)	24
Linoleic (C18:2)	54
Alpha Linolenic (C18:3)	7

---

value) depending on the fatty acid chain length and degree of substitution of the sucrose structure (18). According to the HLB of the sucrose esters, those that have a low HLB value of 3-6 will stabilize w/o emulsions, the ones that have an intermediate HLB number between 8-13 will stabilize o/w emulsions, and those with HLB numbers higher than 13 will work as a solubilizer. Sucrose polysoyate has an HLB number of 4.91 provided in the specification sent by the supplier.

#### 1.4.2 Di-PPG-2 Myreth-10 Adipate

Di-PPG-2 Myreth-10 Adipate is 100% active alkoxyated di-ester of myristyl alcohol and adipic acid. This material is defined as a multifunctional emollient with good irritation mitigation. It solubilizes Benzophenone-3 and hair dyes. It has an HLB number of 4.16, and it is oil soluble and water dispersable (19). The addition of ethylene oxide and propylene oxide to an ester of myristyl alcohol and adipic acid gives an ethoxylated surfactant type property to this emollient. The chemical structure of di-PPG-2 Myreth-10 Adipate is given in the Figure 3.

#### 1.4.3 PPG-3 Benzyl Myristate

PPG-3 Benzyl Myristate is the ester of propoxylated myristic acid and the benzyl alcohol. The chemical structure is presented in the Figure 4. This material is manufactured as an emollient that is superior to silicone in terms of shine and feel enhancement for the personal care products (20). The substance is designed so that the alkoxylation improves the dispersability and the feel characteristics of skin care formulations. The benzyl group enhances the compatibility of the substance in



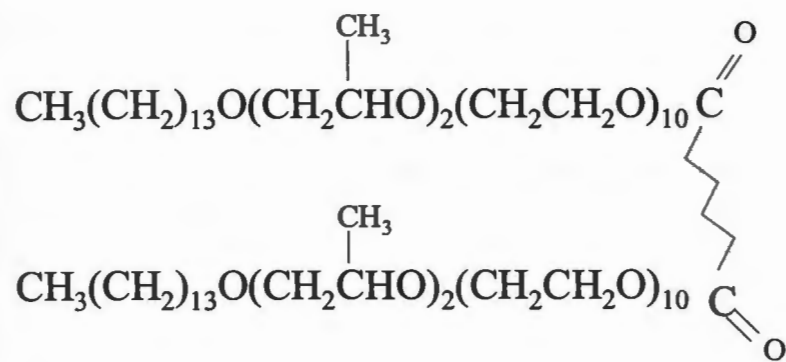


Figure 3. Chemical Structure of Di-PPG-2 Myreth-10 Adipate

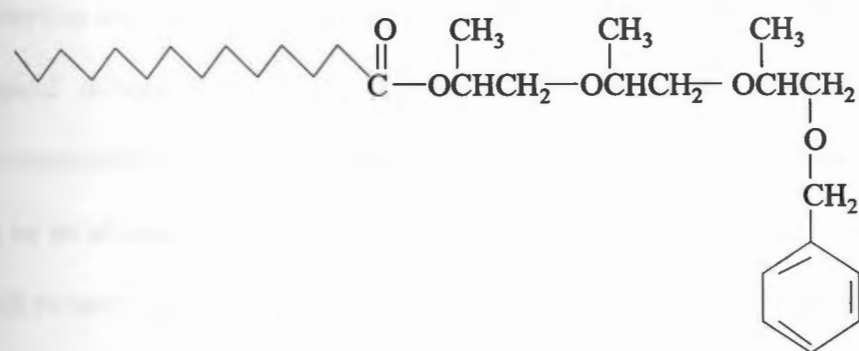


Figure 4. Chemical Structure of PPG-3 Benzyl Myristate

products such as sunscreens and fragrances. It is oil soluble, and has an HLB number of 13.49.

### 1.5 Ketorolac Tromethamine

Ketorolac tromethamine is a nonsteroidal drug that has potent analgesic and moderate anti-inflammatory activity. Figure 5 shows the chemical structure of ketorolac tromethamine. Ketorolac tromethamine is available as an oral dosage form; topical dosage form as an ophthalmic solution and as an injectable that is intramuscularly and intravenously (21). Transdermal delivery of the drug is proposed to be an alternative type of administration, which is considered as non-invasive and will reduce repeated dosing regimens (22). The benefits that are associated with the ketorolac tromethamine administration are listed as: adequate analgesic effect, no sedation, absence of respiratory depression and urinary retention, reducing the excitement that is seen along with the inhalational anesthesia use (23).

### 1.6 In Vitro Drug Release Studies

An experimental method to study the percutaneous absorption of a drug from a topical formulation may be achieved by using in vivo and in vitro techniques. In vitro release experiments using excised human or animal skin are morally more desirable, less expensive and less time consuming compared to in vivo studies. In vitro release experiments are valuable for screening procedures and understanding the effects of physicochemical parameters such as flux rates, partition coefficients, and diffusion

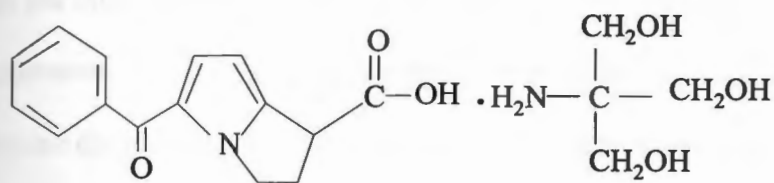
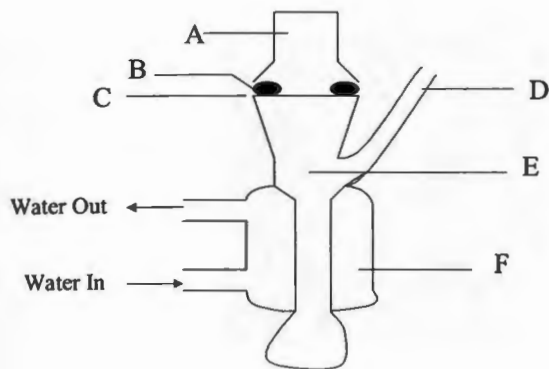


Figure 5. Chemical Structure of Ketorolac Tromethamine

coefficients. One of the commonly used diffusion-cell systems is the Franz diffusion cell. A static Franz cell is represented in the Figure 6, which is composed of a donor compartment and a receptor compartment. The excised human or animal skin or an artificial membrane is placed between the donor and the receptor compartments. The o-ring is inserted to support and maintain the membrane flat throughout the experiment. Then the compartments are clamped. The receptor compartment is usually filled with phosphate buffer to mimic the body fluids, and/or a solution in which the drug solubility is enhanced. The topical formulation is placed on the donor compartment. Aliquots from receptor solution are at specified time intervals to determine drug flux and withdrawn solution volume is replenished to assure the sink conditions. The passage of the drug molecule from the donor compartment to the receptor fluid is quantified (24-25).

Excised skin and artificial membranes are widely used in in-vitro for quick assessment of the product efficacy because of the high cost of screening large numbers of candidate formulations and the need to determine the toxicity levels of novel compounds (26).

Cellulose ester membrane, one of the artificial membranes, is widely used in in-vitro diffusion studies to determine the effect of vehicle or formulation variables on the overall drug availability. Cellulose ester membranes are manufactured from cellulose acetate. The material is processed and extruded into tubular membranes or flat sheets (27). Figure 7 displays an image of cellulose ester membrane. The permeation of a series of steroids through a cellulose acetate membrane was reported



A = Donor Compartment, B= O-ring, C= membrane,  
D= Sampling Compartment, E= Receptor Compartment, F= Water Jacket

Figure 6. Static Franz Cell

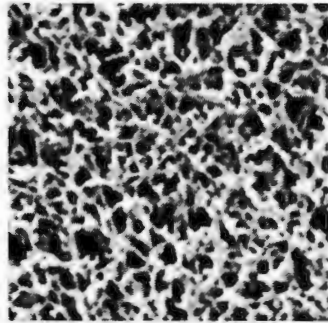


Figure 7. Cellulose Ester Membrane (28)

to be dependent primarily on membrane-water partition coefficients of the steroids so that the least polar compound was permeated the fastest (29). Cellulose acetate and all dialysis membranes are examples of porous barriers. Thus the transportation of the solute or the drug molecule will be through the solution-filled pores. The rate of diffusion is determined by the probability that a molecule will enter a pore as well as the tortuosity of the pores. Although a cellulose acetate membrane cannot be considered an exact model for human skin, its mechanism of activity has been considered as a model of a damaged skin (30).

Silicone sheeting which is a polymethylsiloxane membrane is another artificial membrane used in vitro diffusion studies. The silicone elastomer is considered as a partitioning-membrane system, which is mechanistically relevant membrane model for the skin penetration studies (30).

### 1.7 Objective

Ketorolac tromethamine is rapidly absorbed, and it reaches the maximum plasma concentration in 30 to 40 minutes after oral administration to healthy volunteers. The maximum plasma level is reached within 45 to 50 minutes if it is administered intramuscularly. The systemic availability of ketorolac is reported to be approximately 80% after taken orally. The drug is administered to the patients who have moderate to severe postsurgical pain as single dose regimens, although it is administered 4 times daily up to 7 days to the patients, who have acute musculoskeletal pain (31). Transdermal delivery of ketorolac has been the subject of



pharmaceutical research by many scientists due to the need for repeated dosing regimens. Transdermal delivery is considered as a non-invasive drug administration. It has been reported that when ketorolac tromethamine was included in the solvent mixtures of propylene glycol and linoleic acid in proportions of 7:93 and propylene glycol and oleic acid in proportions of 8:92 and these solvents were applied to the rhesus monkeys that were used as a model for human skin penetration, significantly high ketorolac tromethamine plasma levels were obtained after a 24-hour transdermal patch application (32).

Effects of vehicles and penetration enhancers for ketorolac tromethamine were studied in another study revealed that pure propylene glycol monolaurate enhanced the penetration of ketorolac tromethamine across excised hairless mouse skin. When cosolvent systems were evaluated in this study, it has been concluded that a solution of 20 to 60 % diethylene glycol monoethyl ether either with propylene glycol monocaprylate or propylene glycol monolaurate could be used to enhance the skin permeation of ketorolac tromethamine. In addition, a vehicle that consisted of 10% propylene glycol in caprylic acid has been found out to increase ketorolac permeation (33).

In a study with lecithin-stabilized microemulsions for topical delivery of ketorolac tromethamine, it has been reported that an organogel which is composed of 40% lecithin, and 60% isopropyl myristate that contained 0.6 % w/w of water and 6.5 %w/w of ketorolac tromethamine gave the highest drug release rate in vitro through guinea pig skin as a human skin model (34).

Permeation enhancement of ketorolac tromethamine has also been studied in healthy humans, and a mixture of isopropyl alcohol: water: isopropyl myristate (50:50:1.5) has been suggested as transdermal patch composition that achieved the highest plasma concentration (35).

The objective of this study was to prepare O/W emulsions of ketorolac tromethamine with three different skin emollient substances and study the possible effects of these emollients on in vitro diffusion of this drug across two artificial membranes. These three emollients, which are chemically either sugar esters or the esters of fatty alcohols and acids, are used in the cosmetic preparations because they improve the skin feel, softness and smoothness. Sucrose polysoyate is acknowledged for its moisturization improvement and its protective effect on skin barrier. PPG-3 benzyl myristate has silicone-like feel and functionality with film-forming ability. Di-ppg-2 myreth 10 adipate is proposed to be a good slip enhancer. The moisturization and film forming abilities may lead the hydration of stratum corneum and thus could increase the permeation of the model drug. In our study, we are going to understand the possible effects of these emollients on the release of the model drug across artificial membranes on in vitro diffusion experiments.

## 2.0 Materials

### 2.1 Instrumentation

The concentration determination of Ketorolac tromethamine was determined by using an HPLC (Agilent 1100 Series UV Spectrometer). It consists of a Milton Roy, Consta Metric III metering pump, a monitor, and a Hewlett Packard Integrator. The wavelength was set at 322 nm. Peak heights were automatically programmed by the integrator. Chromatography was achieved using a C-18 (3.9 mm id x 300 mm) column. The mobile phase was prepared by mixing acetonitrile and 1.3 mM Phosphoric acid solution (pH = 3.02) at a ratio of 34:66. The flow rate was kept at 1.5 mL/minute (36). The mobile phase was freshly prepared, mixed with a magnetic stirrer, and then filtered by 0.45  $\mu$ m nylon filters (Millipore, Bedford, MA).

An Advanced Rheometer 2000 TA (New Castle, DE) was used to measure the complex viscosity and the thixotropy values of the emulsions. A 6 cm acrylic cone (New Castle, DE) was used.

### 2.2 Chemicals and Reagents

Ketorolac Tromethamine, USP injectable grade was purchased from Medilom& Co. N.V. (Antwerp, Belgium). Potassium acid phosphate anhydrous, sodium chloride, o-phosphoric acid, and HPLC grade acetonitrile were purchased from Fisher Scientific (Fairlawn, New Jersey). Disodium phosphate anhydrous was purchased from J.T. Baker Chemical Co. Sucrose polysoyate, di-ppg-2-Myreth-10 adipate, and ppg-3-benzyl ether myristate were kindly supplied by Croda Inc. (Edison, New Jersey). Non-reinforced Silicone sheeting was purchased from Advanced Bio-Technologies Inc. (Clearwater, Florida). Cellulose ester membrane was purchased

from Spectrum Lab. Inc. (Rancho Dominguez, CA). Light mineral oil was purchased from Mays Chemical Co. (Indianapolis, IN). Stearyl alcohol was purchased from Henkel Co., Carbopol ETD 2020 was purchased from Noveon Inc. (Cleveland, OH). Yellow beeswax, NF pastilles, were kindly supplied by Strahl&Pitsch Inc. (West Babylon, New York). Brij 721S and Span 60S were kindly supplied by Uniqema (New Castle, DE). Germaben II was kindly supplied by ISP Sutton Labs. (Chatham, New Jersey). Bottled distilled water was purchased from Poland Spring (Greenwich, CT)

### 3.0 Methods

#### 3.1 Preparation of Emulsions

Ketorolac tromethamine (KT) (1.65% w/w) was weighed accurately and dissolved in distilled water. It was stirred with the anchor type-stirring blade to ensure that it was completely dissolved. Carbopol ETD 2020 (0.1 % w/w) was dispersed in the KT solution at an agitation of 500 RPM for 15 min. Sorbitol (5.65 % w/w) and Brij 721S were added to the water phase, and it was heated to 75 °C. The oil phase, which consisted of mineral oil, stearyl alcohol, yellow beeswax and Span 60S, was blended together in a beaker and heated to 75 °C. The oil phase was added to the water phase at 75 °C, and stirred with an agitation of 300 RPM. 0.15 g of 10% (w/v) sodium hydroxide solution was added. The crude emulsion was kept stirring until it cooled to 60 °C, and then homogenized using a Premier Mill Corp. homogenizer for 2 min at 3000 RPM. After the homogenizing process, the emulsion was mixed slowly with a T-shape blade. Germaben II (1.00% w/w) was added to the emulsion at 40 °C, it was kept slowly mixing down to 24-25 °C. All the emulsions contained the same amount of KT, distilled water, carbopol ETD 2020 and Germaben II. Six different emulsions were prepared by adding three different emollients at two different levels (1% and 5%, w/w). The amount of Span 60S and Brij 721S was determined by using the required hydrophilic lipophilic balance calculation for each emollient and levels. A total of 100 g of each emulsion was prepared, and kept in glass jars at room temperature for one week until use. At the time the emulsions were one week old. The pH was adjusted to approximately 6 by adding  $0.15 \pm 0.03$  g of 10% (w/v) sodium hydroxide solution if necessary (Table 2 and 3).

Table 2.

*Water Phase Compositions of the Emulsions (%w/w)*

<b>Emulsion</b>	<b>Brij721S</b>	<b>NaOH (10% sol.)</b>
<i>Control</i>	3.46	0.21
<i>1% Sucrose Polysoyate</i>	3.37	0.15
<i>5% Sucrose Polysoyate</i>	2.78	0.22
<i>1% Di-PPG-2 Myreth-10 Adipate</i>	3.38	0.23
<i>5% Di-PPG-2 Myreth-10 Adipate</i>	2.74	0.15
<i>1% PPG-3-Benzyl Myristate</i>	3.48	0.15
<i>5% PPG-3-Benzyl Myristate</i>	3.57	0.24

All emulsion water phases contain the same % w:

	<u>% w/w</u>
<i>Water</i>	63.45
<i>Sorbitol</i>	5.65
<i>Ketorolac Tromethamine</i>	1.65
<i>Germaben II*</i>	1.0
<i>Carbopol ETD2020</i>	0.1

\* Germaben II includes the following ingredients: Propylene glycol, diazolidinyl urea, methyl and propyl paraben.

Table 3.

*Oil Phase Compositions of the Emulsions\* % (w/w)*

<b>Emulsion</b>	<b>Mineral Oil</b>	<b>S. Alcohol</b>	<b>Y. Beeswax</b>	<b>Span 60S</b>
Control	20.00	2.00	1.00	1.54
<i>1% Sucrose Polysoyate</i>	19.24	1.84	0.92	1.63
<i>5% Sucrose Polysoyate</i>	16.00	1.20	0.80	2.22
<i>1% Di-PPG-2 Myreth-10 Adipate</i>	19.24	1.84	0.92	1.62
<i>5% Di-PPG-2 Myreth-10 Adipate</i>	16.00	1.20	0.80	2.26
<i>1% PPG-3-Benzyl Myristate</i>	19.24	1.84	0.92	1.52
<i>5% PPG-3-Benzyl Myristate</i>	16.00	1.20	0.80	1.43

\* The oil phase contained the % amount of the emollient that is designated with the name of the emulsion. Likewise, 1% Sucrose Polysoyate contains 1% Sucrose Polysoyate in the oil phase.

### 3.2 Release Studies

The formulated emulsions were placed on either a cellulose ester or silicone membrane and the release of ketorolac tromethamine from the emulsions and through the membranes was determined by using a Franz static diffusion cell system. The Franz cell had a radius of 1 cm, and a volume of 10.0 ml. The membranes were placed between the donor and the receiver compartments, and then the o-ring was placed on the rims of the receiver compartment between the donor compartment. The effective area for diffusion was  $3.14 \text{ cm}^2$ . In each experiment, 1.5 g of emulsion containing the drug was placed on the membrane in the donor compartment. The receptor compartment was filled with 10.0 ml of degassed isotonic phosphate buffer solution at pH 7.4. The temperature of the Franz cells was maintained at  $32 \text{ }^\circ\text{C}$  by circulating water through the water jackets of the cells using a circulatory water bath. The receptor solution was stirred with a magnetic stirrer once the console, which was holding the cells, was turned on. 10 ml of receptor solution was withdrawn completely at 0.5, 1, 2, 4, 6, 8, 10 and 12 h. The receptor solution was replaced with fresh isotonic phosphate buffer solution. The withdrawn sample solutions were stored in glass scintillation vials, and kept in the refrigerator until the concentration measurement. The ketorolac tromethamine concentration in each vial was determined by using an HPLC.

### 3.2 Preparation of Membranes

The cellulose ester membrane was soaked in distilled water for 30 min, and was washed with distilled water to get rid of the preservative, sodium azide. Then, it was



placed in a bath of distilled water for 24 h in the refrigerator. Thirty min before the experiment, it was placed in fresh phosphate buffer solution.

The silicone sheet was washed with distilled water, and received the same post treatment as the cellulose ester membrane.

### 3.4 Release Data Analysis

The cumulative amount of ketorolac tromethamine, which was released out of the emulsion and through the membrane, was plotted as a function of time. The release rate ( $\mu\text{g}/\text{cm}^2/\text{h}$ ) of the drug was calculated from the slope of the graph.

### 3.5 Analytical Assay for Ketorolac Tromethamine

An HPLC method was used to detect the amount of ketorolac tromethamine that released from the formulation into the receptor medium. A C-18 column with a 3.9 mm i.d.x 300 mm was used to elute the drug along with mobile phase, which was consisted of acetonitrile and 1.3 mM phosphoric acid solution (pH= 3.02) with a proportion of 34:66 (v/v). The flow rate was programmed as 1.5 ml/min, and the injection volume was 20 $\mu\text{l}$  (36). The retention time of each chromatography was 8 min, and the detection wavelength was set at 322 nm.

### 3.6 Analytical Data Analysis and Validation Study for the Ketorolac Tromethamine Assay

The concentration of ketorolac tromethamine was determined according to two different calibration curves, which were constructed by plotting the peak height obtained from the chromatography versus known drug concentrations.

Concentrations of 0.1, 0.25, 0.5, 1, 3  $\mu\text{g/ml}$  and 5, 7, 10, 15, 20  $\mu\text{g/ml}$  were prepared to construct the calibration curves for the silicone membrane, and cellulose ester membrane, respectively. For some experiments, the drug solution was diluted with the phosphate buffer to appropriate concentrations before analysis.

Both of the calibration curves were found to be linear in the concentration range from 0.1  $\mu\text{g/ml}$  to 3  $\mu\text{g/ml}$  for the silicone membrane (Figure 8), and from 5  $\mu\text{g/ml}$  to 20  $\mu\text{g/ml}$  for the cellulose ester membrane (Figure 9) with mean regression coefficient ( $R^2$ ) values of 0.998.

An inter-day and intra-day analytical method validation study was performed on three different days by constructing the calibration curves for three different concentrations of KT solution in phosphate buffer.

Each solution was injected six times, and RSD and % recovery values were calculated according to the FDA reviewer guidance, validation of chromatographic methods, published by CDER (37). The values obtained are tabulated in a table in Table 4 and 5.

### 3.7 Statistical Analysis

All the experiments were carried out six times. Their mean values, and the standard deviation values were calculated. A linear mixed-effect model was used to test the statistical significance of all the release rates of six emulsions compared to the control. It was assumed that the differences were significant at  $p < 0.05$ . The results of the linear mixed-effect model test are given in Table A1 and A2, Appendix.

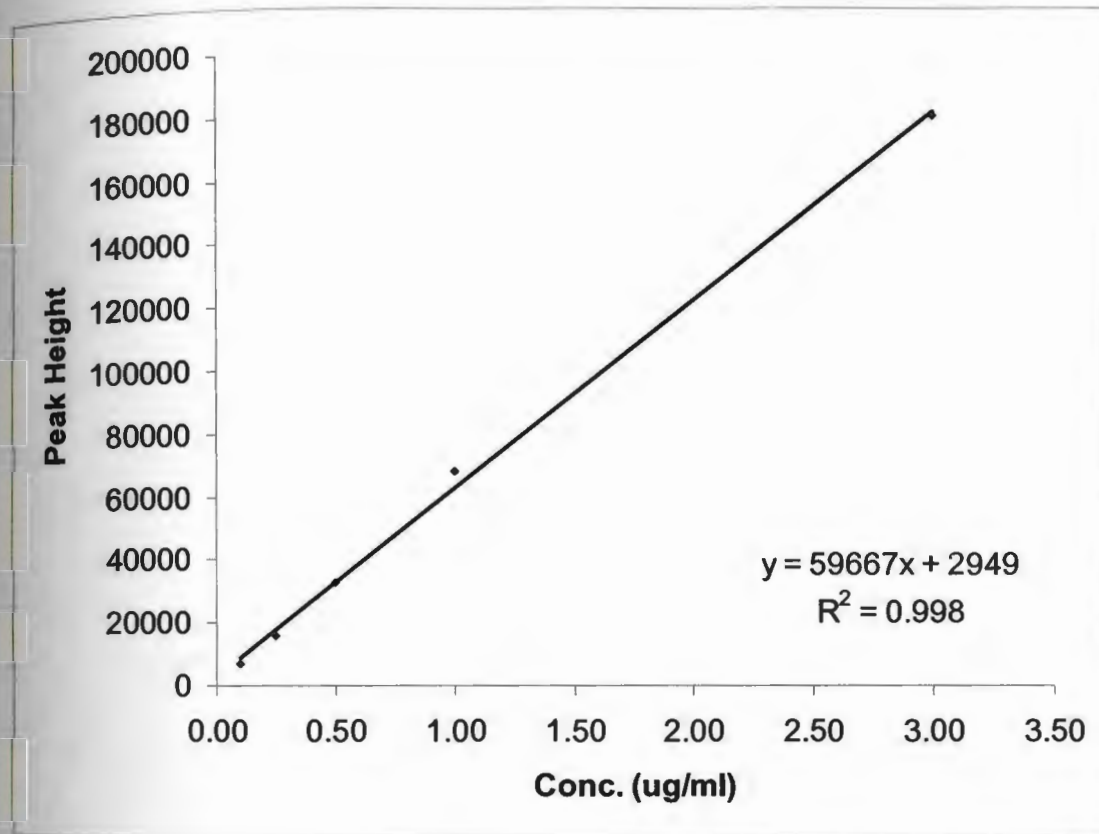


Figure 8. Calibration Curve for Analysis of Ketorolac Tromethamine Used for the Diffusion Experiments Across Silicone Membrane

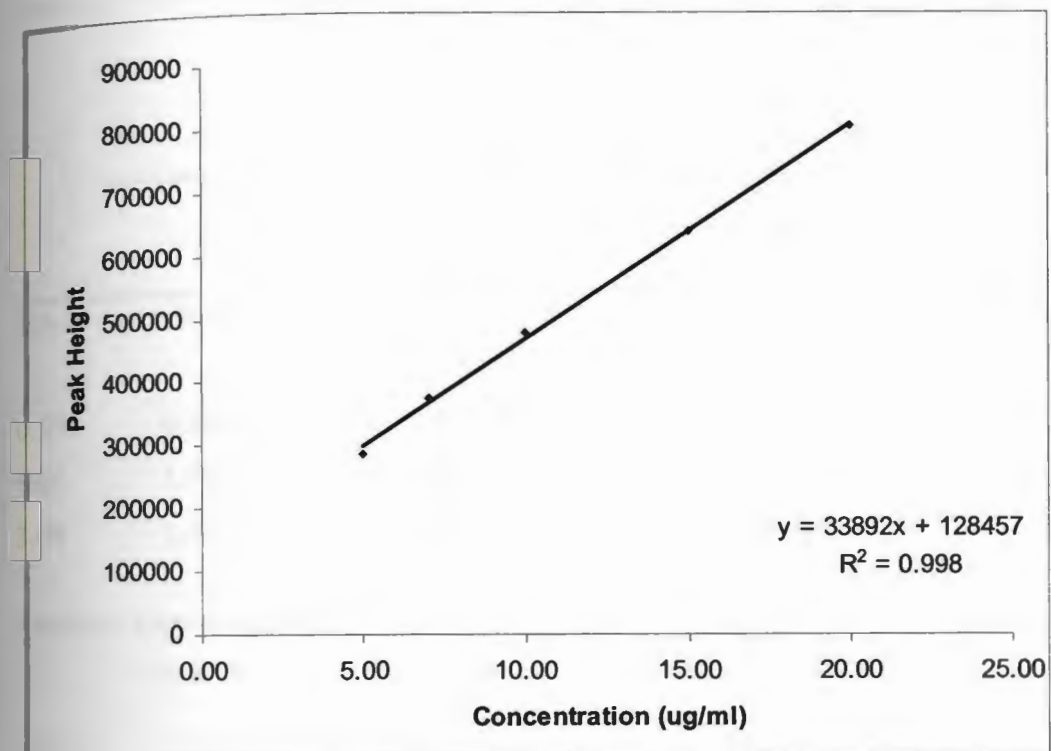


Figure 9. Calibration Curve for Analysis of Ketorolac Tromethamine Used for the Diffusion Experiments Across the Cellulose Ester Membrane

Table 4.

Inter-day Method Validation Data for Ketorolac Tromethamine (KT) for the Cellulose Ester and Silicone Membrane

	<i>KT Added</i>		<i>KT Measured (ug/ml)*</i>		
	DAY I	DAY II	DAY III	Precision, RSD	Accuracy, % Recovery
<i>Silicone membrane concentrations</i>					
0.50	0.50±0.01	0.52±0.01	0.49±0.05	3.03	100.67
1.00	1.00±0.03	0.98±0.03	1.01±0.01	1.53	99.67
3.00	3.00±0.02	3.00±0.02	3.00±0.15	0.00	100.00
<i>Cellulose ester membrane concentrations</i>					
7.00	6.49±0.13	6.80±0.07	6.84±0.07	0.39	97.29
10.00	10.27±0.08	10.27±0.18	10.21±0.07	0.34	102.50
20.00	19.94±0.11	19.94±0.34	19.95±0.17	0.03	99.72

\* The data represents the mean ± standard deviations of six replicates.

Table 5.

Intra-day Method Validation Data for Ketorolac Tromethamine (KT) for Cellulose Ester and Silicone Membranes

	<i>KT Added</i>		<i>KT Measured (ug/ml)*</i>	
	Measurement I	Measurement II	Precision, RSD	Accuracy, % Recovery
<i>Silicone membrane concentrations</i>				
0.50	0.52±0.01	0.52±0.01	0	104.0
1.00	0.98±0.03	1.02±0.02	2.83	100.00
3.00	3.00±0.02	2.95±0.03	1.19	99.17
<i>Cellulose ester membrane concentrations</i>				
7.00	6.84±0.07	6.69±0.17	1.57	96.64
10.00	10.21±0.07	9.99±0.06	1.54	101.00
20.00	19.95±0.17	21.38±0.75	4.56	103.08

\* The data represents the mean ± standard deviations of six replicates.

### 3.8 Rheological Analysis of Emulsions

An Advanced Rheometer 2000 (TA Instruments) was used to assess the rheological characterization of six emulsions and the control. A 6 cm (diameter) acrylic truncated (32 microns) cone was used for all the rheology experiments.

#### 3.8.1 Complex Viscosity Measurement

Before any testing, all the emulsions were placed in a plastic centrifuge tubes, and then centrifuged at 600 rpm for 5 min (38). The emulsions had been stored untouched overnight. For each measurement, a sample of the emulsion was placed on the middle of the lower plate with the help of a spatula. This treatment ensured that all the emulsions had the same rheological history and minimum structural disturbance before testing.

The oscillatory shear method was used to assess rheological parameters such as  $G'$  (the dynamic storage modulus),  $G''$  (the dynamic loss modulus) and the  $\eta^*$  (the complex viscosity).

When an emulsion sample was subjected to an oscillatory stress, the rheometer was able to detect the periodic strain, which was generated from the deformation within the sample.

A strain sweep test was performed in order to obtain the linear viscoelastic region for all the emulsions. It was achieved by varying the stress applied at a given oscillation rate. Thus, the sweep was conducted from the 0.01% to 100% strain range at a rate of 15 rad/sec. All emulsions displayed linear viscoelastic region up to the 1% strain level.

A frequency sweep was also performed in the same oscillatory mode from 1 to 100 rad/sec and 0.6% was determined as the strain level for all of the emulsions, so that stress would never exceed the linear viscoelastic region.

### 3.8.2 Thixotropy Measurement

A flow test method was performed to evaluate the thixotropy of all the emulsions. A continuous ramp with a shear rate from zero to  $50 \text{ sec}^{-1}$  was run in order to construct the up curve. To obtain the down curve, a reversed shear rate from 50 to zero  $\text{sec}^{-1}$  was applied in a second continuous ramp. A pause of 2 min was established between the up and the down curve.

### 3.9 Rheological Data Analysis

The computer automatically generated the complex viscosity values for each of the emulsions. The experiment was performed twice for each emulsion and the average of the two tests were calculated at the frequency of 1 rad/sec for all of the samples.

The thixotropy value for each emulsion was calculated from the hysteresis area which is the area between the ascending curve and the descending curve. The hysteresis area was calculated by using a SAS program. The experiment was repeated three times, and the shear stress and the shear rates that were used to construct the flow chart were the averages of the three experimental results.



## 4.0 Results and Discussion

### 4.1 Results of Ketorolac Tromethamine Analytical Assay and Validation Study

The calibration curves were found to be linear in the concentration ranges from 0.1 µg/ml to 3 µg/ml for the silicone membrane, and from 5 µg/ml to 20 µg/ml for the cellulose ester membrane with mean regression coefficient ( $R^2$ ) values of 0.998 (Figures 8 and 9). The mean interday percent recovery for the three concentrations each representing a low, medium and high concentration in the calibration range for the silicone membrane were 100.67, 99.67, and 100.00 %. The inter-day percent recovery for the three concentrations for the cellulose ester membrane were 97.29, 102.50, and 99.72 % (Table 4). The intra-day percent recovery of these same concentrations were found to be 104.0, 100.0, 99.17 % for the silicone membrane, and the intraday percent recovery for the cellulose ester membrane concentrations were found to be 96.64, 101.00, and 103.08 % (Table 5).

### 4.2. Results of Release Studies

#### 4.2.1 Release of Ketorolac Tromethamine from Emulsions Containing Sucrose Polysoyate Across the Cellulose Ester and the Silicone Membranes.

The release profiles across the cellulose ester membrane for the emulsions containing 1, 5 % sucrose polysoyate and the control are given in Figure 10 and Table 6. They show that there is no lag time for the release of ketorolac tromethamine out of the emulsions. Analysis of the results using the linear mixed effect model indicates that the addition of 1% sucrose polysoyate did not change the release rate significantly from that of the control. However addition of 5% sucrose polysoyate

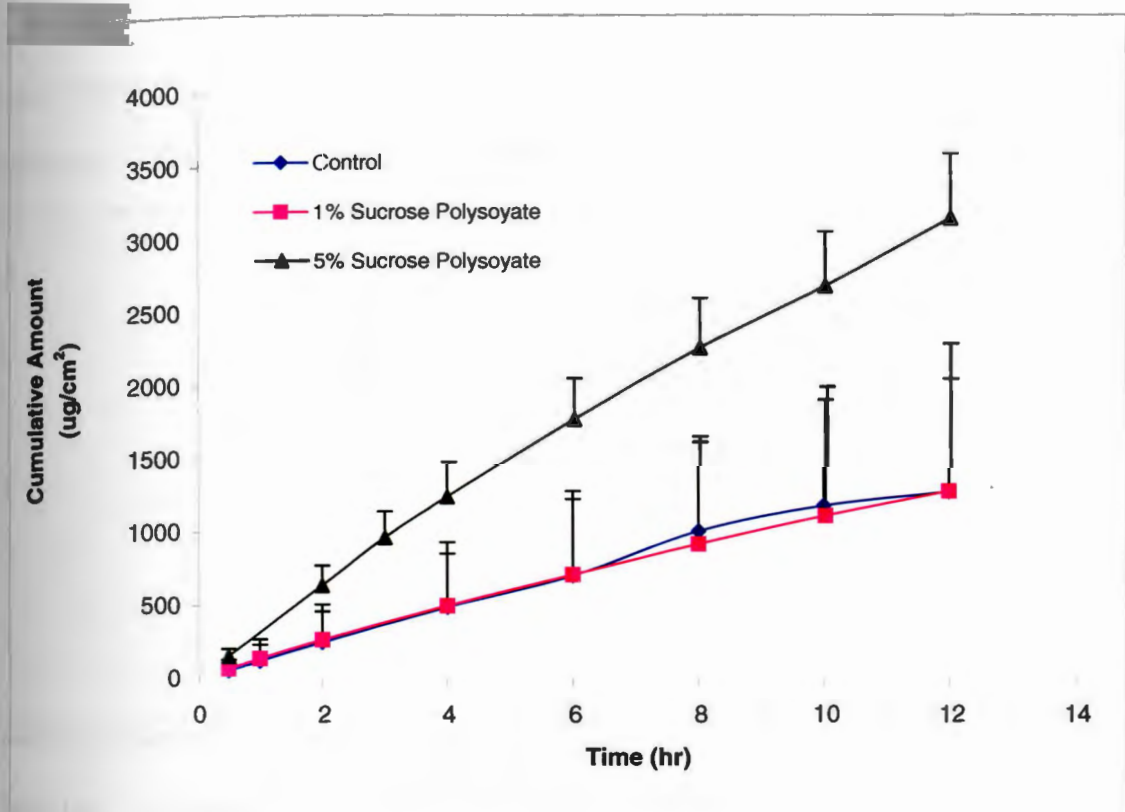


Figure 10. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5% Sucrose Polysoyate Across Cellulose Ester Membrane

Table 6.

*Cumulative Released Amounts of Ketorolac Tromethamine Across Cellulose Ester Membrane from Control Emulsion and the Emulsions Containing 1 and 5% Sucrose Polysoyate*

*Control Emulsion*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	56.52	46.30
1	121.38	113.31
2	250.37	209.77
4	488.88	364.57
6	701.24	522.69
8	1004.57	608.13
10	1178.93	721.87
12	1270.93	772.25

*Emulsion Containing 1% Sucrose Polysoyate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	68.90	62.55
1	138.60	132.66
2	265.94	242.34
4	496.79	433.55
6	707.59	570.81
8	916.15	731.71
10	1108.13	880.20
12	1274.90	1008.96

Table 6 Contd.

*Emulsion Containing 5% Sucrose Polysoyate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	156.55	50.07
2	637.71	134.66
3	962.93	178.12
4	1241.18	235.17
6	1768.19	280.44
8	2255.91	341.68
10	2678.27	374.04
12	3143.09	442.16

increased the release rate significantly ( $256.09 \mu\text{g}/\text{cm}^2/\text{hr}$ ) compared to the release of the 1 % ( $105.54 \mu\text{g}/\text{cm}^2/\text{hr}$ ) and the control ( $111.19 \mu\text{g}/\text{cm}^2/\text{hr}$ ).

The release profile of drug from the emulsions containing 1 and 5% sucrose polysoyate and the control across the silicone membrane is given in Figure 11. Figure 11 and Table 7 show that as was seen with the cellulose ester membrane, there is no lag time in the release of ketorolac tromethamine out of the emulsions and across the silicone membranes. Analysis of the results using the linear mixed effect model indicates that addition of either the 1 and 5% sucrose polysoyate increased the release rate of the ketorolac tromethamine significantly ( $3.50 \mu\text{g}/\text{cm}^2/\text{hr}$  and  $3.44 \mu\text{g}/\text{cm}^2/\text{hr}$ , respectively) compared to the control ( $0.33 \mu\text{g}/\text{cm}^2/\text{hr}$ ). In contrast to the cellulose ester membrane, the increase from emulsion containing sucrose polysoyate from 1 to 5% in the silicone membrane systems did not show a significant difference in diffusion rate across the membrane as a function of emollient concentration. However, the rate of release of both concentrations of sucrose polysoyate was significantly different from the control.

The release rates of ketorolac tromethamine from the control emulsion across the cellulose ester and the silicone membrane were found out  $111.19 \mu\text{g}/\text{cm}^2/\text{hr}$ , and  $0.33 \mu\text{g}/\text{cm}^2/\text{hr}$ , respectively. The overall difference in the observed release rates of drug from the control emulsions across the two different membranes may be attributed to the difference in the chemical natures of these membranes. The cellulose ester membrane is a hydrophilic membrane, whereas the silicone is a lipophilic membrane.

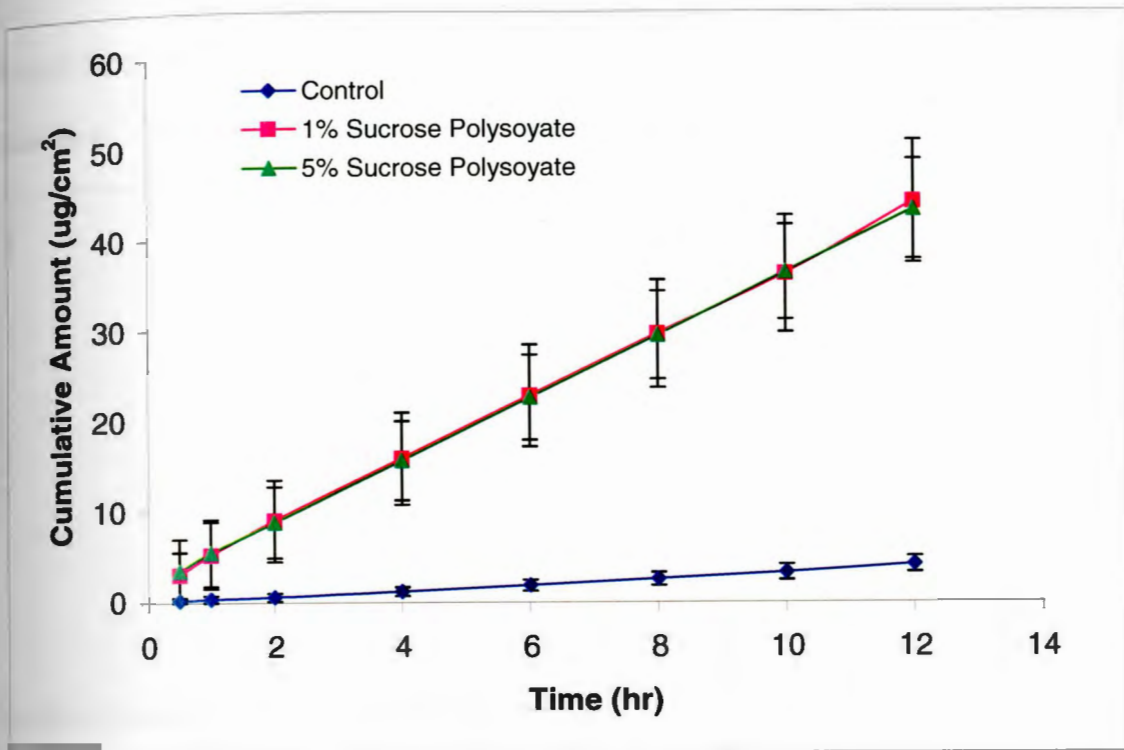


Figure 11. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5 % Sucrose Polysoyate Across Silicone Membrane

Table 7.

*Cumulative Released Amounts of Ketorolac Tromethamine Across Silicone Membrane from Control Emulsion and Emulsions Containing 1 and 5% Sucrose Polysoyate*

*Control Emulsion*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	0.24	0.18
1	0.42	0.37
2	0.62	0.44
4	1.22	0.50
6	1.88	0.62
8	2.57	0.72
10	3.30	0.86
12	4.15	0.87

*Emulsion Containing 1% Sucrose Polysoyate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	3.09	2.50
1	5.25	3.67
2	9.01	4.48
4	15.85	5.06
6	22.74	5.61
8	29.56	5.94
10	36.15	6.44
12	44.10	6.77

Table 7 Contd.

*Emulsion Containing 5% Sucrose Polysoyate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	3.53	3.49
1	5.51	3.68
2	8.85	3.91
4	15.61	4.34
6	22.56	4.69
8	29.42	4.86
10	36.35	5.22
12	43.26	5.52



It is well known that according to the pH-partition hypothesis, only un-ionized molecules pass through lipid membranes (39). The pH of the emulsions are approximately 6.00. At this pH since the pKa of ketorolac tromethamine is 3.5, the ratio of the ionized drug species to the un-ionized species is 316 to 1. Since the ratio of the un-ionized drug species is significantly lower than the ionized species, the release rate across the silicone membrane would be expected to be lower as compared to the release rate across the hydrophilic membrane.

Addition of sucrose polysoyate to the emulsion at the 5% concentration level significantly increases the in vitro diffusion rate of the drug across the cellulose ester membrane. It has been reported in the literature that some sucrose mono-esters, which have a high HLB, increase the absorption of various drugs in both in vivo and in vitro permeation studies (40-42). The sucrose moiety in the sucrose polysoyate structure also may increase the solubility of the drug, and thus we observed a higher drug flux at this concentration.

We observe that the release rate of the drug for the emulsions containing 1 and 5% sucrose polysoyate across the silicone membrane are almost the same, and significantly higher compared to the release rate of the drug from the control emulsion. The reason that we might not be able to see a significant difference in diffusion rates across the silicone membranes as a function of emollient concentration may be that at 5%, the drug could become more water-soluble, and thus this may not show as a big difference in the diffusion rate of the drug across a lipophilic membrane. With regard to in vivo diffusion, it has been proposed that sucrose fatty acid esters enhance drug transport by the interaction/insertion of the fatty acid chain

portions between the lipophilic tails of the stratum corneum bilayer lipids, thus giving space for the sucrose ring to interact with the polar head groups of the lipids (43).

#### 4.2.2 Release of Ketorolac Tromethamine from Emulsions Containing Di-PPG-2-Myreth-10 Adipate Across the Cellulose Ester and the Silicone Membranes.

The release profile of the emulsions containing 1 and 5 % di-ppg-2-myreth-10 adipate versus the control across the cellulose ester membrane is given in Figure 12. According to the evaluation using the linear mixed-effect model, the emulsion containing 5 % of the di-ppg-2-myreth-10 adipate emollient significantly decreased the release rate of the ketorolac tromethamine ( $14.5 \mu\text{g}/\text{cm}^2/\text{hr}$ ) as compared to the control ( $111.19 \mu\text{g}/\text{cm}^2/\text{hr}$ ). The release rate of the emulsion containing 1% di-ppg-2-myreth-10 adipate showed essentially the same rate as the control with neither a significant increase or decrease. Figure 12 and Table 8 show that there is no lag time in the release of ketorolac tromethamine out of the emulsions.

The release profiles of the emulsions containing 1 and 5% di-ppg-2-myreth-10 adipate and the control across the silicone membrane are given in Figure 13. According to analysis using the linear mixed-effect model, when using silicone membranes, the emulsions containing 1 and 5 % di-ppg-2-myreth-10 adipate show a significant increase in the release rate of the ketorolac tromethamine,  $3.09 \mu\text{g}/\text{cm}^2/\text{hr}$  and  $2.19 \mu\text{g}/\text{cm}^2/\text{hr}$ , respectively as compared to the control ( $0.33 \mu\text{g}/\text{cm}^2/\text{hr}$ ). Figure 13 and Table 9 show no lag time in the release of ketorolac tromethamine out of the emulsions.

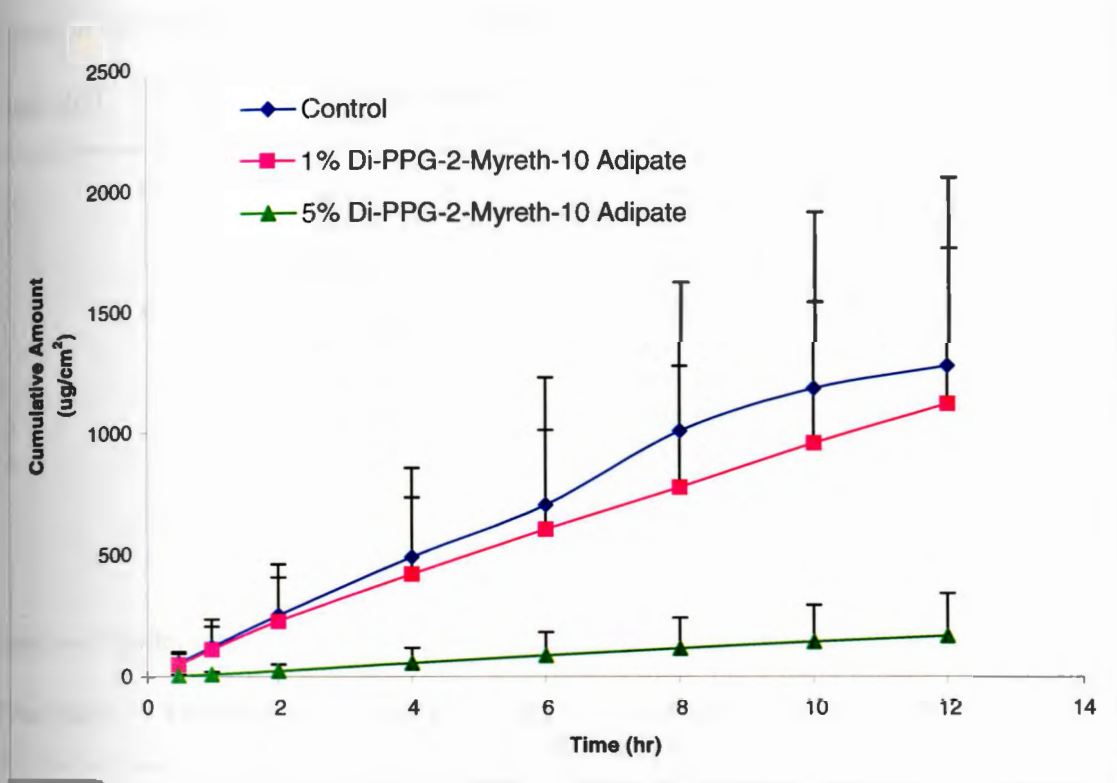


Figure 12. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5 % Di-PPG-2-Myreth-10 Adipate Across Cellulose Ester Membrane

Table 8.

*Cumulative Released Amounts of Ketorolac Tromethamine Across Cellulose Ester Membrane from Emulsions Containing 1 and 5 % Di-PPG-2 Myreth-10 Adipate*

*Emulsion Containing 1% Di-PPG-2 Myreth-10 Adipate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	47.75	47.28
1	110.73	94.10
2	226.65	180.68
4	418.80	313.51
6	601.25	407.14
8	772.99	497.62
10	953.49	578.03
12	1115.22	637.02

*Emulsion Containing 5% Di-PPG-2 Myreth-10 Adipate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	3.88	5.03
1	9.56	11.69
2	23.96	27.27
4	56.36	61.97
6	87.07	95.14
8	116.05	124.63
10	142.55	150.36
12	166.80	173.83

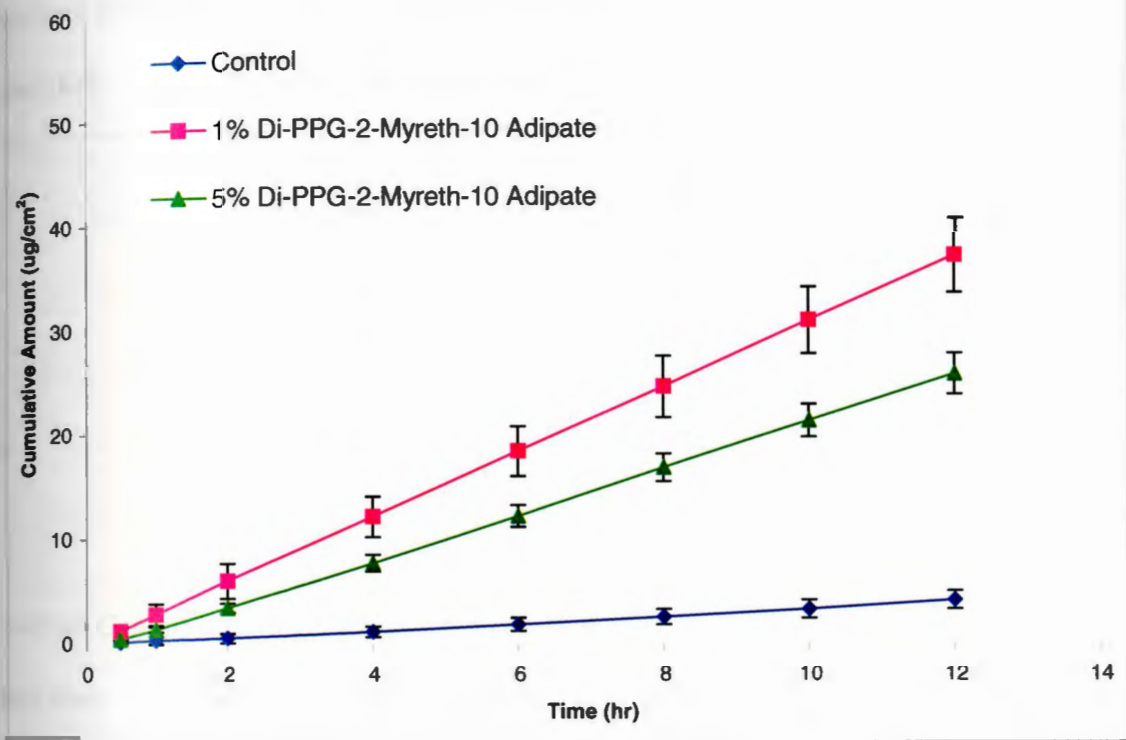


Figure 13. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5 % Di-PPG-2-Myreth-10 Adipate Across Silicone membrane

Table 9.

*Cumulative Released Amounts of Ketorolac Tromethamine Across Silicone Membrane from Emulsions Containing 1 and 5 % Di-PPG-2 Myreth-10 Adipate*

*Emulsion Containing 1% Di-PPG-2 Myreth-10 Adipate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	1.30	0.42
1	2.88	1.03
2	6.05	1.66
4	12.10	1.93
6	18.30	2.38
8	24.40	2.91
10	30.69	3.18
12	36.86	3.52

*Emulsion Containing 5% Di-PPG-2 Myreth-10 Adipate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	0.53	0.06
1	1.46	0.25
2	3.49	0.45
4	7.71	0.80
6	12.15	1.03
8	16.73	1.31
10	21.16	1.56
12	25.60	1.94

We observe that neither the emulsion containing 1% di-ppg-2-myreth-10 adipate emollient nor the emulsion containing 5% di-ppg-2-myreth-10 adipate emollient increased the release rate of ketorolac tromethamine across the cellulose ester membrane. We might explain this observation by looking at the chemical structure of the di-ppg-2-myreth-10 adipate. Di-ppg-2-myreth-10 adipate is an emollient with structural components such as ethylene oxide and propylene oxide that are similar to non-ionic surfactant compounds. It has been stated that unlike the ionic surfactants, micelles are formed by long chain polyoxyethylene non-ionic surfactants where the hydrophilic moiety is large enough to have a place for the solute (44). In our study, addition of 5 % of this emollient may have exceeded its critical micelle concentration so that the drug molecules may be entrapped by the emollient. Thus, we are observing a significant decrease in the release rate of the drug at this concentration across the cellulose ester membrane.

In contrast to what we observed with the cellulose ester membrane systems, we found out that both the emulsions containing 1 and 5 % di-ppg-2-myreth-10 adipate increased the release rate of ketorolac tromethamine across the silicone membranes. However again at the 5% concentration level we saw a slight decrease in the release rate. This behavior may be explained that when the drug molecule interacts with this bulky emollient-with the lowest HLB number- the drug molecule is entrapped by it, and thus becomes more lipophilic. That is why we observe an increase in the release rates of the both of the emulsions across the silicone membrane. In accordance with the expectation of micelle formation at the 5% concentration level, the drug molecules may have become even more lipophilic so that the drug molecules could

not pass through the lipophilic membrane easily at 5% concentration compared to that of at 1%.

#### 4.2.3 Release of Ketorolac Tromethamine from Emulsions Containing PPG-3-Benzyl Myristate Across the Cellulose Ester and the Silicone Membrane.

The release profile of the emulsions containing 1 and 5% ppg-3-benzyl myristate and the control across the cellulose ester membrane is given in Figure 14. Addition of 1 and 5% ppg-3-benzyl myristate to the emulsion increase the release rate of the drug, 200.64  $\mu\text{g}/\text{cm}^2/\text{hr}$  and 190.73  $\mu\text{g}/\text{cm}^2/\text{hr}$ , respectively as compared to 111.19  $\mu\text{g}/\text{cm}^2/\text{hr}$  seen for the control. Both of the emulsion formulations containing emollients release drug at a significantly higher rate as compared to the control. Figure 14 and Table 10 show that there is no lag time in the release of ketorolac tromethamine out of the emulsions across the cellulose ester membrane.

The release profile of the emulsions containing 1 and 5% ppg-3-benzyl myristate and the control across the silicone membrane is given in Figure 15. Both of the emulsions show significantly higher release rates, 1.97  $\mu\text{g}/\text{cm}^2/\text{hr}$  and 3.69  $\mu\text{g}/\text{cm}^2/\text{hr}$  compared to the control with a release rate of 0.33  $\mu\text{g}/\text{cm}^2/\text{hr}$ . The release pattern of the ketorolac tromethamine across the silicone membrane from emulsions containing 1 and 5% ppg-3-benzyl myristate is similar to the release pattern that we observed across the cellulose ester membrane. Figure 15 and Table 11 show that there is no lag time in the release of ketorolac tromethamine out of the emulsions across the silicone membrane.



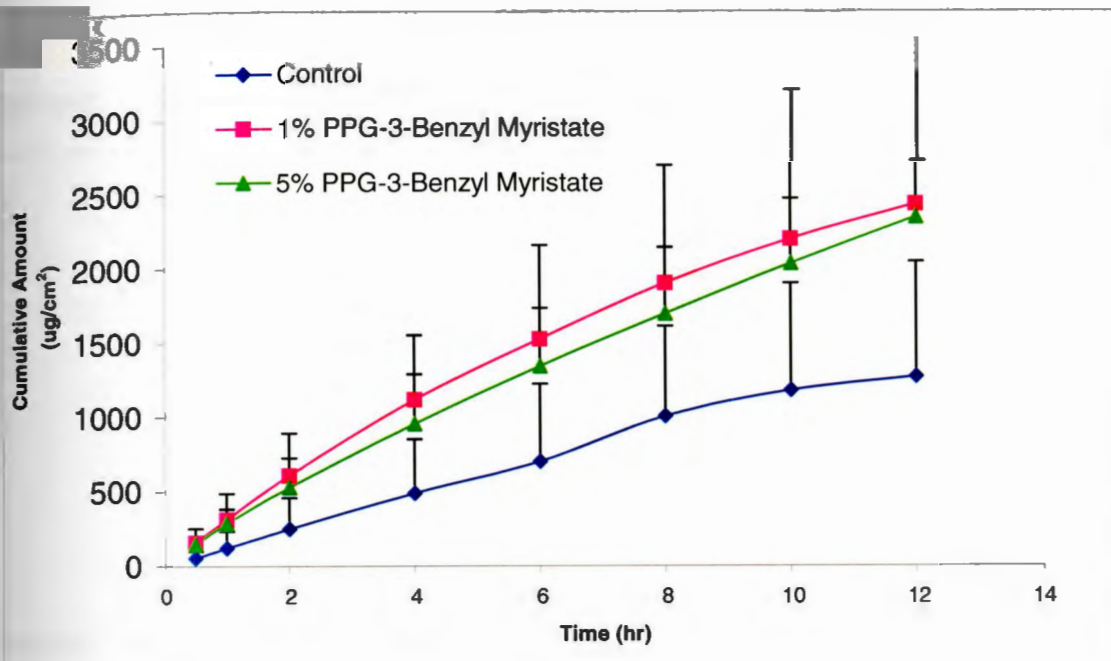


Figure 14. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5 % PPG-3-Benzyl Myristate Across Cellulose Ester Membrane

Table 10.

*Cumulative Released Amounts of Ketorolac Tromethamine Across Cellulose Ester Membrane from Emulsions Containing 1 and 5 % PPG-3 Benzyl Myristate*

*Emulsion Containing 1 % PPG-3 Benzyl Myristate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	159.19	41.36
1	311.82	72.64
2	606.62	120.08
4	1115.94	173.52
6	1522.65	210.84
8	1898.69	243.97
10	2194.96	277.09
12	2430.22	293.88

*Emulsion Containing 5% PPG-3 Benzyl Myristate*

Time (hr)	Cumulative Amount ( $\mu\text{g}/\text{cm}^2$ )	STDEV
0.5	149.26	105.28
1	289.31	200.63
2	530.89	363.05
4	955.14	597.37
6	1343.46	814.64
8	1694.95	1001.84
10	2032.38	1170.76
12	2346.37	1334.88

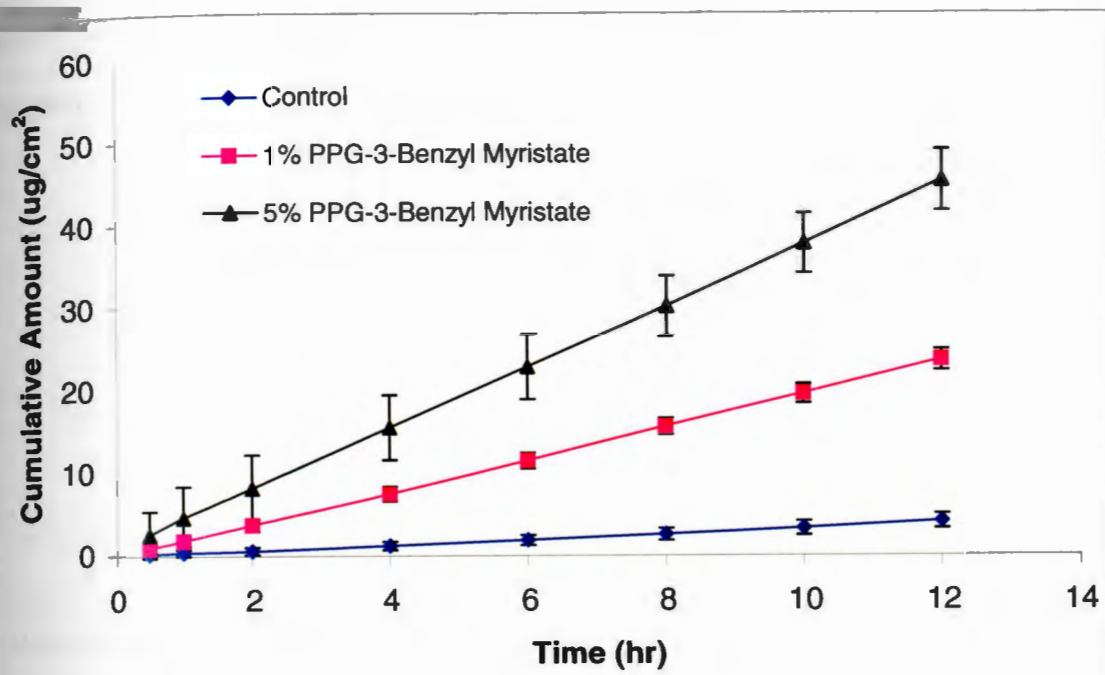


Figure 15. Release Profile of Ketorolac Tromethamine From Emulsions Containing 1 and 5 % PPG-3-Benzyl Myristate Across Silicone Membrane

Table 11.

*Cumulative Released Amounts Cumulative Release of Ketorolac Tromethamine Across Silicone Membrane from Emulsions Containing 1 and 5 % PPG-3 Benzyl Myristate*

*Emulsion Containing 1 % PPG-3 Benzyl Myristate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	0.96	0.49
1	1.85	0.60
2	3.72	0.73
4	7.47	0.85
6	11.46	0.93
8	15.57	0.99
10	19.51	1.15
12	23.58	1.26

*Emulsion Containing 5% PPG-3 Benzyl Myristate*

<b>Time (hr)</b>	<b>Cumulative Amount (<math>\mu\text{g}/\text{cm}^2</math>)</b>	<b>STDEV</b>
0.5	2.62	2.80
1	4.65	3.76
2	8.17	4.05
4	15.47	3.92
6	22.77	3.91
8	30.08	3.66
10	37.70	3.61
12	45.31	3.70

It has been reported that ppg-3-benzyl myristate increases the solubility of benzophenone-3 (45). Thus, ppg-3-benzyl myristate may increase the solubility of the drug in the emulsion, and therefore we observed significantly higher drug release rates at both 1 and 5% concentrations across both of the membranes systems.

#### 4.3 Results of Rheological Measurements

##### 4.3.1 Complex Viscosity Measurement

Most semisolids are such systems that exhibit both solid and liquid behaviors. They are described as viscoelastic bodies that will demonstrate simultaneous viscous and elastic properties. Dynamic oscillatory methods, which do not change the original material structure while applying shear to the material, are preferred to study the rheological properties of emulsions. In this study, a strain sweep test was performed in order to find out the linear viscoelastic region of each emulsion. This region indicates the critical stress point where the elasticity ends and viscous properties dominate.

All the emulsions exhibited viscoelastic behaviour from 0.60 to 1% strain, except the emulsion containing 5% sucrose polysoyate that showed viscoelastic behaviour up to 2% strain as shown in Figures 16-18. All emulsions were viscoelastic when the frequency sweep test was performed. 0.60% strain was used as the strain level for the complex viscosity measurements. The frequency sweep was performed in the oscillatory range from 1 to 100 rad/sec. The complex viscosity values are tabulated in Table 12.

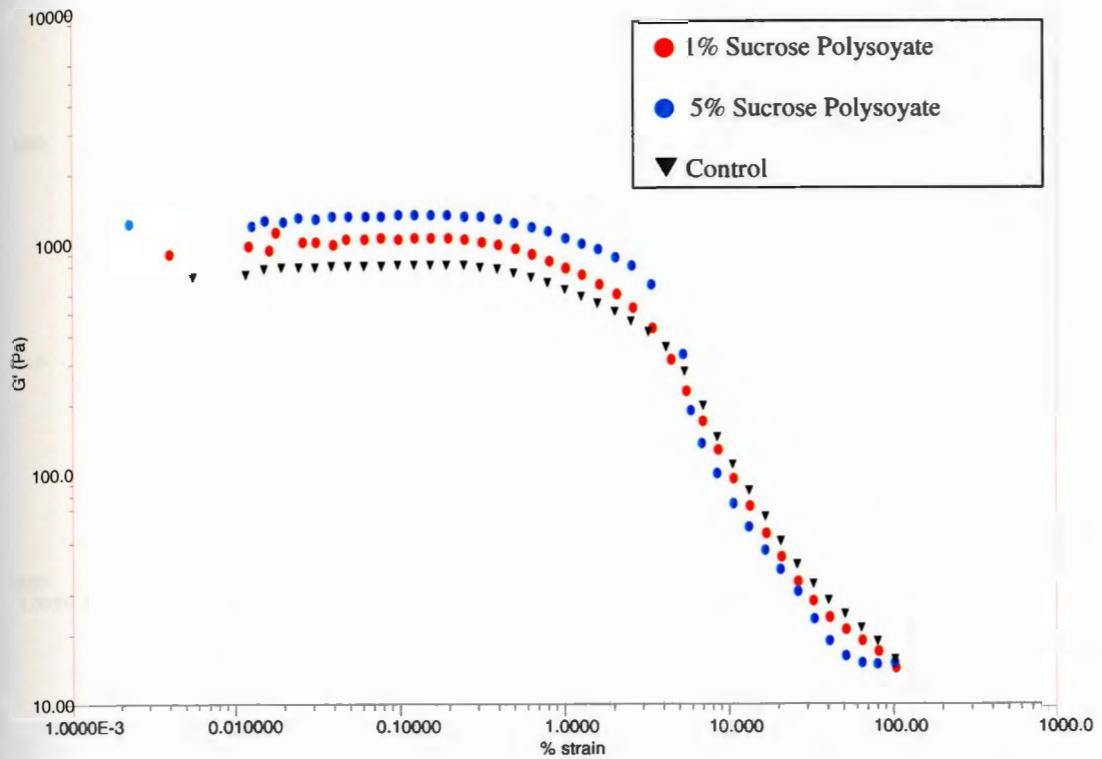


Figure 16. Strain Sweep Test for Emulsions Containing 1 and 5 % Sucrose Polysoyate and the control

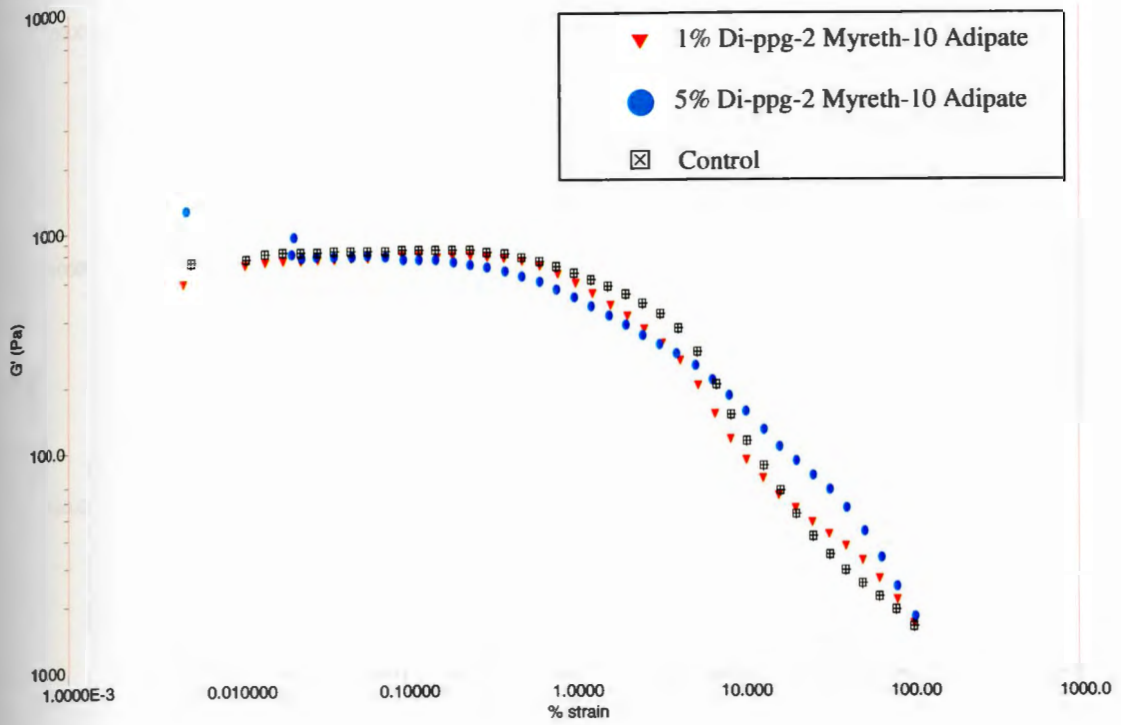


Figure 17. Strain Sweep Test for Emulsions Containing 1 and 5 % Di-PPG-2 Myreth-10 Adipate and the Control Emulsion

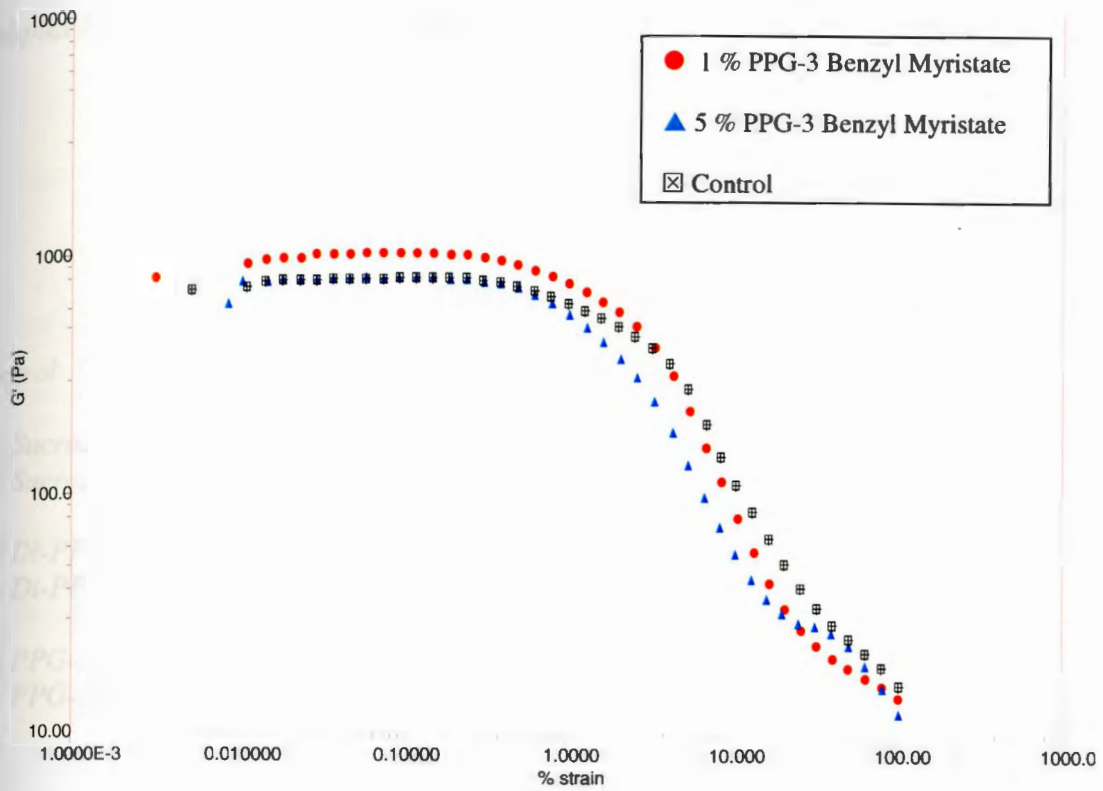


Figure 18. Strain Sweep Test for Emulsions Containing 1 and 5% PPG-3 Benzyl Myristate and the Control Emulsion



Table 12.

*Complex Viscosity Values of the Emulsions*

	<u>Complex Viscosity* (Pa.s)</u>	<u>STDEV</u>
<i>Control</i>	406.5	3.75
<i>1% Sucrose Polysoyate</i>	405.6	16.62
<i>5% Sucrose Polysoyate</i>	471.2	19.52
<i>1% Di-PPG-2-Myreth-10 Adipate</i>	375.3	3.32
<i>5% Di-PPG-2-Myreth-10 Adipate</i>	253.7	15.77
<i>1% PPG-3-Benzyl Myristate</i>	434.71	38.25
<i>5% PPG-3-Benzyl Myristate</i>	410.2	5.66

(\*) The values are an average of duplicated test runs, and the data were obtained at 1 rad/sec frequency and 0.6% strain level for all the emulsions.

The emulsions containing 5% sucrose polysoyate has the highest complex viscosity ( $471 \pm 19.52$  Pa.s) as compared to the control ( $406.5 \pm 3.75$  Pa.s). Addition of 1 % sucrose polysoyate does not increase the complex viscosity as compared to the control.

Addition of 1% di-ppg-2-myreth-10 adipate to the emulsion decreases the complex viscosity to  $375.3 \pm 3.32$  Pa.s, addition of 5% di-ppg-2-myreth-10 adipate decreases the complex viscosity still further to  $253.7 \pm 15.77$  Pa.s.

For the ppg-3-benzyl myristate, the emulsion containing 1% ppg-3-benzyl myristate increases the complex viscosity to  $434.71 \pm 38.25$  Pa.s, however addition of 5% ppg-3-benzyl myristate does not increase the viscosity as much as 1% that has a complex viscosity of  $410.2 \pm 5.66$  Pa.s.

#### 4.3.2 Thixotropy Measurement

Assessment of thixotropic behaviour of an emulsion system is important because all the emulsions will encounter a wide variety of stress starting from their manufacture until they are dispensed and applied on the skin. Although a certain level of shear thinning property is desirable to dispense the product easily, it is also important for the rest of the product to come back to its initial structure.

Thixotropy is one of the most important characteristics of a topical product. It is defined as the decrease in viscosity of a semisolid under stress, and its gradual structure recovery when the stress is removed (46). All emulsions showed a certain degree of thixotropic break down when they were sheared. The hysteresis area, which is the area between the up and down curve, gives an estimation of the energy

required to break down the structure of the emulsion system. Thus a lower thixotropy value would indicate that the emulsion requires a lower amount of energy to break down its structure and recover compared to the one that has a higher thixotropy value. The thixotropy values for the emulsions are given in Table 13. According to Table 13, the emulsion containing 1% sucrose polysoyate has a slightly lower thixotropy value ( $690.83 \text{ Pa}\cdot\text{s}^{-1}$ ) compared to the control ( $716.62 \text{ Pa}\cdot\text{s}^{-1}$ ). The emulsion containing 5% sucrose polysoyate has a thixotropy value of  $914.54 \text{ Pa}\cdot\text{s}^{-1}$ , which is significantly higher than either the 1% or the control. This finding is in line with their measured complex viscosities. The emulsion containing 5% sucrose polysoyate has the highest viscosity, thus would require the highest energy to break its structure.

The thixotropy values for the emulsions containing 1 and 5 % di-ppg-2-myreth-10 adipate are  $658.57$  and  $595.11 \text{ Pa}\cdot\text{s}^{-1}$ , respectively. This indicates that addition of di-ppg-2-myreth-10 leads to lower thixotropy values compared to the control emulsion. This finding is also in accordance with the complex viscosity values in which we have observed that addition of di-ppg-2-myreth-10 adipate decreased the viscosity of the emulsion system, and decreased the thixotropic break down energy.

As Table 13 displays, the thixotropic break down is higher for the emulsion containing 1% ppg-3-benzyl myristate with a value of  $908.61 \text{ Pa}\cdot\text{s}^{-1}$  compared to the emulsion containing 5% ppg-3-benzyl myristate that has a thixotropy value of  $524.50 \text{ Pa}\cdot\text{s}^{-1}$ . This is also in accordance with the findings of complex viscosities of these two emulsions. Addition of ppg-3-benzyl myristate more than 1% to the emulsion did not increase more neither its viscosity nor its thixotropic break down compared to the control.

Table 13.

*Thixotropy Values of the Emulsions*

	<u>Thixotropy* (Pa.s<sup>-1</sup>)</u>
<i>Control</i>	716.62
<i>1% Sucrose Polysoyate</i>	690.83
<i>5% Sucrose Polysoyate</i>	914.54
<i>1% Di-PPG-2-Myreth-10 Adipate</i>	658.57
<i>5% Di-PPG-2-Myreth-10 Adipate</i>	595.11
<i>1% PPG-3-Benzyl Myristate</i>	908.61
<i>5% PPG-3-Benzyl Myristate</i>	524.50

(\*) Thixotropy values are calculated hysteresis area on the flow charts of the emulsions.

The flow chart data were obtained as the average of three experiments.

The flow charts that were obtained by plotting shear rate versus shear stress are given in Figures 19-25. The data that show the average of three flow tests for shear stress versus shear rate values for all the emulsions and the control are given in Appendix A3.

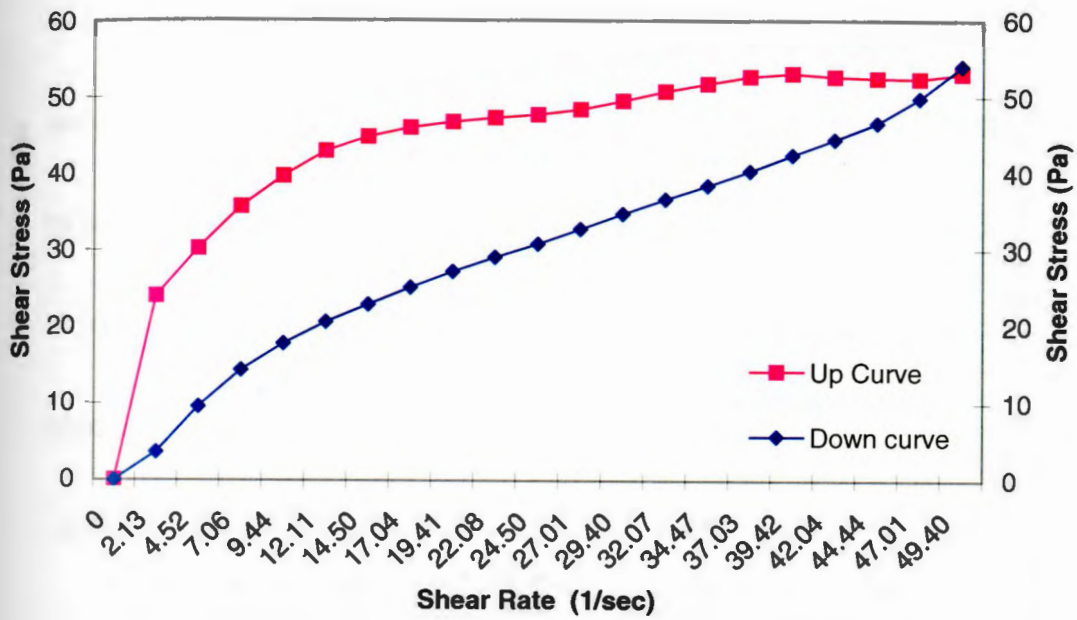


Figure 19. Flow Chart of the Control Emulsion

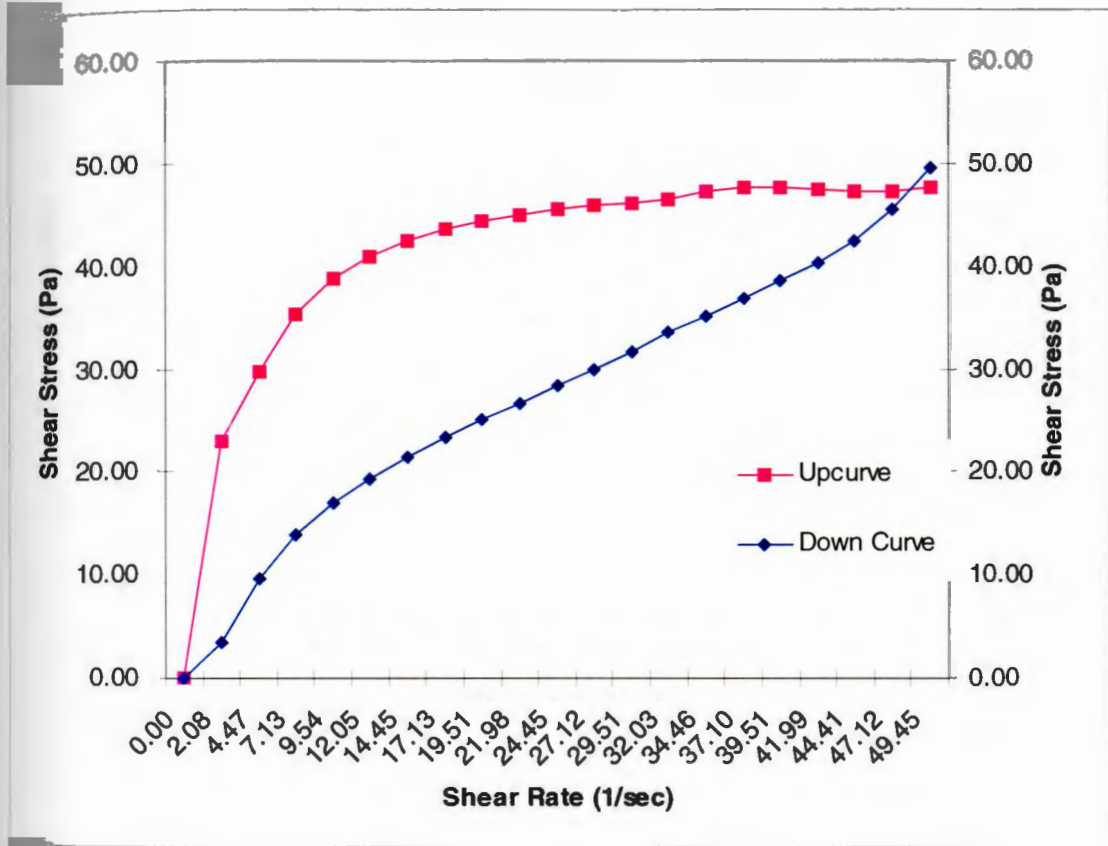


Figure 20. Flow Chart of the Emulsion Containing 1% Sucrose Polysoyate

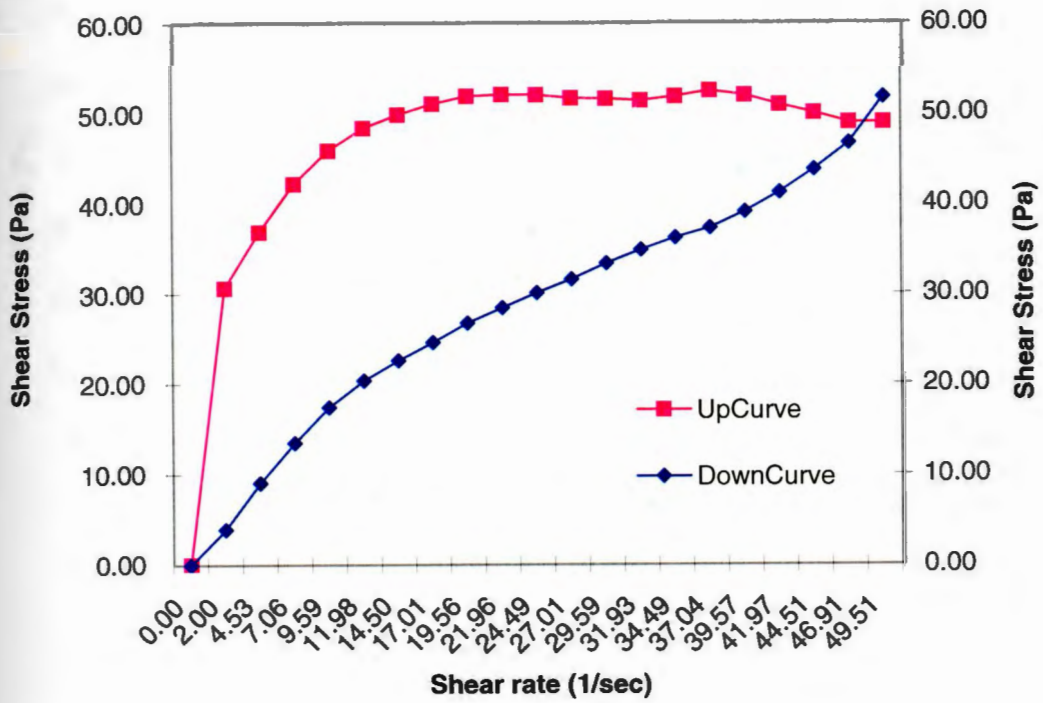


Figure 21. Flow Chart of the Emulsion Containing 5 % Sucrose Polysoyate



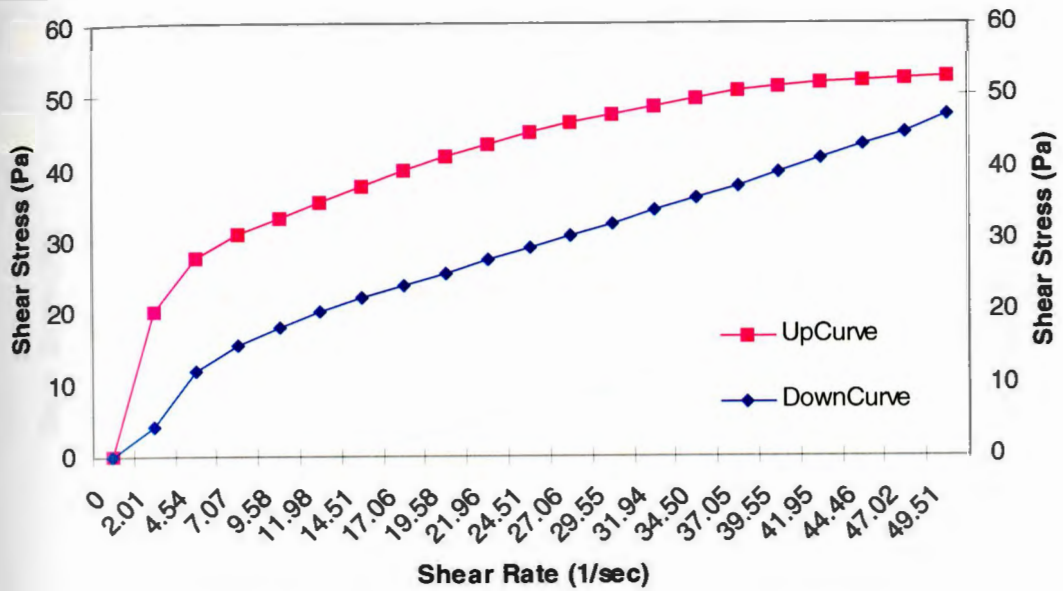


Figure 22. Flow Chart of the Emulsion Containing 1% Di-PPG-2 Myreth-10 Adipate

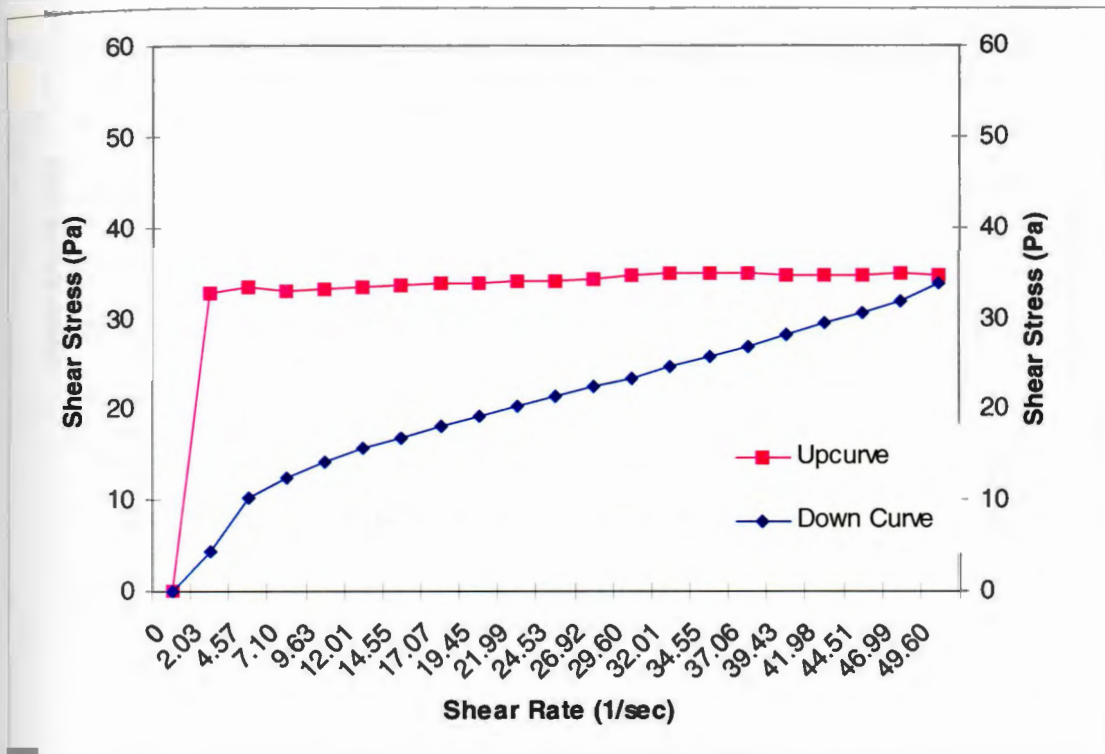


Figure 23. Flow Chart of the Emulsion Containing 5 % Di-PPG-2 Myreth-10 Adipate

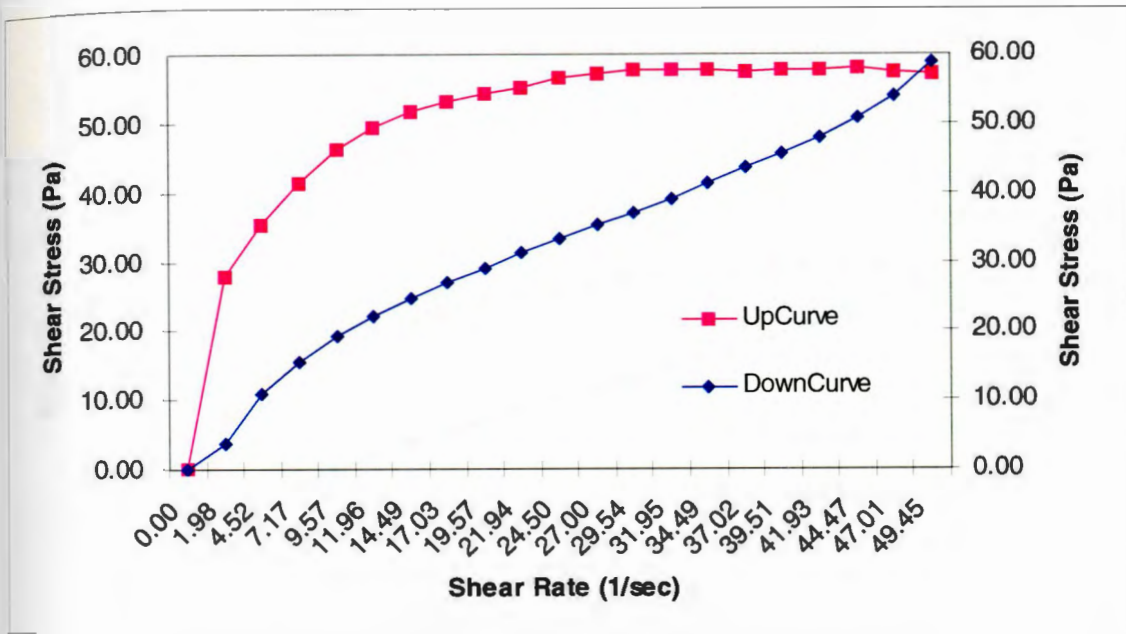


Figure 24. Flow Chart of the Emulsion Containing 1% PPG-3 Benzyl Myristate

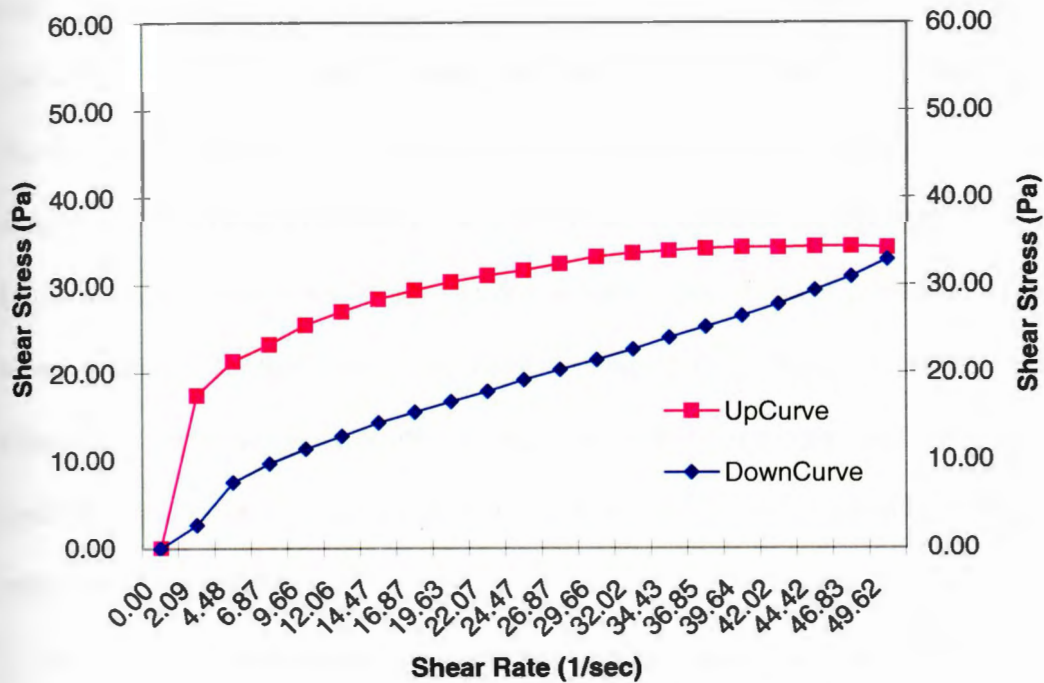


Figure 25. Flow Chart of the Emulsion Containing 5% PPG-3 Benzyl Myristate

## 5.0 Conclusions

Ketorolac tromethamine is a better alternative analgesic and anti-inflammatory drug compared to drugs such as aspirin, indomethacin, and naproxen. Transdermal delivery of ketorolac tromethamine seems to be a potential method of administration that will be non-invasive and eliminate repeated dosing regimen. It has been reported that the bioavailability of an 85 mg ketorolac tromethamine, when administered transdermally in rhesus monkeys, is 35%. Thus, to increase the systemic delivery of ketorolac tromethamine use of penetration enhancers would be of great interest in this research area. In this study, we have examined the effects of three emollient substances- sucrose polysoyate, di-ppg-2-myreth-10 adipate and ppg-3-benzyl myristate as o/w emulsions- on in vitro diffusion of ketorolac tromethamine across artificial skin membranes.

Addition of 5% sucrose polysoyate significantly increased the ketorolac tromethamine in vitro diffusion across the cellulose ester membrane. We have seen a different diffusion pattern across the silicone membrane such that both emulsions containing 1 and 5% sucrose polysoyate increased the diffusion rate of the drug.

Neither the emulsion containing 1% di-ppg-2-myreth-10 adipate, nor the emulsion containing 5% di-ppg-2-myreth-10 adipate increased the release rate of ketorolac tromethamine across the cellulose ester membrane. Furthermore, the emulsion containing 5% di-ppg-2-myreth-10 adipate significantly decreased the release rate of the drug across the cellulose ester membrane. We have not observed this release pattern across the silicone membrane systems with this emollient. We observed that

both emulsions containing 1 and 5% di-ppg-2-myreth-10 adipate increased the release rate of the drug significantly across the silicone membrane.

The emulsions containing 1 and 5% ppg-3-benzyl myristate were able to significantly increase the release rate of ketorolac tromethamine across the cellulose ester and the silicone membranes.

Although in vitro studies do not replace with in vivo studies, they are vital because these studies add appreciably to the development and evaluation of new dosage forms and help in understanding underlying principles controlling absorption (47). In our study, these in vitro test results gave us an idea whether these emollient substances could be utilized as potential permeation enhancer substances. Although this needs to be further assessed with the in vivo studies, we can conclude that all of the emollient substances namely, sucrose polysoyate, di-ppg-2-myreth-10 adipate and ppg-3-benzyl myristate increased the release rate of ketorolac tromethamine significantly through the silicone membrane. Except di-ppg-2-myreth-10 adipate, which decreased or had no effect on release rate of ketorolac tromethamine across the cellulose ester membrane, the other two emollients sucrose polysoyate and ppg-3-benzyl myristate were able to increase the release rate of the drug across cellulose ester membrane. Further, this research identified the inadvertent effect that emollient excipients may have on the permeation of other components when used for their emollient effects in various skin preparations.

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## Appendix

Table A1.

*Table representing the results of the linear-mixed effect model test for the differences of release rates of the emulsions across the cellulose ester membrane*

<b>Effect</b>	<b>Group</b>	<b>Estimate</b>	<b>StdErr</b>	<b>DF</b>	<b>tValue</b>	<b>Probt</b>
Intercept		29.40411	5896.846	314	0.004986	0.996025
Group	A1	18.86651	7984.367	314	0.002363	0.998116
Group	A5	125.4184	7984.37	314	0.015708	0.987477
Group	B1	-0.38182	7984.367	314	-4.8E-05	0.999962
Group	B5	-32.4676	7984.367	314	-0.00407	0.996758
Group	C1	159.6486	7984.367	314	0.019995	0.98406
Group	C5	98.92669	7984.367	314	0.01239	0.990122
Group	Re	0				
TIME		111.1863	27.32632	33.9968	4.068836	0.000266
TIME*Group	A1	-5.64999	37.00001	33.9968	-0.1527	0.879536
TIME*Group	A5	142.847	37.01195	34.04068	3.859484	0.000483
TIME*Group	B1	-18.8943	37.00001	33.9968	-0.51066	0.612893
TIME*Group	B5	-96.6868	37.00001	33.9968	-2.61316	0.013266
TIME*Group	C1	89.44959	37.00001	33.9968	2.417556	0.021136
TIME*Group	C5	79.45004	37.00001	33.9968	2.147298	0.038987
TIME*Group	Re	0				

A1: emulsion containing 1% sucrose polysoyate, A5: emulsion containing 5% sucrose polysoyate, B1: emulsion containing 1% di-ppg-2-myreth-10 adipate, B5: emulsion containing 5% di-ppg-2-myreth-10 adipate, C1: emulsion containing 1% ppg-3-benzyl myristate, C5: emulsion containing 5% ppg-3-benzyl myristate, Re: Control

Table A2.

*Table representing the results of the linear-mixed effect model test for the differences of release rates of the emulsions across silicone membrane*

Effect	Group	Estimate	StdErr	DF	tValue	Probt
Intercept		-0.01638	0.919739	33.00604	-0.01781	0.985894
Group	A1	2.000422	1.300707	33.00604	1.53795	0.133594
Group	A5	1.93819	1.300707	33.00604	1.490105	0.145692
Group	B1	-0.19652	1.300707	33.00604	-0.15109	0.880826
Group	B5	-0.78727	1.300773	33.01277	-0.60523	0.549165
Group	C1	-0.18241	1.300707	33.00604	-0.14024	0.889321
Group	C5	0.784718	1.454234	33.00604	0.539609	0.593089
Group	Re	0				
TIME		0.333906	0.09101	33.00411	3.668888	0.000852
TIME*Group	A1	3.066142	0.128708	33.00411	23.82252	2.29E-22
TIME*Group	A5	3.108281	0.128708	33.00411	24.14991	1.49E-22
TIME*Group	B1	2.752897	0.128708	33.00411	21.38874	6.49E-21
TIME*Group	B5	1.855545	0.128783	33.08035	14.4083	8.2E-16
TIME*Group	C1	1.636795	0.128708	33.00411	12.71714	2.86E-14
TIME*Group	C5	3.35859	0.1439	33.00411	23.33981	4.33E-22
TIME*Group	Re	0				

A1: emulsion containing 1% sucrose polysoyate, A5: emulsion containing 5% sucrose polysoyate, B1: emulsion containing 1% di-ppg-2-myreth-10 adipate, B5: emulsion containing 5% di-ppg-2-myreth-10 adipate, C1: emulsion containing 1% ppg-3-benzyl myristate, C5: emulsion containing 5% ppg-3-benzyl myristate, Re: Control

Table A3.

*Shear Stress versus Shear Rate Data for the Emulsions***CONTROL****UP CURVE**

<b>Shear Stress (Pa)</b>	<b>Shear Rate (1/sec)</b>
23.97	2.13
30.14	4.52
35.59	7.06
39.60	9.44
42.84	12.11
44.72	14.50
45.92	17.04
46.65	19.41
47.19	22.08
47.63	24.50
48.34	27.01
49.43	29.40
50.70	32.07
51.68	34.47
52.63	37.03
53.02	39.42
52.64	42.04
52.42	44.44
52.34	47.01
52.99	49.40

**DOWN CURVE**

<b>Shear Stress (Pa)</b>	<b>Shear Rate (1/sec)</b>
3.64	0.50
9.57	2.89
14.35	5.42
17.78	7.94
20.57	10.48
22.86	12.85
25.11	15.41
27.15	17.96
29.02	20.48
30.77	22.87
32.70	25.37
34.72	27.93
36.61	30.42
38.40	32.86
40.27	35.34
42.41	37.93
44.44	40.48
46.57	42.85
49.83	45.35
54.02	47.90

**Emulsion Containing 1% Sucrose Polysoyate****UP CURVE**

<b>Shear Stress (Pa)</b>	<b>Shear Rate (1/sec)</b>
22.99	2.08
29.71	4.47
35.35	7.13
38.78	9.54
40.97	12.05
42.37	14.45
43.53	17.13
44.31	19.51
44.99	21.98
45.62	24.45
45.94	27.12
46.17	29.51
46.55	32.03
47.22	34.46
47.65	37.10

**DOWN CURVE**

<b>Shear Stress (Pa)</b>	<b>Shear Rate (1/sec)</b>
3.44	0.41
9.57	2.94
13.98	5.47
17.01	7.99
19.33	10.36
21.46	12.91
23.41	15.44
25.11	17.86
26.70	20.39
28.30	22.91
29.99	25.41
31.72	27.84
33.52	30.37
35.20	32.86
36.93	35.42



47.59	39.51	38.68	37.83
47.50	41.99	40.35	40.32
47.28	44.41	42.35	42.86
47.27	47.12	45.52	45.44
47.72	49.45	49.54	47.91

**Emulsion Containing 5% Sucrose Polysoyate**

UP CURVE

DOWN CURVE

Shear Stress (Pa)	Shear Rate (1/sec)	Shear Stress (Pa)	Shear Rate (1/sec)
30.61	2.00	3.91	0.55
36.81	4.53	9.04	2.94
42.16	7.06	13.45	5.32
45.88	9.59	17.42	7.98
48.35	11.98	20.38	10.54
49.85	14.50	22.59	12.91
51.03	17.01	24.57	15.31
51.87	19.56	26.72	18.13
52.06	21.96	28.42	20.51
52.03	24.49	30.07	22.91
51.67	27.01	31.59	25.32
51.61	29.59	33.36	28.09
51.38	31.93	34.84	30.49
51.83	34.49	36.18	32.93
52.46	37.04	37.27	35.30
51.98	39.57	39.07	37.92
50.93	41.97	41.22	40.46
50.00	44.51	43.75	42.90
48.96	46.91	46.69	45.30
48.96	49.51	51.76	47.95

**Emulsion Containing 1% di-ppg-2-myreth-10 adipate**

UP CURVE

DOWN CURVE

Shear Stress (Pa)	Shear Rate (1/sec)	Shear Stress (Pa)	Shear Rate (1/sec)
20.15	2.01	4.24	0.58
27.39	4.54	11.85	2.97
30.71	7.07	15.41	5.36
33.09	9.58	17.94	7.88
35.22	11.98	20.16	10.54
37.38	14.51	21.98	12.95
39.54	17.06	23.68	15.35
41.55	19.58	25.42	17.89
43.25	21.96	27.18	20.53
44.78	24.51	28.82	22.94
46.14	27.06	30.46	25.34
47.30	29.55	32.22	27.83
48.45	31.94	34.05	30.51
49.66	34.50	35.72	32.91
50.63	37.05	37.46	35.31

51.30	39.55	39.29	37.84
51.84	41.95	41.25	40.56
52.06	44.46	43.08	42.93
52.30	47.02	44.99	45.35
52.55	49.51	47.25	47.88

**Emulsion Containing 5% di-ppg-2-myreth-10 adipate**

*UP CURVE*

*DOWN CURVE*

<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>	<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>
32.74	2.03	4.33	0.42
33.32	4.57	10.29	2.95
33.03	7.10	12.52	5.34
33.16	9.63	14.22	7.88
33.33	12.01	15.64	10.41
33.57	14.55	16.90	12.93
33.74	17.07	18.10	15.34
33.83	19.45	19.23	17.97
33.97	21.99	20.29	20.39
34.14	24.53	21.36	22.92
34.32	26.92	22.39	25.44
34.65	29.60	23.42	27.81
34.83	32.01	24.61	30.40
34.81	34.55	25.78	32.93
34.83	37.06	26.78	35.34
34.80	39.43	28.09	38.00
34.73	41.98	29.42	40.49
34.79	44.51	30.47	42.91
34.85	46.99	31.82	45.26
34.76	49.60	33.87	47.97

**Emulsion Containing 1% ppg-3-benzyl myristate**

*UP CURVE*

*DOWN CURVE*

<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>	<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>
27.72	1.98	3.81	0.37
35.35	4.52	10.98	3.03
41.38	7.17	15.64	5.42
46.30	9.57	19.24	7.95
49.49	11.96	22.05	10.34
51.55	14.49	24.76	13.02
53.05	17.03	26.95	15.41
54.22	19.57	29.12	17.91
55.12	21.94	31.18	20.32
56.44	24.50	33.41	23.01
57.14	27.00	35.23	25.41
57.71	29.54	37.13	27.89
57.80	31.95	39.04	30.31
57.62	34.49	41.46	33.02

57.54	37.02	43.53	35.37
57.59	39.51	45.63	37.93
57.79	41.93	47.90	40.29
57.93	44.47	50.75	42.98
57.47	47.01	53.99	45.38
57.22	49.45	58.81	47.90

**Emulsion Containing 5% ppg-3-benzyl myristate**

*UP CURVE*

*DOWN CURVE*

<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>	<i>Shear Stress (Pa)</i>	<i>Shear Rate (1/sec)</i>
17.42	2.09	2.65	0.40
21.29	4.48	7.50	3.06
23.23	6.87	9.66	5.46
25.43	9.66	11.32	7.86
26.96	12.06	12.77	10.26
28.35	14.47	14.28	13.05
29.39	16.87	15.50	15.45
30.32	19.63	16.70	17.86
31.04	22.07	17.84	20.24
31.63	24.47	19.15	23.03
32.39	26.87	20.30	25.43
33.20	29.66	21.43	27.85
33.64	32.02	22.64	30.22
33.90	34.43	23.97	33.02
34.15	36.85	25.20	35.43
34.29	39.64	26.44	37.82
34.25	42.02	27.79	40.25
34.36	44.42	29.38	43.05
34.40	46.83	30.94	45.44
34.23	49.62	32.91	47.81

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